

Balancing Potency of Platelet Inhibition with Bleeding Risk in the Early Treatment of Acute Coronary Syndrome

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Objective: To review available evidence and examine issues surrounding the use of advanced antiplatelet therapy in an effort to provide a practical guide for emergency physicians caring for patients with acute coronary syndromes (ACS).

Data Sources: American College of Cardiology/American Heart Association (ACC/AHA) 2007 guidelines for the management of patients with unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI), AHA/ACC 2007 focused update for the management of patients with STEMI, selected clinical articles identified through the PubMed database (1965-February 2008), and manual searches for relevant articles identified from those retrieved.

Study Selection: English-language controlled studies and randomized clinical trials that assessed the efficacy and safety of antiplatelet therapy in treating patients with all ACS manifestations.

Data Extraction and Synthesis: Clinical data, including treatment regimens and patient demographics and outcomes, were extracted and critically analyzed from the selected studies and clinical trials. Pertinent data from relevant patient registries were also evaluated to assess current clinical practice.

Conclusions: As platelet activation and aggregation are central to ACS pathology, antiplatelet agents are critical to early treatment. A widely accepted first-line treatment is aspirin, which acts to decrease platelet activation via inhibition of thromboxane A2 synthesis. Thienopyridines, which inhibit ADP-induced platelet activation, and glycoprotein (GP) receptor antagonists, which bind to platelet GP IIb/IIIa receptors and hinder their role in platelet aggregation and thrombus formation, provide complementary mechanisms of platelet inhibition and are often employed in combination with aspirin. While the higher levels of platelet inhibition that accompany combination therapy improve protection against ischemic and peri-procedural events, the risk of bleeding is also increased. Thus, the challenge in choosing appropriate therapy in the emergency department lies in balancing the need for potent platelet inhibition with the potential for increased risk of bleeding and future interventions the patient is likely to receive during the index hospitalization.

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INTRODUCTION

Acute coronary syndrome (ACS) describes a spectrum of atherothrombosis, including unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). As treatment decisions are driven by ACS type and severity,

initial risk stratification in the emergency department (ED) is essential. In addition to historical factors and hemodynamic stability, electrocardiographic and cardiac biomarker findings play an important role in differentiating UA/NSTEMI from STEMI (Figure 1). Patients with acute STEMI are candidates for immediate reperfusion therapy

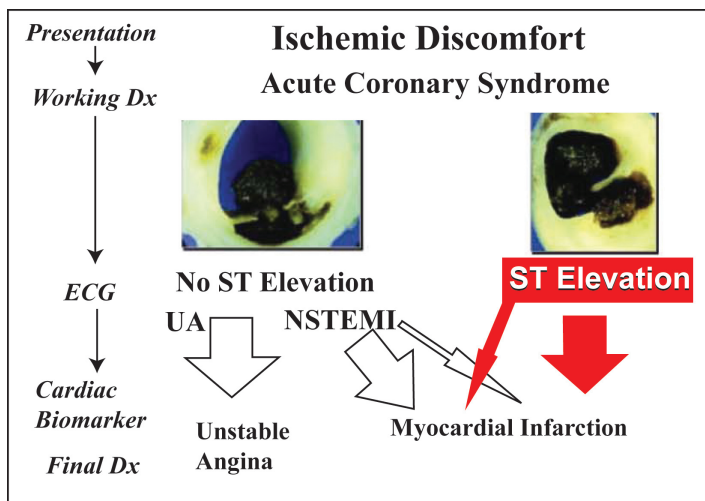


Figure 1. Spectrum of acute coronary syndromes. Adapted with permission from ©2004 American Heart Association, Inc.⁶³

with adjunctive antiplatelet and antithrombotic therapy. The optimal strategy (percutaneous coronary intervention [PCI] vs. fibrinolysis) depends on the patient's clinical condition, timing of presentation, and the availability of interventional resources. In patients with UA/NSTEMI, diagnostic tools such as the 7-point Thrombolysis in Myocardial Infarction (TIMI) risk score can be used for semi-quantitative assessment of the risk of cardiac ischemic complications, where the risk of mortality or adverse cardiovascular events increases with the scale score.¹ It is recommended that high- and intermediate-risk UA/NSTEMI patients be managed with an early invasive strategy (i.e., diagnostic angiography followed by revascularization [PCI or coronary artery bypass graft (CABG)]).^{2,3} The choice of optimal revascularization depends on the patient's coronary anatomy, left ventricular function, and the presence of co-morbidities such as diabetes. Lower-risk patients can receive medical management, with diagnostic angiography deferred unless deterioration occurs.³

Since platelet activation and aggregation are pivotal to ACS pathology, antiplatelet therapy, including aspirin, thienopyridines and glycoprotein IIb/IIIa receptor inhibitors (GPIs), is central to ACS treatment. Aspirin, which inhibits platelet activation by irreversibly binding to cyclooxygenase-1, is widely accepted as first-line treatment in ACS patients.² By irreversibly binding the platelet P2Y₁₂ receptor, thienopyridines inhibit adenosine diphosphate-mediated platelet activation. GPIs prevent activated platelets from cross-linking with fibrinogen, and ultimately decrease the trapping of red blood cells that leads to early vessel thrombus formation, obstruction, and/or distal small vessel embolization. "Dual" antiplatelet therapy (aspirin plus GPIs or aspirin plus thienopyridines) is appropriate in some patients, while in others, "triple" therapy including all three agents is suitable.

Emergency physicians (EPs) must choose appropriate antiplatelet therapy based on the underlying risk of ischemic complications and the anticipated course of treatment, i.e. medical vs. interventional management.⁴ Ideally, evidence-based, predetermined ACS protocols should be in place so that optimal antiplatelet therapy can occur concurrently with maximum protection against bleeding complications. Ongoing collaboration among EPs, cardiologists, hospitalists and cardiovascular surgeons will undoubtedly improve care for ACS patients. Data from CRUSADE, a national health quality improvement initiative, showed significant improvement in adherence to guideline recommendations for ACS management in the acute setting, as participating hospitals developed more thorough cross-disciplinary pathways and protocols.⁵ It is through such institutional-level collaboration that EPs can be empowered to initiate early, appropriate anti-ischemic therapy rather than being dependent on the individual, often varied, preferences of on-call specialists.

In addition to disease-related ischemia and necrosis, high-risk patients who undergo angiography face the potential added burden of periprocedural ischemia. It is hypothesized that microvascular embolization downstream of the target vessel plays a predominant role in the development of periprocedural infarction risk.⁶ Hence, it is important to recognize the adjuvant role of pre-catheterization ("upstream") antiplatelet agents and anticoagulation during coronary intervention to offer protection against both disease-related and periprocedural ischemic insults. Appropriate therapy must balance the need for potent platelet inhibition with the potential for increased bleeding.

This review aims to examine issues and barriers surrounding antiplatelet therapy use and to provide a practical guide for EPs regarding their optimal use in ACS patients. While not a purely systematic review, we sought to identify relevant controlled studies and randomized clinical trials that assessed the efficacy and safety of antiplatelet therapy in treating patients with all ACS manifestations. Other data sources included 1) the 2007 American College of Cardiology/American Heart Association (ACC/AHA) ACS treatment guidelines, 2) relevant clinical data extracted from patient registries, and 3) selected clinical articles identified through the PubMed database (1965-February 2008) using appropriate search terms (e.g. acute coronary syndrome, antiplatelet agents, atherosclerosis, blood platelets, myocardial infarction, thrombosis).

Variability of platelet response

Available secondary prevention therapies do not provide cures. They decrease associated risks. Despite receiving "adequate" antiplatelet therapy, approximately 8-10% of patients experience recurrent cardiovascular ischemic events after ACS.⁷⁻⁹ This phenomenon is loosely referred to as "resistance" without a clear, consensus definition.^{10,11} In most

Table 1. Factors affecting inter-individual variability in response to antiplatelet therapy.

Adherence
Intestinal absorption ³¹
Genetic polymorphism resulting in variable cytochrome P450-dependent enzyme activity ^{14,15,17}
Pretreatment platelet reactivity ⁷²
Drug resistance ⁷²

instances, what is described as resistance is actually either hyporesponsiveness to therapy, which falls under platelet response variability, or patient non-adherence, which may or may not be obvious.^{12,13} There are many potential reasons for platelet response variability, including adherence, non-absorption, and genetic polymorphisms (Table 1).

True pharmacological resistance is probably uncommon and likely the result of genetic polymorphism. Some evidence suggests that variability in cytochrome P450-dependent enzyme activity due to genetic polymorphism may contribute to inter-patient variation in aspirin and clopidogrel response.^{14,15} ACS patients are likely to be taking multiple medications for co-morbid conditions, including statins and/or calcium-channel blockers, that are metabolized by cytochrome P3A4 (CYP 3A4). Non-dihydropyridines such as verapamil and diltiazem are known to inhibit CYP 3A4, and most statins, with the exception of pravastatin, compete with clopidogrel for binding to CYP 3A4; this could lead to reduced metabolism or clearance of one or both of the drugs involved.¹⁶ Conversely, a study conducted in healthy volunteers showed that St. John's Wort amplified the effects of clopidogrel, turning non-responders into responders.¹⁷ Recently, the FDA reported that additional studies would be conducted to better characterize the impact of genetic factors and concomitant administration of other drugs on the efficacy of clopidogrel.¹⁸

Laboratory platelet aggregation tests, traditionally used to evaluate bleeding disorders, have recently been employed to correlate *ex vivo* results of antiplatelet therapy with clinical outcomes. However, using these inhibition of platelet activity (IPA) results is problematic and currently clinically non-interpretable, partly due to the lack of a standard test for IPA. For each given test, there is considerable variation among laboratories as the methodology is difficult to standardize. Further, results of these tests are temporally variable for any given patient. More importantly, there have been no data definitively linking IPA with clinical outcomes. In studies of patients presenting to the ED with acute chest pain or ACS, the success of platelet function testing in predicting the severity of MI or other adverse cardiac events has been variable.^{19,20} In particular, results of IPA tests suggest 'resistance' upwards of 35%; in reality, however, only 8%-

10% of patients show clinical signs of hyporesponsiveness or resistance.²¹ Clearly, platelet response variability to antiplatelet therapy is a controversial and widely debated topic that requires more research to discern its true clinical impact and whether any practice changes are necessary. Such changes are likely to occur first in the chronic management of coronary artery disease, but at some point in the future may impact ED decision-making as well.

Loading Dose

Rapid inhibition of platelet aggregation is often accomplished by administering a loading dose of an antiplatelet agent. As shown in the CURE,^{8,22} CREDO,⁷ and CLARITY^{23,24} trials, as well as a meta-analysis thereof,²⁴ addition of a 300-mg clopidogrel loading dose resulted in significant relative risk reductions in endpoints among all ACS patients, regardless of their intervention strategy (Table 2). The optimal loading dose of clopidogrel necessary to safely achieve rapid platelet inhibition has been an area of investigation. Compared to the standard 300-mg loading dose, a 600-mg dose has been shown to inhibit platelet aggregation more rapidly, reducing the time required to achieve maximum platelet inhibition from six to two hours.²⁵⁻³¹

Although a higher clopidogrel loading dose more rapidly inhibits platelet aggregation, it is unclear whether this translates into improved clinical outcomes. In the ARMYDA-2 study of UA/NSTEMI patients undergoing PCI, a 600-mg clopidogrel loading dose reduced the risk of periprocedural events by 50% compared to a 300-mg loading dose without increasing the risk of bleeding (Table 2).³⁰ In the CLEAR PLATELETS and ISAR-REACT 2 studies, addition of a GPI following a 600 mg clopidogrel loading dose further reduced the risk of adverse events and myocardial necrosis without significantly increasing the risk of bleeding.^{9,25} However, the added clinical benefits relative to the safety (bleeding risk) of higher loading doses remain to be fully established. This is being evaluated in the ongoing CURRENT OASIS-7 trial.

Current U.S. guidelines reflect the uncertainty of the optimal clopidogrel loading dose. Both the PCI and UA/NSTEMI guidelines specifically mention this uncertainty.^{2,32} The UA/NSTEMI guidelines don't make a specific recommendation, while the PCI guidelines recommend a 600-mg loading dose.^{2,32} The STEMI guidelines maintain a recommendation of 300 mg for patients receiving fibrinolysis or no reperfusion.³³

Loading doses of the recently approved antiplatelet agent, prasugrel, have also been assessed. In PRINCIPLE, a 60-mg prasugrel loading dose resulted in greater platelet inhibition compared to a 600-mg clopidogrel loading dose as early as 30 minutes after intake.³⁴ Although PRINCIPLE was not powered to detect clinical outcomes, hemorrhagic adverse events were more common in patients taking prasugrel. The excess

Table 2. Selected clinical trials and meta-analyses of relevant antiplatelet therapies. The trials are presented according to the antiplatelet therapy and ACS type investigated.

	Study	Treatment	Duration	Relative Risk Reduction	Safety outcomes
Antiplatelet Therapy vs. Placebo					
Acute MI	Antithrombotic Trialists' Collaboration ⁷³	Dependent on trial and antiplatelet therapy used	Mean = 1 month	38 fewer vascular events (SE=5) per 1,000 patients treated	1-2 additional extracranial bleeds
Clopidogrel + Aspirin vs. Aspirin alone					
NSTEMI	CURE ⁸	300 mg loading dose clopi + 75 mg/day clopi + 75-325 mg/day ASA vs. 75-325 mg/day ASA + Placebo	Mean = 9 months Range = 3-12 months	20% (95% CI, 0.72-0.90; P<0.001) in CV death, IS, or non-fatal reinfarction at 12 months	1% excess of major bleeding (3.7% vs. 2.7%; RR, 1.38; P=0.001) and 0.3% excess of life-threatening bleeding (2.1% vs. 1.8%; P=0.13) with dual therapy vs. ASA alone
PCI	PCI-CURE ²²	300 mg loading dose clopi + 75 mg/day clopi + 75-325 mg/day ASA vs. 75-325 mg/day ASA + Placebo	Mean = 8 months Range = 3-12 months	30% (95% CI, 0.50-0.97; p=0.03) for CV death, MI or urgent TVR within 30 days	No excess of any bleeding between PCI and 30 days, but a 1.4% excess of minor bleeding (RR, 1.68; 95% CI, 1.06-2.68; p=0.03) after 30 days with dual therapy vs. ASA alone
	CREDO ⁷	300 mg clopi loading dose + 75 mg/day clopi + 75-325 mg/day ASA vs. 75-325 mg/day ASA + Placebo	12 months	27% (95% CI, 3.9-44.4%; P=0.02) for CV death, MI, or IS at 12 months	2.1% (8.8% vs. 6.7%; P=0.07) increase in the risk of major bleeding at 12 months with dual therapy vs. ASA alone
STEMI	CLARITY ²³	300 mg clopi loading dose + 75 mg/day clopi + 75-162 mg ASA vs. 75-162 mg ASA + Placebo	30 days	36% (95% CI, 24-47%; P<0.001) for an occluded infarct-related artery upon angiography or death or recurrent MI prior to angiography; 20% (OR, 0.80; 95% CI, 0.65-0.97; P=0.03) for CV death, recurrent MI, or urgent TVR within 30 days	0.2% increase (1.3% vs. 1.1%; P=0.64) in the risk of major bleeding through 30 days
	COMMIT ⁷⁴	75 mg/day clopi + 162 mg/day ASA vs. 162 mg/day ASA + Placebo	Mean = 15 days Max = 28 days Quartiles = 9, 14, and 21 days	9% (OR, 0.91; 95% CI, 0.86-0.97; p=.002) for death, recurrent MI, or stroke during hospitalization; 7% (OR, 0.93; 95% CI, 0.87-0.99; p=0.03) for all-cause death during hospitalization	0.03% (0.58% vs. 0.55%; p=0.59) excess of major bleeding 0.5% (3.6% vs. 3.1%; p=0.005) excess of minor bleeding
600 mg clopidogrel loading dose vs. 300 mg clopidogrel loading dose					
PCI	ARMYDA-2 ³⁰	600 mg clopi loading dose + 75 mg/day clopi + 100 mg/day ASA vs. 300 mg clopi loading dose + 75 mg/day clopi + 100 mg/day ASA	30 days	50% (OR, 0.48; 95% CI, 0.15-0.97; P=0.044) for periprocedural MI with 600 mg vs. 300 mg clopi loading dose	No excess bleeding of any type
Prasugrel + Aspirin vs. clopidogrel + Aspirin					
PCI	TRITON-TIMI 38 ⁷⁵	60 mg prasugrel loading dose + 10 mg/day prasugrel + 75-162 mg/day ASA vs. 300 mg clopi loading dose + 75 mg/day clopi + 75-162 mg/day ASA	Median = 14.5 months	29% (HR, 0.81; 95% CI, 0.73-0.90; P<0.001) for cardiovascular death, non-fatal MI, or non-fatal stroke	Excess non-CABG-related TIMI major (2.4% vs. 1.8%; P=0.03), life-threatening (1.4% vs. 0.9%; P=0.01), major or minor (5.0% vs. 3.8%; P=0.002) and CABG-related TIMI major (13.4% vs. 3.2%; P<0.001) bleeding

GP IIb/IIIa Inhibitor + ASA vs. ASA alone					
NSTEMI	Meta-analysis ⁵⁶	Dependent on trial	Dependent on trial	9% (OR, 0.91; 95% CI, 0.84-0.98; p=0.015) in death or MI at 30 days	1% (2.4% vs. 1.4%; p<0.0001) excess of major bleeding
PCI	Meta-analysis ⁷⁶	Dependent on trial	Dependent on trial	31% (RR, 0.69; 95% CI, 0.53-0.90) 21% (RR, 0.79; 95% CI, 0.64-0.97) in death at 30 days and 6 months, respectively	Excess major bleeding only when heparin continued after PCI (RR, 1.70; 95% CI, 1.36-2.40 vs. RR, 1.02; 95% CI, 0.85-1.24)
GP IIb/IIIa Inhibitor + Fibrinolytic vs. Fibrinolytic alone					
STEMI	INTEGRITI ⁷⁷	180 mcg/kg bolus eptifibatide + 2 mcg/kg/min infusion + 180 mcg/kg bolus eptifibatide 10 minutes later + 0.27 mg/kg TNK +ASA vs. 0.54 mg/kg TNK + ASA + Placebo	60 minutes	10% (59% vs. 49%; p=0.15) increase in TIMI grade 3 flow at 60 minutes	5.1% (7.6% vs. 2.5%; p=0.14) excess of major hemorrhage 9.2% (13.4% vs. 4.2%; p=0.02) excess of transfusions
	SPEED ⁷⁸	0.25 mg/kg bolus abciximab + 12 hour 0.125 mg/kg/min abciximab infusion + 2 5U boluses of reteplase + ASA vs. 2 10 U boluses of reteplase + ASA + Placebo	12 hours	7% (54% vs. 47%; p=0.39) increase in TIMI grade 3 flow at 60-90 minutes	6.1% (9.8% vs. 3.7%; p=0.11) excess of major bleeding

ARMYDA-2, Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty; ASA, aspirin; clopi, clopidogrel; CLARITY, Clopidogrel as Adjunctive Reperfusion Therapy; COMMIT, Clopidogrel and Metoprolol in Myocardial Infarction Trial; CREDO, Clopidogrel for the Reduction of Events During Observation; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; CV, cardiovascular; GP, glycoprotein; INTEGRITI, Integrilin and Tenecteplase in Acute Myocardial Infarction; IS, ischemic stroke; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; RR, relative risk; SE, standard error; SPEED, Strategies for Patency Enhancement in the Emergency Department; STEMI, ST elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; TRITON, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel; TVR, target vessel revascularization.

bleeding associated with prasugrel was more pronounced in TRITON, in which efficacy and safety were compared in PCI patients receiving prasugrel or clopidogrel (standard 300-mg dose); in this study, all classes of TIMI bleeding were significantly greater in patients taking prasugrel.³⁵ In light of these findings, the U.S. prescribing information for prasugrel includes a black box warning highlighting its associated bleeding risks. Specifically, prasugrel is contraindicated in patients with active pathological bleeding or a history of stroke or TIA, should not be given to patients likely to undergo CABG, and is generally not recommended for patients aged ≥ 75 years.

CABG

In ACS patients who undergo CABG, the addition of clopidogrel to aspirin increases bleeding risk if surgery is performed within five days after discontinuation.⁸ A dilemma thus arises, as it is difficult to predict prior to

diagnostic angiography which patients will require urgent, early CABG.^{8,36} The EP can take one of two approaches to starting clopidogrel: 1) Initiate clopidogrel in the ED in all high-risk UA/NSTEMI patients, with a view to withdraw before emergency CABG or five to seven days before semi-elective or elective CABG; or 2) defer clopidogrel treatment until after angiography, therefore avoiding treatment in patients who require emergency CABG. The first strategy, recommended by the European Society of Cardiology (ESC),³⁷ offers the advantages of reducing early ischemic events (relative risk reduction of 20%) and optimal timing for pre-PCI administration, but at the cost of increased peri-operative bleeding for patients who undergo early CABG.^{36,38} The second strategy offers the advantage of avoiding excess bleeding during early CABG, but at the cost of ischemic events and loss of pre-treatment benefit in PCI patients.^{8,39}

It is important to remember the CRUSADE data, where only 12% of UA/NSTEMI patients underwent

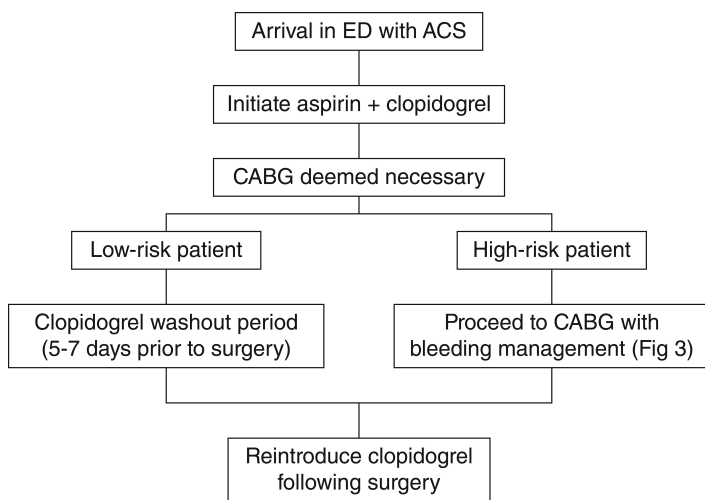


Figure 2. Suggested antiplatelet therapy management algorithm for patients presenting to the ED with ACS and requiring CABG. *Consider withholding antiplatelet therapy in patients at a high risk of CABG (e.g., those with cardiogenic shock, mitral regurgitation, impaired left ventricular function). ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; ED, emergency department.

CABG during their index hospitalization.⁴⁰ Other studies estimate rates of CABG between 8% and 25% during index hospitalization.^{8,41-44} Emergency CABG rates are seemingly lower, from 0.3% to 0.6%.⁴⁵ Since the majority of patients are suitable for PCI or medical management, most high-risk ACS patients would thus benefit from early dual antiplatelet inhibition. Furthermore, among patients in CURE who underwent CABG, lower ischemic event rates were observed with clopidogrel treatment before CABG.³⁶ Taking these considerations into account, it has been suggested that most patients requiring CABG will benefit from initiating clopidogrel and aspirin on admission (i.e. in the ED) and then stopping clopidogrel five days before surgery to minimize bleeding risk (Figure 2).^{36,46} Even if urgent CABG is required, evidence indicates that an experienced surgeon can perform CABG within five days of clopidogrel washout via judicious use of a bleeding management algorithm.⁴⁷ One study found that CABG performed within five days of clopidogrel washout resulted in postoperative mortality rates similar to patients who were not exposed to clopidogrel within five days before CABG.⁴⁷

Patients with hemodynamic instability (cardiogenic shock), mechanical complications (acute mitral regurgitation), diabetes, impaired left ventricular function, concomitant vascular disease, and multivessel disease are at higher risk for urgent CABG.^{2,48} As shown in the Bypass Angioplasty Revascularization Investigation study of patients with diabetes,⁴⁹ such patients may have improved survival with CABG compared to PCI. It would therefore be prudent to

withhold clopidogrel in these patients. For patients for whom clopidogrel pre-treatment is withheld pending angiography, data from ISAR-REACT 2 suggest that GPIs be administered upstream of the catheterization lab in troponin-positive patients⁹

Based on an analysis of NSTEMI patients from the TACTICS-TIMI-18 trials, Sadanandan et al.⁵⁰ developed a predictive risk score to identify patients who are likely to require CABG during index hospitalization. Mehta et al.⁵¹ have also developed a multivariate model, based on CRUSADE data, identifying 13 presenting clinical characteristics significantly associated with undergoing CABG during initial hospital stay. However, identification in the ED of patients likely to need urgent CABG remains problematic as these prediction scores are often unreliable prior to diagnostic angiography. Because of the difficulty in predicting which ACS patients will require emergency CABG, it is essential that emergency physicians, cardiologists, cardiovascular surgeons, and hospitalists develop clear, institution-specific indications for clopidogrel and GPI administration. Such collaboration decreases reliance on personal preferences and empowers emergency physicians to initiate care and gain ischemia-related reductions while simultaneously maximizing patient safety.

Safety Considerations

The risk of bleeding is the most important safety consideration when initiating antiplatelet therapy. This risk must be weighed against observed clinical benefits in all ACS patients. As might be expected based on higher levels of platelet inhibition, bleeding risk is increased by combining antiplatelet agents (Table 2). Among ACS patients, adding clopidogrel to aspirin is associated with an absolute 0.2% to 1.0% increase in major bleeding.⁵² However, the statistical significance of this increased bleeding varied among the trials. This may be partly due to the definition used to classify bleeding events. For example, the excess bleeding in CURE was significant when the OASIS scale was used but insignificant using the TIMI and GUSTO scales.⁸ Importantly, even using the stringent OASIS scale, life-threatening bleeding was not significantly greater among dual aspirin and clopidogrel recipients in CURE.

In contrast to the well-established safety and efficacy data of dual treatment with aspirin and clopidogrel, data related to dual therapy with aspirin and prasugrel are only emerging, and their overall clinical significance is yet unknown. In TRITON, the superior efficacy of prasugrel and aspirin was accompanied by significant excesses of non-CABG-related TIMI major and minor bleeding, life-threatening and fatal bleeding, bleeding requiring transfusion, and CABG-related TIMI major bleeding (Table 2).³⁵ The risk of bleeding was particularly prominent in patients with a history of stroke or TIA and those aged ≥ 75 years or with a body weight < 60

kg. The resultant unfavorable net benefit in these patient subgroups led to the inclusion of the aforementioned black box warning in the prasugrel prescribing information. Additional data are required to fully establish the net benefit of dual therapy with aspirin and prasugrel.

The safety profiles of AZD6140 and cangrelor, two emerging antiplatelet agents which are reversible inhibitors of the P2Y₁₂ receptor, also remain to be determined. In early trials, AZD6140 induced hypotension and dyspnea, potentially problematic side effects that may mimic symptoms of recurrent atherothrombotic events.⁵³ Additionally, AZD610 has a higher IPA than clopidogrel and may lead to an increased risk of bleeding in certain patient populations.⁵³ While cangrelor did not show significant excess bleeding in early trials,^{54,55} more data are needed.

GPI inhibition is associated with a small, significant increased incidence of bleeding, most commonly at the vascular access site (Table 2). In a meta-analysis, GPI use in UA/NSTEMI patients was associated with a significant excess of major bleeding complications (2.4% vs. 1.4%, $p < 0.0001$), though intracranial bleeding was not increased significantly.⁵⁶ It is important to note, however, that this increased bleeding risk was offset by significant reductions in death and MI, particularly in high-risk patients. Among STEMI patients treated by fibrinolysis, GPI therapy is not associated with a net clinical benefit as major bleeding is significantly increased in the absence of any mortality reductions (Table 3).^{57,58} In contrast, the ADMIRAL⁵⁹ and CADILLAC⁶⁰ studies showed that benefits from upstream GPI therapy in PCI patients were not compromised by any important increased bleeding risk. In the ACUTY trial,⁶¹ which investigated an early invasive strategy in UA/NSTEMI patients, the combination of bivalirudin, a direct thrombin inhibitor, with GPI therapy was associated with comparable clinical outcomes and a lower bleeding risk compared with heparin plus GPI therapy.

Overall, a large body of evidence supports an acceptable safety profile for dual antiplatelet therapy with aspirin and clopidogrel in all ACS patients, a differential safety profile with GPIs, and an unclear safety profile for the novel agents prasugrel, AZD6140, and cangrelor.

Evidence-based, practical solutions for antiplatelet therapy

The 2007 ACC/AHA guidelines recommend that all ACS patients receive aspirin and clopidogrel (loading dose followed by a maintenance dose) as soon as possible regardless of reperfusion strategy (Table 3).² Antiplatelet therapy should not be withheld prior to catheterization. If the patient has already received clopidogrel and elective CABG is deemed necessary, clopidogrel should be discontinued for five to seven days prior to surgery in order to balance antiplatelet efficacy with bleeding risk. The addition of a GPI depends on the management strategy and risk level of the patient.² In UA/NSTEMI patients, a GPI should be given upstream

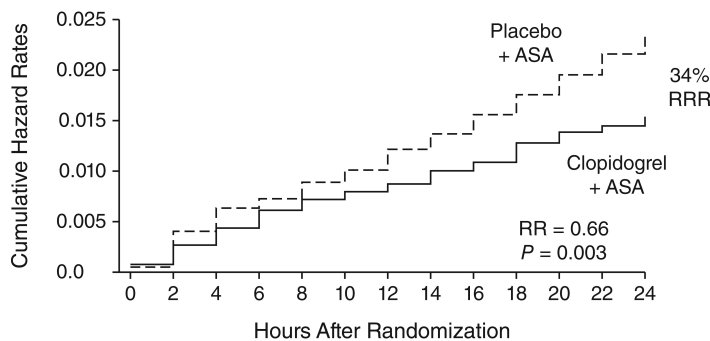


Figure 3. Cardiovascular death, myocardial infarction, stroke and severe ischemia within the first 24 hours after randomization to aspirin plus placebo or aspirin plus clopidogrel in the CURE study. With permission. Yusuf et al. Early and Late Effects of Clopidogrel in Patients with Acute Coronary Syndromes. *Circulation*. 2003;107:966-72.⁸⁰

of, or immediately prior to, PCI. The guidelines advocate GPI administration as early as possible in STEMI patients undergoing PCI,^{32,33,62,63} which supports initiating treatment in the ED.

Results from various studies supporting these guidelines are of particular interest to EPs. One example is the finding from CURE supporting *early* initiation of dual antiplatelet inhibition in UA/NSTEMI patients. A statistically significant benefit of dual antiplatelet therapy over aspirin alone in reducing ischemic events was evident as early as 24 hours after randomization, with the curves separating qualitatively at 12 hours (Figure 3).⁸ Other evidence supports pretreatment with a clopidogrel loading dose prior to PCI.^{7,22} Among UA/NSTEMI patients in CREDO and those undergoing PCI in CURE, adding a clopidogrel loading dose resulted in significant relative risk reductions in endpoints (Table 2).²² The CLARITY and COMMIT trials, which evaluated clopidogrel treatment in conjunction with fibrinolytics, aspirin and heparin in STEMI patients, reported significant cardiovascular event reductions in patients pretreated with clopidogrel (Table 2).²³

CREDO also raised the issue of timing in UA/NSTEMI patients, suggesting that longer intervals between dosing and PCI might show greater benefit, ostensibly by allowing clopidogrel to achieve maximum platelet inhibition.⁷ It should be emphasized that one of the most compelling reasons to initiate clopidogrel therapy as early as possible is to decrease periprocedural ischemia.³⁰ In the ARMYDA-2 trial, patients were randomized to loading doses of either 600-mg or the conventional 300-mg 4-8 hours prior to angiography.³⁰ The primary endpoint was the 30-day occurrence of death, MI, or target vessel revascularization. The primary endpoint occurred in 4% of patients in the high-loading dose group versus 12% of those in the conventional-loading dose group ($P = 0.041$) and was due entirely to periprocedural MI. However, in a small study of patients with ACS undergoing stent implantation, no difference was found with three days of clopidogrel pretreatment compared with standard post-procedural

Table 3. Current antiplatelet therapy recommendations and adverse effects. The data is presented according to class of antiplatelet therapy and ACS condition. Recommendations were compiled from references 2, 32, 33, 63 and 79.

Antiplatelet	Condition	Recommendation	Adverse Effects	Comments
Thromboxane A₂ Inhibitors				
Aspirin	NSTEMI, PCI, and STEMI	Daily consumption initiated immediately following symptom onset and continued indefinitely by all patients with a history of CAD or ACS and without aspirin allergy	1. Increased risk of bleeding complications; 2. Monotherapy associated with high risk of stent thrombosis after PCI	1. The most studied and well-established of the antiplatelet therapies; 2. Efficacious; 3. Good safety profile; 4. Low cost; 5. Aspirin resistance may occur
Thienopyridine Inhibitors				
Clopidogrel	NSTEMI, PCI, and STEMI	An alternative in secondary prevention if aspirin is contraindicated		1. 10 years of experience; 2. Well-established efficacy in preventing adverse events following revascularization when used with aspirin; 3. Clopidogrel resistance is a documented phenomenon
	NSTEMI	1. A loading dose followed by daily maintenance for at least 1 month and ideally up to 1 year as part of early conservative management; 2. Withhold in the 5-7 days prior to CABG	1. Increased risk of bleeding when used in combination with aspirin; 2. Increased risk of bleeding when used in the 5-7 days prior to CABG	
	PCI	A loading dose initiated prior to PCI, followed by maintenance dose daily for at least 1 month, and ideally up to 1 year, following BMS implantation and at least 12 months following DES implantation	Increased risk of bleeding when used in combination with aspirin	
Prasugrel	STEMI	1. A loading dose followed by daily maintenance for at least 14 days; 2. Withhold in the 5-7 days prior to CABG	Increased risk of bleeding when used <5 days prior to CABG	
	NSTEMI	None		Under assessment
	PCI	None	Increased risk of bleeding, especially in patients with a history of stroke or TIA, those aged ≥75 years, and those with a body weight <60 kg	1. Higher IPA than clopidogrel, which could mean greater risk of bleeding; 2. No statistically powered evidence showing superiority over clopidogrel
	STEMI	None		Under assessment

treatment in troponin I or creatinine kinase-MB serum levels up to 24 hours after PCI.⁶⁴

Although it is important for EPs to appreciate the added periprocedural protection that upstream administration of advanced antiplatelet therapy affords their ACS patients, the ideal timing of clopidogrel initiation is uncertain. The guidelines recommend administration as soon as possible, and as the time from administration to PCI increases, so does the periprocedural protection. The ARMYDA-2 trial gave a loading dose 4-6 hours prior to PCI, but the EP is often dealing with a 90-minute treatment window, making the ARMYDA-2 results relevant primarily to those ACS patients not going emergently for PCI.

Similarly, the optimal timing for GPI initiation prior to PCI is unclear.⁴ In PURSUIT, the reduction in death and MI was inversely associated with the time from symptom

onset to GPI initiation;⁴ however, data from PRISM and NRMI 4 suggest no difference in outcomes as long as the drug was initiated within 24 hours of symptom onset.^{65,66} In the absence of clear evidence, ED physicians must carefully weigh each individual patient's characteristics and clinical symptoms when making a decision concerning GPI initiation.

The adjunctive use of GPIs in STEMI patients depends on the planned treatment course. In the setting of PCI, the ADMIRAL study showed a significant reduction in death/reinfarction/urgent revascularization at both 30 days and six months when adjunctive abciximab was administered prior to the procedure.⁵⁹ The CADILLAC study confirmed the protective effect of abciximab in the short term (35% relative risk reduction for death, MI, target vessel revascularization or stroke at 30 days), although this benefit

GP IIb/IIIa Inhibitors				
Abciximab	NSTEMI	Not recommended		No benefit
	PCI	1. Initiate as soon as possible as ancillary therapy in high risk patients undergoing PCI only if there is no appreciable delay to angiography; otherwise, eptifibatide or tirofiban is preferred; 2. Early initiation to improve pre-procedural TIMI grade 3 flow	1. Insignificant excess risk of bleeding; 2. Significantly increased risk of disabling stroke	1. Abciximab has not been shown to reduce the risk of target vessel reocclusion; 2. Combination abciximab and reteplase or tenecteplase should not be given to patients aged >75 years due to an increase risk of ICH
	STEMI	May be considered for reperfusion in combination with half-dose reteplase or tenecteplase in high-risk patients	Increased risk of ICH in patients aged ≥75 years	Treatment does not translate to survival advantage at 30 days or 1 year
Eptifibatide	NSTEMI	May be considered in high-risk patients undergoing early conservative management	Increased risk of bleeding	Benefits seem to be restricted to high-risk patients
	PCI	Initiate as soon as possible as ancillary therapy	Increased risk of minor bleeding	Benefits seem to be restricted to high-risk patients
	STEMI	None		
Tirofiban	NSTEMI	May be considered in high-risk patients undergoing early conservative management	Increased risk of bleeding	Benefits seem to be restricted to high-risk patients
	PCI	Initiate as soon as possible as ancillary therapy	1. Increased risk of death, MI, stroke, and target vessel failure at 30 days when used with paclitaxel-eluting stents; 2. Insignificant risk of major bleeding when used in combination with heparin	Benefits seem to be restricted to high-risk patients
	STEMI	None		
Non-thienopyridine P₂Y₁₂ Inhibitors				
AZD6140	NSTEMI	None	1. Bleeding risk similar to clopidogrel; 2. Higher rates of dyspnea, hypotension, and nausea compared to clopidogrel	1. Higher IPA, which could mean greater risk of bleeding in other patient populations; 2. Short half-life; 3. No published evidence showing superiority over clopidogrel
	PCI	None		Assessment underway
	STEMI	None		Assessment underway
Cangrelor	NSTEMI	None	Insignificant excess risk of bleeding	1. Does not require liver metabolism to produce active compound and can therefore be used IV; 2. High IPA
	PCI	None		Assessment underway
	STEMI	None		Assessment underway

ACS, acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DES, drug-eluting stent; GP, glycoprotein; ICH, intracranial hemorrhage; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction

was no longer apparent at one year.⁶⁰ Data from ADMIRAL and CADILLAC, conducted in the PCI setting, show that the protective benefits of pre-procedural abciximab are not compromised by any important increase in bleeding risk. In contrast, the ASSENT-3 and GUSTO V trials demonstrated

that the combination of a GPI with half-dose thrombolytic reduced ischemic events but increased bleeding; furthermore, there was no short- or long-term survival benefit.⁶⁷⁻⁷¹ These findings suggest that adding a GPI is not justified during fibrinolytic treatment of STEMI.

Table 4. Summary of the Class I recommendations of the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for antiplatelet therapy in UA/NSTEMI,² STEMI,^{33,63} and PCI³² patients.

UA/STEMI	STEMI	PCI
<ul style="list-style-type: none"> Initiate aspirin as soon as possible after hospital presentation and continue indefinitely; substitute clopidogrel in patients who have aspirin intolerance 	<ul style="list-style-type: none"> Initiate aspirin as soon as possible after hospital presentation and continue indefinitely, substitute clopidogrel for aspirin in cases of intolerance 	<ul style="list-style-type: none"> Patients already taking preventative aspirin should take 75 mg-325 mg prior to PCI. Patients not currently taking aspirin should receive 300 mg -325 mg at least 2, preferably 24, hours prior to PCI
<ul style="list-style-type: none"> Add clopidogrel (loading dose followed by maintenance dose) to aspirin therapy as soon as possible after admission if an early non-invasive strategy is planned and continue clopidogrel for at least 1 month and ideally for 1 year 	<ul style="list-style-type: none"> Add clopidogrel (loading dose followed by maintenance dose) to aspirin therapy regardless of the planned reperfusion strategy and continue for at least 14 days in all patients and ≥ 1 month but ≤ 9 months in patients undergoing PCI. 	<ul style="list-style-type: none"> Add 600 mg loading dose of clopidogrel before or at the time of PCI. If fibrinolytic therapy was received in the previous 12-24 hours, a 300 mg loading dose may be considered.
<ul style="list-style-type: none"> Add clopidogrel (loading dose followed by maintenance dose) or an intravenous GP IIB/IIIa inhibitor (abciximab if there is no delay to angiography and PCI is likely; otherwise, eptifibatid or tirofiban are preferred) to aspirin if an initial invasive strategy is planned 	<ul style="list-style-type: none"> If elective CABG surgery is planned, withhold clopidogrel for 5-7 days beforehand 	
<ul style="list-style-type: none"> If elective CABG surgery is planned, withhold clopidogrel for 5-7 days beforehand 		

UA/STEMI, unstable angina ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; PCI, percutaneous coronary intervention.

CONCLUSION

The EP's role in treating ACS patients is to provide rapid, accurate diagnosis and institute timely, risk-directed treatment. Increasing the potency of platelet inhibition by adding a thienopyridine or GPI to standard therapy early in the treatment course improves protection against ischemic and periprocedural events but must be balanced against any unjustifiable increase in bleeding risk. Clopidogrel plus aspirin is a safe and effective therapy recommended by national guidelines for use in ACS patients, regardless of treatment strategy (Table 4).

Choice and timing of antiplatelet therapy in the ED must also take into consideration future interventions the patients may receive during their hospital course. In addition to standard aspirin therapy, early initiation of clopidogrel in the ED is often justified in ACS patients, regardless of their subsequent treatment strategy (medical or interventional). However, care should be taken regarding patients who are highly likely to require early CABG. Early administration of a GPI is also often justified in ACS patients in the PCI setting and in high-risk UA/NSTEMI patients in whom medical management is planned. Results from the ASSENT-3 and GUSTO-V trials do not support a favorable balance of benefit over bleeding risk for GP inhibition in STEMI patients undergoing fibrinolysis. This finding illustrates the complexity

of balancing increased antiplatelet potency with bleeding risk.

Emerging investigational antiplatelet agents may show promise in ACS treatment; however, use of these agents should be approached with caution. Although touting increased IPA, it should be recalled that traditionally this has been a measure of bleeding, not potency. Therefore, long-term risks for bleeding and compliance may become issues. As the science of emergency cardiology care continues to mature and evolve at a rapid pace, continuous, evidence-based, multidisciplinary collaboration is paramount for delivering optimal and safe care for ACS patients. Given the variability in treatment preferences and awareness of guideline recommendations, there is an important need for developing institutional protocols and order sheets in order to improve adherence to treatment guidelines.

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