Optimizing Antiplatelet Therapy for the ACS Patient: Reacting to Clinical Trial Data from the ISAR-REACT-2 Studies

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Antiplatelet therapy is the cornerstone of treatment for patients with an acute coronary syndrome (ACS). However, patients presenting with possible ACS are a heterogeneous population, and there is a choice of many potential combination antiplatelet therapies, with aspirin, thienopyridines (eg, clopidogrel), and glycoprotein (GP) IIb/IIIa antagonists. The ISAR-REACT-2 trial investigated the optimal application of triple (aspirin + thienopyridine + GP IIb/IIIa inhibitor) versus dual (aspirin + thienopyridine) antiplatelet therapy for patients with ACS undergoing percutaneous coronary intervention. Abciximab was associated with a significant 25% relative reduction in risk for the 30-day combined endpoint of death, myocardial infarction, or urgent target vessel revascularization. All of this benefit was confined to the patients with elevated troponin levels. The data indicate that troponin can be used as a biomarker to identify patients most likely to benefit from the addition of a GP IIb/IIIa antagonist.
[Rev Cardiovasc Med. *2006;7(suppl 4):S12-S19*]

Key words: Antiplatelet therapy • GP IIb/IIIa antagonists • Troponin

Nearly 5 million patients present to US hospitals annually with a complaint of chest pain or, more specifically, to be "ruled out" or "ruled in" for an acute coronary syndrome (ACS). This "possible acute coronary syndrome" population is an extremely heterogeneous group, whereas patients with a "true" ACS, manifested pathologically as coronary thrombosis related to atherosclerotic plaque rupture or endothelial erosion, represent a more homogeneous population. While still a substantial fraction, only about a quarter of the patients presenting with chest pain are eventually diagnosed with a new

myocardial infarction (MI). For these individuals, there is irrefutable evidence of the role of the platelet-rich thrombus in both the presentation and associated complications of the ACS, as well as substantial evidence to support the salutary role of antiplatelet therapy. Therefore, it is this population, in particular, for which optimal antiplatelet therapy is especially critical. This review explores the available clinical trial data in order to provide guidance on how best to utilize the 3 classes of antiplatelet agents currently available for treating patients with an ACS.

Aspirin

Aspirin has been available clinically for nearly 110 years. Its potential benefit for patients with coronary disease was first suggested in 1949, but not until the late 1960s was its effect on platelets described.[1,2] Over the ensuing years it was shown that aspirin specifically and irreversibly inhibits platelet cyclooxygenase-1 (COX-1) through acetylation of the amino acid serine at position 529,[3,4] thereby blocking arachidonic acid access to the COX-1 catalytic site through steric hindrance.[5] Because the non-nucleated platelets lack the biosynthetic capability to synthesize new protein, the aspirin-induced defect cannot be repaired for the 8- to 10-day lifespan of the platelet.

A wide range of aspirin doses, preparations, and methods of ingestion have been evaluated to determine the best way to achieve maximal antiplatelet activity in the acute setting. In a study that evaluated the acute antiplatelet effects of 40, 100, 300, and 500 mg doses of aspirin, the 300 and 500 mg doses were found to achieve equal levels of platelet inhibition 2 hours after ingestion by a variety of techniques, suggesting that when a noncoated aspirin pill is swallowed, doses $>$ 300 mg do not influence the rate at which the maximal antiplatelet effect is achieved.[6] Time required for aspirin absorption and the onset of antiplatelet activity is significantly shortened, however, by chewing an aspirin or drinking solubilized aspirin (eg, Alka-Seltzer®, Miles Laboratories, Elkhart, IN). A study of 12 volunteers compared 325 mg of buffered aspirin, either chewed or swallowed, with Alka-Seltzer. Chewing the pill or drinking the solution resulted in maximal inhibition of serum thromboxane B_2 (TXB_2) production within 20 to 30 minutes of ingestion, whereas just swallowing the pill required approximately 60 minutes.[7] In another study of 18 volunteers, chewing an 81, 162, or 324 mg aspirin pill led to equivalent reduction in TXB_2 production, but maximal inhibition by 15 minutes after ingestion was achieved only after the 162 and 324 mg doses.[8] The results of these and other studies suggest that to achieve the maximal effects of aspirin rapidly (~15 min), at least 162 mg should be chewed and swallowed.

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The first randomized trial to study aspirin in the early treatment of ACS (within 48 hours of admission for unstable angina) was the Veterans Administration Cooperative Study.[9] In this trial, 1266 men with unstable angina were randomized to 324 mg of buffered aspirin daily for 12 weeks or to matching placebo. Treatment with aspirin was found to decrease the risk of death or acute MI (AMI) by 51% (5.0% vs 10.1%; $P = .0005$). Three subsequent placebo-controlled trials reinforced the findings of this initial study, with a consistent 50% or greater risk reduction by the early initiation of aspirin therapy in the combined endpoint of death or MI (Figure 1).[10-13]

The ISIS-2 (Second International Study of Infarct Survival) study unequivocally established the beneficial role of aspirin in patients experiencing an ST-elevation MI (STEMI).[14] In this trial, 17,187 patients admitted within 24 hours of the onset of a suspected AMI were randomized to streptokinase alone (1.5 MU), aspirin alone (162.5 mg/day for 30 days), a combination of both, or neither. Patients receiving aspirin alone experienced a significant 23% relative reduction in vascular mortality during the 5 weeks following admission compared with those receiving placebo tablets (9.4% vs 11.8%; $P <$ .00001), with randomization to streptokinase being associated with a similar 25% reduction in 5-week mortality (9.2% for streptokinase vs 12.0% for placebo infusion; $P <$ .00001). The greatest benefit, however, was found in patients treated with the combination of aspirin and streptokinase. This cohort experienced a 42% reduction in vascular mortality compared with placebo-allocated patients (8.0% vs 13.2%; $P <$ .00001) and had significantly better outcomes than did the cohorts receiving either active therapy alone.

Glycoprotein IIb/IIIa Antagonists

The glycoprotein (GP) IIb/IIIa receptor (α_{IIb}/β_3) belongs to the integrin family of adhesion receptors found on many types of cells. Unlike other integrins, the GP IIb/IIIa receptor is

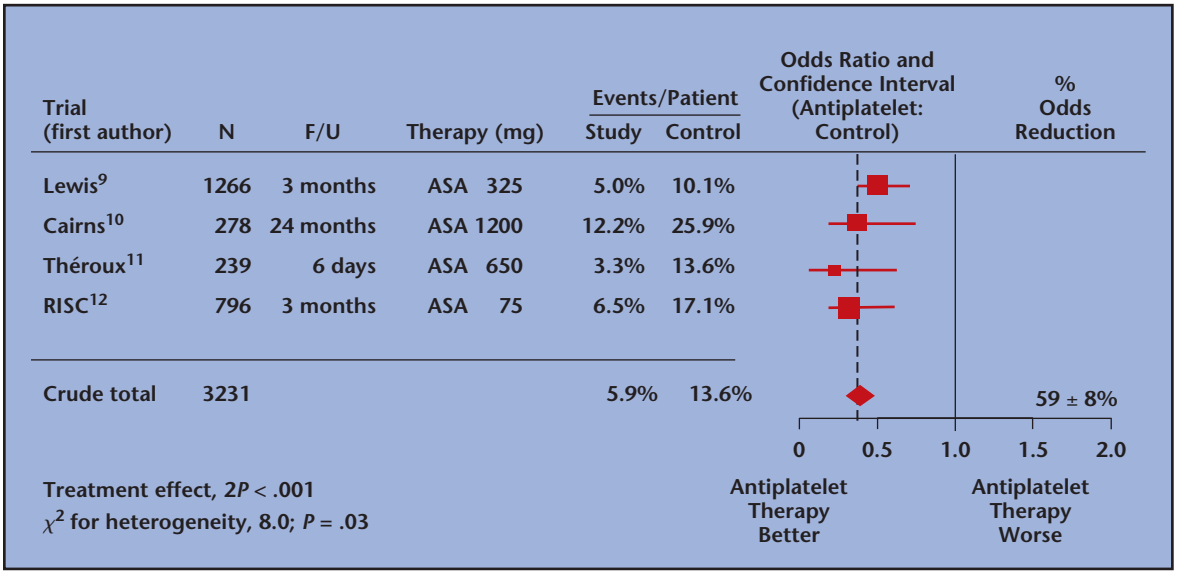

Figure 1. *Combined analysis of the influence of aspirin (ASA) compared with placebo on the incidence of death or myocardial infarction in 4 randomized trials involving patients with unstable angina or a non-ST-segment elevation myocardial infarction. F/U, follow-up. Adapted with permission from White HD.*[13]

found only on platelets and megakaryocytes.[15] Each platelet has approximately 80,000 GP IIb/IIIa receptors. Studies in some animal models found that to achieve nearly complete inhibition of platelet aggregation and arterial thrombus formation, 80% or more of these receptors had to be blocked.[16] When activated, the receptor can bind adhesion proteins such as vitronectin, fibronectin, von Willebrand factor, and fibrinogen, the latter 2 proteins being the principal ones involved in platelet aggregation.[17] All of these adhesion proteins contain a common peptide segment that is involved in binding to the GP IIb/IIIa receptor, with the Arg-Gly-Asp (RGD) amino acid sequence present at least once in all such proteins. Elucidation of the function and structure of the GP IIb/IIIa receptor has led to the development of several antagonists, which have been evaluated clinically in the treatment of patients with ACS.

The role of parenteral GP IIb/IIIa antagonists in the treatment of patients with ACS has been studied in placebo-controlled trials involving more than 31,000 patients. The results of a recent meta-analysis highlight some of the practical concerns remaining about how best to apply this proven therapy.[18] A statistically significant 9% relative reduction in the odds of death or MI was found in the analysis overall, but the absolute 1% difference in thrombotic events (10.8% for GP IIb/IIIa antagonists vs 11.8% for placebo; odds ratio [OR] 0.91, $P = .015$) was balanced by a 1% absolute increase in major bleeding complications (2.4% vs 1.4%; $P < .0001$). As the absolute treatment benefit is greatest in the highest-risk patients, and the diagnosis of a suspected ACS encompasses a very heterogeneous population of patients, targeting those subgroups most likely to achieve the greatest benefit would optimize the effectiveness of GP IIb/IIIa antagonist therapy.

Any abnormal elevation of cardiac markers, predominantly troponins, at the time of presentation with an ACS seems to be the single most predictive objective criterion for an increased risk of death or reinfarction in the ensuing weeks, with several studies showing a direct association between the extent of troponin elevation and the level of risk.[19,20] Elevated myocardial markers have also been shown to identify a subgroup of patients with ACS who derive the greatest benefit from the addition of GP IIb/IIIa antagonist therapy (Figure 2). Thus, patients with unstable angina who have elevated cardiac markers have an increased risk for recurrent events, and this is a subgroup of patients more likely to

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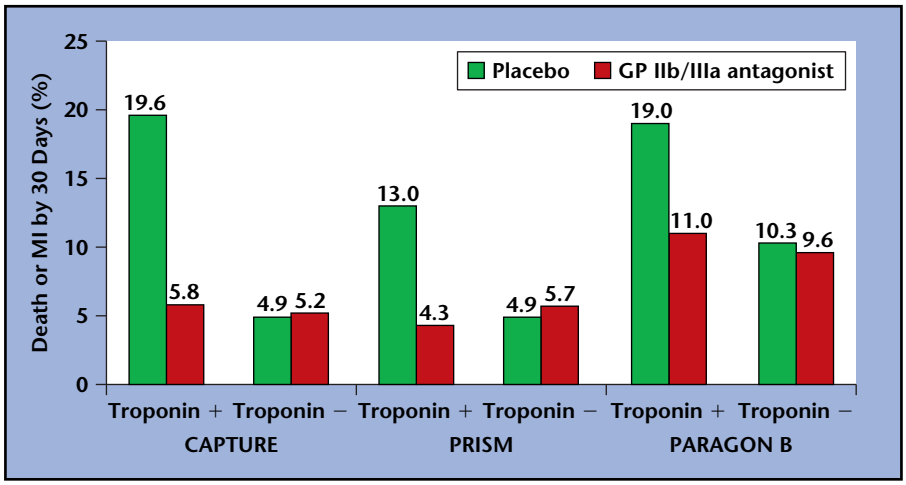


Figure 2. *Thirty-day death and myocardial infarction (MI) based on baseline troponin status in 3 placebo-controlled trials (CAPTURE, PRISM, and PARAGON B) of glycoprotein (GP) IIb/IIIa antagonists in the treatment of patients with a non-ST-segment elevation myocardial infarction. Data extracted from the CAPTURE investigators,[23] the PRISM-PLUS investigators,[24] and Newby LK et al.[44]*

benefit from the addition of a GP IIb/IIIa antagonist to their antithrombotic regimen.

Another subgroup of ACS patients found to derive particular benefit from treatment with a GP IIb/IIIa antagonist is composed of those with diabetes mellitus. The presence of diabetes mellitus has long been recognized as a risk factor for adverse outcomes after an ACS, and this may be related, at least in part, to in vitro and ex vivo abnormalities of platelet function. A meta-analysis of the 6,458 diabetic patients enrolled in the placebo-controlled ACS trials of GP IIb/IIIa antagonists found a striking benefit of treatment, with a significant reduction in mortality at 30 days (4.6% vs 6.2%; OR 0.74, $P = .007$).[21] This mortality benefit of GP IIb/IIIa inhibitor treatment was even more pronounced (OR 0.30, $P = .002$) among diabetic patients undergoing a percutaneous coronary intervention (PCI).

Another consistent finding of all trials evaluating parenteral GP IIb/IIIa antagonists in patients with ACS is the markedly enhanced benefit in the subgroup of patients undergoing PCI during treatment. Based on the consistency of this finding among all trials, as well as the heightened benefit of treatment with a GP IIb/IIIa antagonist in patients with a diagnosis of unstable angina in the PCI trials, the available data solidly support the use of these agents during PCI in patients with unstable angina. However, the optimal time to start a GP IIb/IIIa antagonist for a patient in the emergency room with a possible ACS remains less clear. There is an as yet unresolved conflict about the potential harm associated with prolonged infusion of abciximab, as highlighted in the GUSTO IV-ACS (Global Utilization of Strategies to Open Occluded Coronary Arteries Trial IV in Acute Coronary Syndrome) results, versus the proven superiority of abciximab over tirofiban in a PCI population, especially in the ACS subset of these patients, as shown in the TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Outcome Trial?) study.[22] The question is: Is greater benefit derived from starting an infusion of eptifibatide or tirofiban in the emergency room or from starting abciximab—or maybe a higher, PCI-dose of eptifibatide—in the catheterization laboratory after the diagnostic angiogram is completed? Although analysis of data from the CAPTURE[23] (Chimeric 7E3 AntiPlatelet Therapy in Unstable Angina Refractory to Standard Treatment), PRISM-PLUS[24] (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms), and PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trials found a benefit to starting these agents early,[25] the magnitude of the benefit was small within the first 24 hours in all except the CAPTURE trial. Therefore, high-risk patients who are likely to undergo a PCI but who will be medically stabilized for $>$ 24 hours may derive additional protection from starting a small-molecule GP IIb/IIIa receptor inhibitor early in their hospital course.

It is this gap in available data that has led to the recommendation by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina) that GP IIb/IIIa antagonists should be used in all high-risk patients eligible for such therapy, in particular those for whom revascularization is anticipated, but that such treatment can be initiated either early or in the catheterization laboratory just prior to the PCI.[26]

Thienopyridines

The thienopyridines, the prototype ticlopidine, were initially synthesized in 1974 and somewhat serendipitously found to possess antiplatelet properties.[27,28] Approximately 10 years later, because of several important adverse effects of ticlopidine, the search for a safer and more active antiplatelet agent in the chemical class of the thienopyridines led to the development of clopidogrel. Prasugrel,

the newest thienopyridine, is currently undergoing phase 3 testing.

Although an antiplatelet effect of ticlopidine can be detected within hours after a 500 mg oral dose, clinically relevant platelet inhibition seems to require 2 to 3 days, and maximal effects require almost 1 week of therapy.[29,30] Clopidogrel, unlike ticlopidine, can be given as a much larger loading dose, which allows for a much more rapid onset of action. In an early study of 10 healthy volunteers that used a 375 mg loading dose, significant platelet inhibition was already detected by 30 minutes, and maximal effects by 5 hours.[31] More recent studies specifically comparing a standard 300 mg loading dose with both 600 and 900 mg doses clearly demonstrated a significantly faster and greater antiplatelet effect with 600 mg than with 300 mg.[32] While one published study comparing 900 and 600 mg doses of clopidogrel found no significant difference, a second study did find faster platelet inhibition with 900 mg.[33] On a molar basis, clopidogrel has a greater platelet inhibitory effect than ticlopidine, but dosing of 75 mg/day was designed to provide a platelet inhibitory effect equivalent to that of 500 mg of ticlopidine.[34] Prasugrel, on the other hand, has been specifically dosed to achieve a higher level of platelet inhibition than the other agents.

Ticlopidine has also been evaluated in a placebo-controlled trial for the acute treatment of unstable angina.[35] Ticlopidine started within 48 hours of admission for unstable angina was associated with a 46.3% decrease in the risk of vascular death or MI at 6 months compared with placebo (7.3% vs 13.6%; $P = .009$).

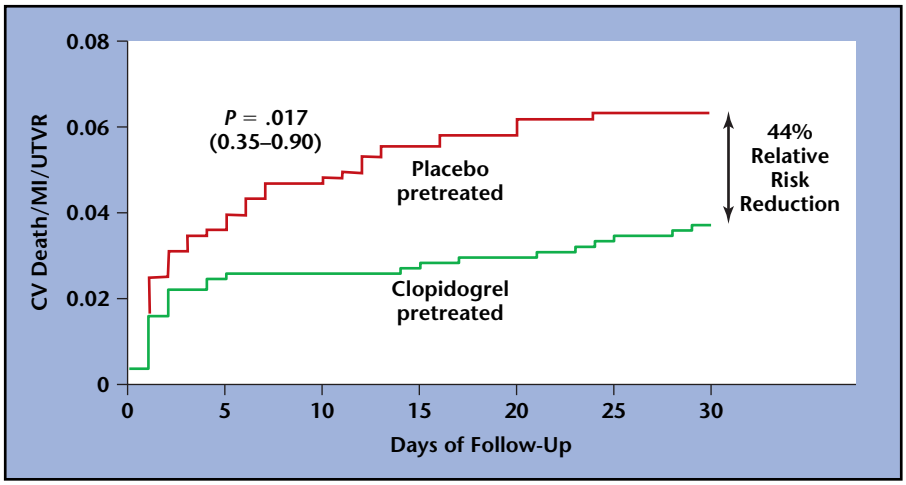


Figure 3. *Incidence of the combined endpoint of cardiovascular (CV) death, myocardial infarction (MI), and urgent target vessel revascularization (UTVR) among the subset of patients from the CURE trial undergoing percutaneous coronary intervention, based on randomization to clopidogrel or placebo (patients pretreated with open-label thienopyridines excluded). Adapted with permission from Mehta S et al.[37]*

The first trial to evaluate the clinical benefit of prolonged dual antiplatelet therapy compared with aspirin alone was the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial.[36] The 12,562 patients with non-STEMI (NSTEMI) coronary syndrome were randomized to aspirin plus a 300 mg clopidogrel loading dose followed by aspirin (75-325 mg) plus clopidogrel 75 mg/day, or to aspirin plus matching placebo, and followed up for a maximum of 1 year, with a mean follow-up of 9 months. The primary endpoint was the first occurrence of any component of cardiovascular death, MI, or stroke. By 9 months, patients randomized to combination antiplatelet therapy experienced a 20% relative reduction in risk compared with those receiving aspirin alone (9.28% vs 11.47%; risk ratio 0.80, 95% confidence interval [CI] 0.72-0.89, $P = .00005$). Some of the greatest early benefit was seen in the subset of patients who underwent a PCI at the discretion of their physician (Figure 3).[37] The overall efficacy benefit was balanced by an absolute increase in major bleeding of 0.9% (2.7% vs 3.6%; $P = .003$) as well as an almost doubling in minor bleeding (8.6% vs 15.3%; $P = .0001$), but no significant increase in life-threatening bleeding (1.8% vs 2.1%; $P = .27$). This concern about bleeding, especially in patients requiring bypass surgery within 5 days of their last clopidogrel dose, has a significant impact on the early use of clopidogrel in ACS patients with NSTEMI.

This concern about bleeding, especially in patients requiring bypass surgery within 5 days of their last clopidogrel dose, has a significant impact on the early use of clopidogrel in ACS patients with non-ST-elevation MI.

The role of clopidogrel plus aspirin versus aspirin alone in patients with STEMI treated with thrombolytics has been evaluated in 2 randomized trials. In the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28) study, 3491 patients (≤ 75 years of age) with STEMI receiving thrombolytic therapy were randomized to a clopidogrel 300 mg loading dose followed by 75 mg/day, or to matching placebo, in addition to aspirin and heparin.[38] The primary

endpoint was infarct-artery patency at the time of angiography, which was performed at a median of 84 hours. Randomization to clopidogrel was associated with a 6.7% absolute decrease and 36% relative decrease in the incidence of an occluded artery. This translated into a clinical benefit at 30 days of a 20% relative reduction in risk for the combined endpoint of cardiovascular death, recurrent MI, or recurrent ischemia leading to the need for urgent revascularization. In the COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) study, 45,852 individuals with 24 hours of a suspected AMI (93% presumed STEMI) were randomized to clopidogrel 75 mg/day, without a loading dose, or placebo, in addition to standard therapy including aspirin.[39] Treatment was continued until hospital discharge, or for up to 4 weeks (mean 5 days). Despite the lack of a loading dose, randomization to clopidogrel was associated with a significant 9% relative reduction in risk for the combined endpoint of death, reinfarction, and stroke, as well as a significant 7% proportional reduction in death alone.

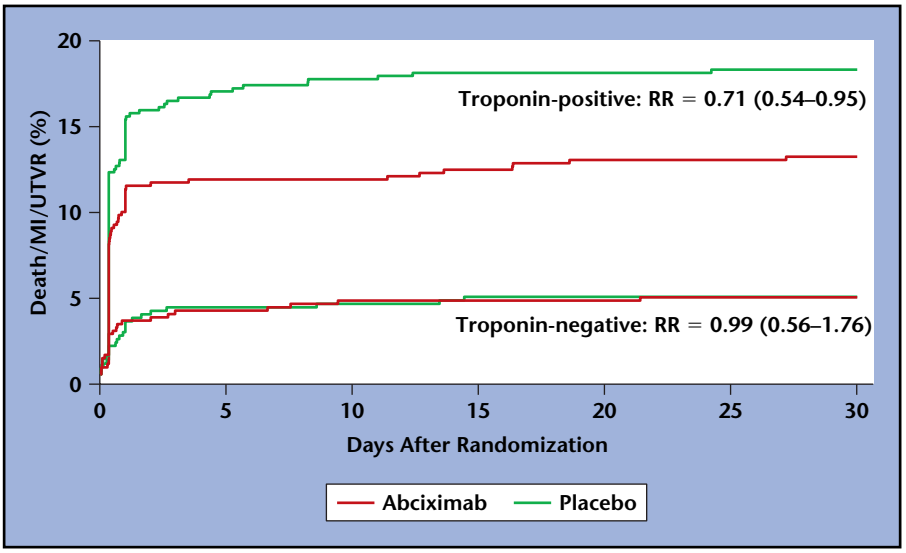
Combining Antiplatelet Therapies

In treating a patient with a suspected ACS, one of the easiest decisions is to start aspirin. The only exception would be the true aspirin-allergic (not just intolerant) patient, for whom clopidogrel should be substituted for aspirin and initiated with at least a 300 mg loading dose and, for faster efficacy, perhaps 600 or even 900 mg. After aspirin, the addition of clopidogrel is recommended in all individuals, with the caveats noted earlier. Therefore, the question of which patient will benefit from even further platelet inhibition with a GP IIb/IIIa antagonist remains the most challenging decision.

The strongest clinical evidence guiding the use of triple (aspirin + clopidogrel + GP IIb/IIIa antagonist) versus double (aspirin + clopidogrel) antiplatelet therapy comes from a series of studies by ISAR (Intracoronary Stenting and Antithrombotic Regimen). Importantly, all of these trials were carried out only in the setting of PCI and used a 600 mg clopidogrel loading dose for all patients, along with aspirin, given at least 2 hours before PCI. In this population, the ISAR investigators systematically studied the additional benefit of adjunctive abciximab in low- to intermediate-risk PCI patients,[40] patients undergoing revascularization of small-diameter (≤ 2.5 mm) vessels,[41] and patients with diabetes.[42] In none of these trials was abciximab found to provide even a trend toward additional benefit when given in addition to adequate pretreatment with clopidogrel. However, by design, none of these trials included high-risk ACS patients—the subgroup of patients who seem to derive the greatest benefit from adjunctive GP IIb/IIIa antagonist therapy.

The ISAR-REACT-2 (ISAR–Rapid Early Action for Coronary Treatment) trial was designed specifically to answer the question about the optimal application of triple versus dual antiplatelet therapy for patients with ACS undergoing PCI.[43] This trial was similar in design to all previous ISAR trials noted above, but it enrolled only patients with objective evidence of an ACS as manifest by anginal symptoms at rest or minimal exertion accompanied by elevated troponin-T or new ST-segment deviation or bundle branch block. Just over half of the 2022 patients enrolled had elevated troponins. Overall, and in contrast to previous ISAR studies, randomization to abciximab was associated with a significant 25% relative reduction in risk for the 30-day combined endpoint of death, MI, or urgent target vessel revascularization. Interestingly, all of this benefit was confined to the 1049 patients with elevated troponin, for whom abciximab decreased the occurrence of the primary endpoint by 29% (Figure 4).[43] Troponin-negative

Figure 4. *Primary outcomes of 30-day death, myocardial infarction (MI), and urgent target vessel revascularization (UTVR) in patients with non-ST-segment elevation acute coronary syndrome randomized to either abciximab or placebo in addition to a 600 mg loading dose of clopidogrel initiated at least 2 hours before percutaneous coronary intervention, separated based on troponin status. RR, risk ratio. Adapted with permission from Kastrati A et al.[43] JAMA, April 5, 2006, 295;1535,*



patients experienced substantially lower and almost identical event rates irrespective of randomized therapy. These results are very much in line with those from the troponin substudy of the CAPTURE trial.[20]

The results of this and the previous ISAR trials studying the role of abciximab in clopidogrel-pretreated patients before undergoing PCI provide compelling evidence that GP IIb/IIIa antagonists remain critically important in the treatment of patients with a true (troponin-positive) ACS. It seems even more likely, although clinical evidence is lacking, that the same would hold true in the setting of primary PCI in patients with an ST-segment elevation ACS.

Conclusion

Antiplatelet therapy has been and will remain the cornerstone of therapy for the patient presenting with an acute coronary syndrome. However, given that patients presenting with a possible ACS are such a heterogeneous population, and given the large numbers of potential combinations of antiplatelet therapies available, the possibility of over- or undertreating a specific patient is always present. The use of a novel biomarker such as troponin to identify patients most likely to benefit from the addition of a GP IIb/IIIa antagonist represents a true success story in modern medicine. There are very few other therapies in medicine in which a simple, easily available test is such a powerful predictor of therapeutic benefit. By using myocardial necrosis biomarkers to guide therapy, the safety and efficacy of antiplatelet therapies can and should be optimized in the patient with ACS. ■

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Main Points

- In a study that evaluated the acute antiplatelet effects of 40, 100, 300, and 500 mg doses of aspirin, the 300 and 500 mg doses were found to achieve equal levels of platelet inhibition 2 hours after ingestion by a variety of techniques, suggesting that when a noncoated aspirin pill is swallowed, doses of 300 mg do not influence the rate at which the maximal antiplatelet effect is achieved.
- Studies in some animal models found that to achieve nearly complete inhibition of platelet aggregation and arterial thrombus formation, 80% or more of these receptors had to be blocked.
- The American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina) recommend use of GP IIb/IIIa antagonists for all high-risk patients, but treatment can be initiated either early or in the catheterization laboratory just prior to PCI.
- In the first trial to evaluate the benefit of double antiplatelet therapy (aspirin + clopidogrel), patients randomized to combination antiplatelet therapy experienced a 20% relative reduction in risk compared with those receiving aspirin alone; the overall efficacy benefit was balanced by an increase in bleeding.
- The strongest clinical evidence guiding the use of triple (aspirin + clopidogrel + GP IIb/IIIa antagonist) versus double antiplatelet therapy comes from studies by ISAR in patients undergoing percutaneous coronary intervention (PCI).
- The ISAR investigators also studied the additional benefit of adjunctive abciximab in low- to intermediate-risk PCI patients, patients undergoing revascularization of small-diameter ($\leq$ 2.5 mm) vessels, and patients with diabetes; in none of these trials was abciximab found to provide even a trend toward additional benefit.
- The ISAR-REACT-2 trial studied the optimal application of triple versus dual antiplatelet therapy for patients with ACS undergoing PCI; randomization to abciximab was associated with significant benefit, all of which was confined to the 1049 patients with increased troponin levels.

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