Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

The rationale and evidence for triple antiplatelet therapy in acute coronary syndromes

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The platelet response to endothelial injury is central to the process of atherothrombosis, the pathophysiologic hallmark of acute coronary syndromes (ACS). Multiple antiplatelet agents have been developed to inhibit key components of this platelet activity. The use of two or more antiplatelet agents in patients with ACS reduces ischemic events but increases bleeding risk. Triple antiplatelet therapy utilizing aspirin, P2Y12 antagonists and glycoprotein IIb/IIIa inhibitors, remains indicated in select ACS populations. In ST-elevation myocardial infarction, triple antiplatelet therapy may be beneficial in subjects receiving percutaneous coronary intervention without adequate thienopyridine preloading and in those with large thrombus burden. In subjects with non-ST elevation ACS, triple antiplatelet therapy is reserved for those at highest ischemic risk (e.g., elevated troponin or refractory ischemia) and for those with thrombotic complications at the time of percutaneous coronary intervention. The focus of this review is to summarize the rationale and evidence supporting the use of triple antiplatelet therapies in the management of patients with ACS.

Keyterms: acute coronary syndrome • antiplatelet agents • glycoprotein IIb/IIIa inhibitor • P2Y12 receptor antagonists • percutaneous coronary intervention • thienopyridines

Antiplatelet therapy is a cornerstone of the treatment of acute coronary syndromes (ACS). An improved understanding of platelet pathophysiology has led to the development of antiplatelet therapies that target different mechanisms of platelet activation and aggregation in ACS. The result has been the strategy of using combinations of antiplatelet agents, which have been associated with reduced ischemic events in large multicenter randomized clinical trials [1]. Guidelines now recommend that all ACS patients be treated with at least two antiplatelet agents irrespective of whether they are managed with a conservative or an invasive strategy. In addition, the use of glycoprotein IIb/IIIa inhibitors (GPIs) as a third antiplatelet agent in the management of ACS patients remains indicated in certain clinical settings [2].

The adoption of invasive ACS management in high-risk patients has influenced the antiplatelet management of a large number of patients with ACS. On the one hand, novel antiplatelet agents with more rapid and potent inhibition [3,4] that limit percutaneous coronary intervention (PCI)-related ischemic events (i.e., periprocedural myocardial infarction [MI] and stent thrombosis) are the focus of drug development. On the other hand, these agents are associated with increased bleeding risk and data suggest that major bleeding in the setting of ACS is associated with increased morbidity and mortality [5]. Moreover, new antithrombin regimens aimed at reducing the bleeding risk have been developed, potentially obviating the need for parenteral antiplatelet therapy in lower risk ACS patients [6]. Thus, understanding the benefits, risks and clinical role of antiplatelet strategies is critical to optimizing

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the outcomes of ACS patients [7]. A critical appraisal of this topic is timely and the following discussion aims to review the rationale and evidence supporting the use of triple antiplatelet therapy in ACS (hereafter defined as the combination of aspirin, P2Y12 inhibitors – thienopyridines and non-thienopyridines and GPI).

Role of platelets in ACS

Normal platelet function leads to hemostasis through three processes: adhesion, activation and aggregation. In ACS, these processes are amplified and promote the production of platelet-rich thrombi that either completely obstruct the vascular lumen leading to myocardial necrosis or variably obstruct the lumen through a process of autolysis resulting in unstable angina [8]. The pathophysiology of ACS is therefore highly dependent on platelets [9] and provides the rationale for combined antiplatelet strategies for managing and improving the outcomes of ACS patients.

Plaque rupture or erosion, which is a common feature of ACS, initiates the process of platelet adhesion by exposing circulating platelets to subendothelial tissue products such as von Willebrand factor and collagen [10]. Platelet activation and aggregation proceed through multiple molecular signaling mechanisms. The arachidonic acid-prostacyclin pathway maintains platelet quiescence under normal conditions; following vascular injury, amplified cyclooxygenase (COX)-1 activity increases thromboxane A2 production sustaining the initial platelet response. Activated platelets secrete a host of other substances including ADP which binds the P2Y12 receptor thereby promoting further platelet activation and recruitment. Platelet conformational changes expose receptors that initiate inflammation through platelet-leukocyte interactions. Finally, glycoprotein IIb/IIIa receptor activation with subsequent fibrinogen binding results in platelet aggregation and fibrin-clot formation. These processes act in concert, promote positive feedback, and are initiated through multiple cellular pathways [9,11]. While ensuring 'hemostatic certainty', this redundancy highlights the need for combined antiplatelet therapy to optimize platelet inhibition in ACS. Each antiplatelet strategy addresses a specific part of the aforementioned pathway.

Available antiplatelet agents – pharmacological properties

Aspirin

Aspirin is an oral antiplatelet agent that is hydrolyzed by gastrointestinal esterases to its active metabolite salicylic acid (Table 1). This agent inhibits platelet COX pathways thereby minimizing the production of thromboxane A2, a potent stimulant for platelet aggregation. Though the half-life of aspirin is only 15–20 min, its irreversible inhibition of COX allows for durable antiplatelet effects that are overcome only with the production of new platelets [12,13].

P2Y12 antagonists

Interaction of ADP with P2Y12 receptors is important in the growth and stabilization of thrombus. Clopidogrel and ticlopidine are oral thienopyridines that irreversibly bind the ADP P2Y12 receptor on platelets. Clopidogrel is a prodrug that requires conversion to its active metabolite via a two-step conversion utilizing the hepatic cytochrome system. The result is a relatively slow onset of action and variable patient response that is highly dependent on the efficiency of the conversion to the active metabolite. Ticlopidine has significant gastrointestinal side effects and has been associated with granulocytopenia and thrombotic thrombocytopenia purpura. While thrombocytopenia purpura has also been described with clopidogrel [14], it is significantly less common than with ticlopidine. Therefore the use of ticlopidine has generally been reserved for patients who are intolerant of other thienopyridines [2].

Prasugrel is a newer thienopyridine similar to clopidogrel in that it irreversibly binds the P2Y12 receptor and requires hepatic conversion to its active metabolite. Both have similar half-lives of 7–8 h. The metabolism of prasugrel differs from clopidogrel in several important ways. First, with the initial hydrolysis of clopidogrel, 85% of the drug is converted to an inactive metabolite; the yield of active metabolite following prasugrel conversion is much higher. Second, the conversion of clopidogrel to its active form requires two steps using the hepatic cytochrome system compared with one with prasugrel [15]. Peak antiplatelet activity using standard loading doses of prasugrel is achieved in 30 min, and antiplatelet effects exceed those achieved with clopidogrel [16]. Prasugrel thus results in more rapid, potent, and predictable platelet inhibition when compared with clopidogrel [17].

Ticagrelor is an oral, non-thienopyridine P2Y12 antagonist with a half-life of 7–8 h. It is not a prodrug and thus does not require conversion to an active metabolite. Unlike clopidogrel and prasugrel, its binding to the P2Y12 receptor is reversible. The result is rapid, potent inhibition and its shorter half-life mandates twice daily dosing to maintain platelet inhibition. The shorter half-life is potentially advantageous in that it has a faster offset compared with clopidogrel or prasugrel. This could provide a shorter window of time between cessation of therapy and surgical procedures [18].

Recent data have identified some interesting observations related to genetic background and clinical response with the P2Y12 antagonists. Nearly 30% of subjects have been reported to carry at least one

Table 1. Non-aspirin antiplatelet agents.

Antiplatelet agents	Class	Route of administration	Half-life	Dosing (loading & maintenance)	Renal dosing
Clopidogrel	Thienopyridine	Oral	7–8 h	300–600 mg, 75 mg daily	No adjustment
Prasugrel	Thienoyridine	Oral	7 h	60 mg, 5–10 mg daily	No adjustment
Ticlopidine	Thienopyridine	Oral	12 h	500 mg, 250 mg twice-daily	No adjustment
Ticagrelor	Non-thienopyridine	Oral	7–8 h	180 mg, 90 mg twice-daily	No adjustment
Eptifibatide	Glycoprotein IIb/IIIa inhibitor	Parenteral	2.5 h	180 µg/kg, 2 µg/kg/min	Reduce infusion dose by 50% if GFR <50 cc/min
Abciximab	Glycoprotein IIb/IIIa inhibitor	Parenteral	10–30 min	0.25 mg/kg, 0.125 µg/kg/min	No adjustment
Tirofiban	Glycoprotein IIb/IIIa inhibitor	Parenteral	2 h	0.4 µg/kg, 0.1 µg/kg/min	Reduce bolus and loading dose by 50% if GFR <30 cc/min

GFR: Glomerular filtration rate.

loss-of-function allele on the CYP2C19 gene, a critical enzyme involved in clopidogrel metabolism. Individuals with this genotype produce lower levels of the active clopidogrel metabolite. A recent meta-analysis involving 9685 patients receiving clopidogrel (54.5% with ACS) demonstrated that heterozygous carriers of these alleles are at increased risk of a composite of death, MI or stroke (hazard ratio [HR]: 1.55; 95% CI: 1.11–2.17) and stent thrombosis (HR: 2.67; 95% CI: 1.24–2.50) compared with noncarriers. Homozygotes for the loss-of-function allele were at even greater risk [19]. Prasugrel is unaffected by this genetic variability [20]. A substudy of PLATO, a landmark study comparing ticagrelor to clopidogrel, demonstrated that the benefits of ticagrelor with regard to a composite end point of death, MI or stroke were maintained irrespective of CYP2C19 allele status, though subjects in the clopidogrel group were at higher risk if an allelic variant was present [21].

■ Glycoprotein IIb/IIIa inhibitors

Platelet inhibitors occupy the IIb/IIIa receptor preventing fibrinogen binding thereby inhibiting the final common pathway in platelet aggregation [22]. Three GPI are available for use in the USA and all are parenteral agents. Abciximab is a large-molecule, chimeric antibody that binds nonspecifically to the IIb/IIIa receptor. It has a short half-life of 15–30 min. Tirofiban and eptifibatide are small-molecule, selective inhibitors of the IIb/IIIa receptor. Both have half-lives of 2–3 h. In contrast to abciximab, tirofiban and eptifibatide are renally cleared and require dose reductions in the setting of renal insufficiency [23]. All three GPI have been shown to reduce ischemic events such as recurrent MI and periprocedural MI when used in conjunction with unfractionated or low molecular weight heparins [24–26], though the magnitude of benefit may depend on the specific clinical setting [27,28].

Rationale for triple antiplatelet therapy

As compared with aspirin monotherapy, dual antiplatelet therapy in which either a thienopyridine or GPI is combined with aspirin, has been shown to reduce ischemic end points across a wide range of ACS patients. These anti-ischemic benefits are present in subjects with ST-elevation MI (STEMI) and non-ST elevation ACS; these benefits are present irrespective of whether or not PCI is performed [1,28–32].

The theoretical benefits of triple antiplatelet therapy stem from the following observations. First, ischemic events still occur in subjects on dual antiplatelet therapy [1] suggesting that greater platelet inhibition has the opportunity to reduce ischemic events further. Second, platelet reactivity is not completely suppressed in all individuals treated with dual antiplatelet therapy, particularly during ACS events [33]. Finally, platelet activation in ACS occurs through a variety of distinct pathways and therapeutic agents are available that target several of them. Utilizing three antiplatelet agents with different mechanisms of action could potentially suppress platelet reactivity further translating into reductions in adverse ischemic events.

Triple antiplatelet therapy in STEMI

The treatment of STEMI relies fundamentally on restoration of flow through the occluded infarct-related artery with either fibrinolysis or primary PCI [34]. Triple antiplatelet therapy has been investigated with each of these approaches in large randomized clinical trials.

Prior to the routine practice of clopidogrel preloading, several studies demonstrated benefit with a combined antiplatelet strategy utilizing abciximab. In a pooled analysis of 1737 STEMI patients who received stenting, use of abciximab during PCI reduced the 30-day composite end point of death, MI and target vessel revascularization (TVR; odds ratio [OR]: 0.56;

95% CI: 0.37–0.85). These benefits were sustained at 6 months (OR: 0.71; 95% CI: 0.53–0.96), though the reductions in events were driven solely by TVR. No significant reductions in death or MI were noted [35]. However, abciximab-treated STEMI patients experienced higher rates of significant bleeding and blood transfusions as well (OR: 1.74; 95% CI: 1.11–1.72) [36]. These data provide a historical perspective that GPI are beneficial when there is infrequent use of dual aspirin and thienopyridine therapy.

Several trials (Table 2) have examined the use of GPI in primary PCI in the modern stenting era on a background of dual oral antiplatelet therapy (aspirin and thienopyridine). BRAVE-3 was a randomized, double-blind study enrolling 800 patients with STEMI. All received aspirin 500 mg and clopidogrel 600 mg prior to undergoing primary PCI. Abciximab or placebo was administered for 12 h. The primary end point was left ventricular infarct size as assessed by single-photon emission computed tomography. Infarct size, expressed as a percentage of the entire left ventricle, was 15.7% in the abciximab group versus 16.6% in the placebo group (p = 0.47). At 30 days, the composite of death, MI, stroke or revascularization of the infarct-related artery was similar in the abciximab and placebo groups (5.0 vs 3.8%; p = 0.40, respectively) [37]. Similar event rates using this same composite end point were noted at 1 year (23% abciximab vs 25.7% placebo; p = 0.46), though the rate of death, MI or stroke showed a nonsignificant increase in the abciximab group (9.3 vs 6.0%; p = 0.09) [38].

ON-TIME 2 was a multicenter, randomized, blinded study of 984 patients with STEMI. Prior to PCI, patients were pretreated with aspirin and clopidogrel (600 mg) and randomized to placebo or high-dose tirofiban (0.25 µg/kg bolus followed by 0.15 µg/kg/min infusion for 18 h). Mean time from symptom onset to tirofiban administration was 75 min, and it was administered at first medical contact even if prior to hospital arrival (e.g., in-ambulance). The primary end point of residual ST-segment elevation was reduced in the tirofiban group (3.6 vs 4.8 mm; p = 0.03), but no differences in thrombolysis in myocardial infarction (TIMI) flow rate or myocardial blush grade were noted. At 30 days, the composite end point of death, MI, TVR or bailout tirofiban use was significantly lower with tirofiban than placebo (26.0 vs 32.9%; p = 0.02), though this difference was driven solely by bailout tirofiban use (tirofiban 19.9% vs placebo 28.5%; p = 0.02). Net clinical benefit, defined as a composite of death, MI, TVR or bleeding, was not different between groups (9.3% tirofiban vs 11.7% placebo; p = 0.221) [39].

The HORIZONS-AMI trial was a multicenter, open-label study randomizing 3602 STEMI patients undergoing planned primary PCI to bivalirudin versus heparin plus GPI (abciximab or eptifibatide). All subjects received PCI pretreatment with aspirin and thienopyridines (clopidogrel 300–600 mg loading dose, ticlopidine 500 mg loading dose for clopidogrel-intolerant patients). Primary end points included major bleeding (intracranial or intra-ocular hemorrhage, hematoma >5 cm or requiring intervention, >4 mg/dl hemoglobin drop without overt source, >3 mg/dl with source, blood transfusion, need for re-operation) and net adverse clinical events defined as a composite of major bleeding, death, MI, TVR or stroke. At 30 days, both major bleeding and net adverse clinical events were significantly reduced with bivalirudin compared with heparin plus GPI (major bleeding 4.9 vs 8.3%; p < 0.001, net adverse clinical events 9.2 vs 12.1%; p = 0.005, respectively). The reduction in net adverse events was driven solely by bleeding; death, MI and revascularization rates were similar in the bivalirudin and heparin plus GPI groups (5.5 vs 5.4%; p = 0.95, respectively). Interestingly, bivalirudin, compared with heparin plus GPI, was associated with a significant increase in acute (within 24 h of PCI) stent thrombosis, but also a significant reduction in 30-day mortality (1.8 vs 2.8%, respectively; p = 0.045). There was no difference in stent thrombosis at 30 days (2.5 vs 1.9%, respectively; p = 0.30,) [40].

Both BRAVE-3 and ON-TIME 2 were randomized comparisons of GPI to placebo in STEMI patients receiving primary PCI. Both used nonclinical, surrogate primary end points (BRAVE-3 single photon emission computed tomography infarct size, ON-TIME 2 residual ST-segment elevation), and neither was powered to detect differences in clinically meaningful secondary end points. In ON-TIME 2, high-dose tirofiban was administered at first medical contact (ambulance administration prior to hospital arrival). Furthermore, average time to symptom onset was 75 min compared with over 2 h in BRAVE-3 and HORIZONS-AMI. ON-TIME 2 did not demonstrate significant reductions in death, MI or revascularization in the tirofiban arm. The clinical end points were driven only by bailout GPI use, an end point that is potentially subjective. Similarly, BRAVE-3 also demonstrated no reductions in clinical outcomes with abciximab. In comparison, HORIZONS-AMI demonstrated significant mortality benefit with bivalirudin use in place of heparin plus GPI. The lack of bleeding excess seen with GPI use in ON-TIME 2 might be explained by less aggressive anticoagulation (average ACT, ON-TIME 2 181 vs 264 s, HORIZONS-AMI), differences in bleeding definitions or perhaps use of vascular closure devices (70% in ON-TIME 2, data not provided for HORIZONS-AMI) [37,39,40].

In summary, in the modern PCI era, no randomized trial has shown benefit with respect to clinical events in STEMI patients receiving triple antiplatelet therapy with

Table 2. Modern trials of triple antiplatelet therapy in ST-elevation myocardial infarction.

Trial	Arms	Subjects	Thienopyridine dosing	Heparin dosing	GPI dosing	Primary end point(s)†	Secondary end point(s)†	Miscellaneous	Ref.
BRAVE-3	Abciximab vs placebo	800	Clopidogrel, 600 mg prior to PCI	60 U/kg if assigned to GPI, 70 U/kg if assigned to placebo	0.25 mg/kg bolus followed by 0.125 µg/kg/min infusion for 12 h	Infarct size via SPECT: 15.7 vs 16.6% (p = 0.47)	30-day death, MI, stroke and revascularization: 5 vs 3.8% (p = 0.40)	Bleeding rates: 1.8% in each group	[37]
ON-TIME 2	Tirofiban vs placebo	984	Clopidogrel, 600 mg prior to PCI	5000 U, additional 2000 U given prior to PCI if ACT <200 s	25 µg/kg bolus followed by 0.125 µg/kg/min infusion for 18 h	Residual ST-elevation post-PCI: 3.6 vs 4.8 mm (p = 0.003)	30-day death/MI/TVR/thrombotic bailout: 26.0 vs 32.9% (p = 0.02)	Bleeding rates similar: 2.9 vs 4.0% (p = 0.36); no difference in death/MI/TVR: 8.2 vs 7.0% (p = 0.49)	[39]
HORIZONS-AMI	Bivalirudin vs heparin + GPI	3602	Clopidogrel, 300–600 mg (61.6% received 600 mg load)	60 U/kg, additional doses given to target ACT: 200–250 s	Abciximab: 0.25 mg/kg bolus followed by 0.125 µg/kg/min infusion for 12 h; or eptifibatide: 80 µg/kg double bolus followed by infusion of 2 µg/kg/min for 12–18 h	Major bleeding: 4.9 vs 8.3% (p < 0.001); net adverse clinical events: 9.2 vs 12.1% (p = 0.005)	30-day stent thrombosis: 2.5 vs 1.9% (p = 0.3); cardiac death: 1.8 vs 2.8% (p = 0.045)	-	[40]

†Data are listed as GPI vs placebo (BRAVE-3 and ON-TIME 2) or bivalirudin vs heparin plus GPI (HORIZONS-AMI).

ACT: Activated clotting time; GPI: Glycoprotein IIb/IIIa inhibitor; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; SPECT: Single-photon emission computed tomography; TVR: Target vessel revascularization; U: Units.

aspirin, thienopyiridines and GPI over dual antiplatelet therapy [38,39]. Current ACC/AHA guidelines recommend selective use of GPI in the setting of STEMI at the time of PCI, particularly in those with large thrombus burden or those without adequate thienopyridine preloading. Furthermore, the guidelines acknowledge that the routine use of upstream GPI prior to primary PCI in STEMI subjects is uncertain [41]. These guideline recommendations are contradicted by recent data from the EUROTRANSFER registry, which has shown reductions in 1 year mortality with early versus in-lab use of GPI in patients undergoing primary PCI (8.7 vs 15.8%; p = 0.01) [42]. Similarly, a recent meta-analysis of facilitated PCI trials suggests that early GPI use may improve surrogate end points such as ST-segment resolution in patients transferred for PCI [43]. Therefore, there may be utility to early GPI use in addition to aspirin and P2Y12 inhibition in selected patients undergoing primary PCI. Whether these new data will affect future guideline recommendations remains to be seen.

Triple antiplatelet therapy in unstable angina/non-ST elevation MI

Pivotal trials examining GPI use in high-risk, non-ST elevation ACS demonstrated 30–60% reductions in short- and long-term ischemic end points [44,45]. These benefits were present in those at highest risk (i.e., individuals with positive troponin levels) [46]. These trials were conducted prior to the advent of routine coronary stenting, thienopyridine preloading and before the development of newer anticoagulation strategies. Trials conducted using these additional strategies have not consistently replicated prior beneficial results [6,25,27].

The ISAR-REACT 2 trial enrolled 2012 patients with high risk, non-ST elevation ACS (Table 3). All patients received unfractionated heparin, aspirin and clopidogrel 600 mg at least 2 h prior to PCI. They were then randomly assigned at the time of PCI to abciximab or placebo. At 30 days, the primary end point of death, MI or TVR was significantly reduced in the group assigned to abciximab (8.9 vs 11.9%; p = 0.03) driven entirely by the subgroup of patients with elevated troponin values at baseline (relative risk: 0.71, 95% CI: 0.54–0.95). No benefit was seen among patients without elevated troponin values. There was no difference between the groups with respect to TIMI major bleeding. This study underscores the principle described above – higher risk patients benefit from more aggressive therapies. It is important to note that unfractionated heparin was used as the antithrombin agent in this trial [25].

In contrast to the findings of the ISAR-REACT 2 trial, the ACUITY trial showed no benefit of routine GPI added to either unfractionated heparin or bivalirudin compared with bivalirudin alone. The ACUITY trial was an open-label study of 13,819 patients with moderate to high-risk ACS undergoing an early invasive strategy who were randomized to either unfractionated heparin or enoxaparin plus GPI (given either early or in the cath lab in the event of PCI), bivalirudin plus GPI (given either early or in the cath lab for PCI) or bivalirudin with provisional GPI (given only for ischemic bailout or procedural complications). The primary end point was the composite of 30-day death, MI, urgent TVR or major bleeding. This trial employed a noninferiority design for the comparison of ischemic events (death, MI or TVR) using a wide margin of 25%. There was no significant difference in the rate of the primary end point between groups assigned to heparin plus GPI and those assigned to bivalirudin plus GPI (11.7 vs 11.8%, respectively; p = 0.93). In contrast, the strategy of bivalirudin with provisional GPI was associated with noninferior rates of ischemic events but significantly lower rates of major bleeding [6]. This resulted in overall superiority of bivalirudin alone for the quadruple composite end point. There were some interesting findings with respect to the use of thienopyridines. Subjects not receiving a thienopyridine prior to angiography or PCI had significantly more ischemic events when receiving bivalirudin compared with heparin plus GPI (9.1 vs 7.1%; relative risk: 1.29; 95% CI: 1.03–1.63). Another subgroup that showed a benefit with GPI was patients with visible thrombus prior to PCI [47]. These data call into question the role of routine triple antiplatelet therapy in the setting of non-ST-segment elevation ACS when bivalirudin is used as the antithrombin agent. However, there are significant limitations to the ACUITY trial. It utilized an open label study design, had high rates of crossover among the arms, included events that may not be considered clinically significant in the definition of major bleeding (e.g., vascular access site hematoma >5 cm), and had a wide noninferiority margin (25%) [7].

Despite these limitations, the finding that routine GPI use is of little benefit in the modern era of ACS management is supported by another large clinical trial. The EARLY-ACS trial randomized 9492 patients with high-risk non-ST elevation ACS undergoing a planned invasive strategy to early, upstream use of eptifibatide (double bolus followed by 12 h infusion) versus delayed, provisional use at the time of PCI. Approximately 75% of the subjects received early clopidogrel loading (300 mg). The primary composite end point of death, MI, revascularization or thrombotic bailout at 96 h was not different between groups (9.3% early vs 10.0% delayed; p = 0.23). Compared with those in the delayed group, patients in the early eptifibatide group experienced higher rates of TIMI major hemorrhage (2.6 vs 1.8%; p = 0.02) and required more blood transfusions (8.6 vs

Table 3. Modern trials of triple antiplatelet therapy in non-ST elevation acute coronary syndromes.

Trial	Arms	Subjects	Thienopyridine dosing	GPI dosing	Primary end point(s)	Secondary end point(s)	Miscellaneous	Ref.
ISAR-REACT 2	Heparin + abciximab vs heparin + placebo	2022 patients with non-ST elevation ACS	Clopidogrel 600 mg >2 h prior to PCI	0.25 mg/kg bolus followed by 0.125 µg/kg/min for 12 h	30-day death/MI/revascularization: 8.9 vs 11.9% (p = 0.03) in favor of abciximab	Major bleeding: 1.4 vs 1.4% (RR: 1.0; 95% CI: 0.50–2.08); minor bleeding: 4.2 vs 3.3% (RR: 1.27; 95% CI: 0.81–1.99)	Primary end point if troponin (+): 13.1 vs 18.3% (p = 0.02) favoring GPI; if troponin (–): 4.6 vs 4.6% (p = 0.98)	[25]
EARLY-ACS	Upstream eptifibatide vs delayed, provisional in-lab use	9492 patients with non-ST elevation ACS	300 mg load if given early, 600 mg load if started in lab	Double bolus of 180 µg/kg with infusion at 2 µg/kg/min	Death, MI, revascularization or thrombotic bailout at 96 h: 9.3 vs 10.0% (p = 0.23)	Death or MI at 30 days similar: 11.2 vs 12.3% (p = 0.079); TIMI, major or minor bleed higher in early group: 5.8 vs 3.4% (p < 0.001)	No difference seen in subgroups receiving early clopidogrel loading or in those with elevated troponin	[27]
ACUITY	Heparin or LMWH + GPI vs bivalirudin + GPI vs bivalirudin		Per treating physician, at least 300 mg load No more than 2 h after PCI recommended	Standard dosing of tirofiban or eptifibatide (if upstream), or eptifibatide or abciximab (if given in lab), continued for 12–8 h post-PCI	Death, MI, revascularization, bleeding: bivalirudin + GPI noninferior to heparin + GPI: 11.8 vs 11.7% (95% CI: 0.90–1.12)	Ischemic end points similar in bivalirudin and heparin + GPI groups: 7.8 vs 7.3%, (p = 0.32); major bleeding lower in bivalirudin group compared with both GPI groups: 3.0 vs 5.3 and 5.7% (p < 0.001)	Ischemic events higher with bivalirudin vs heparin + GPI in groups not receiving clopidogrel preloading: 9.1 vs 7.1% (RR: 1.29; 95% CI: 1.03–1.63)	[6]

ACS: Acute coronary syndromes; GPI: Glycoprotein IIb/IIIa inhibitor; LMWH: Low molecular weight heparin; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; RR: Relative risk; TIMI: Thrombolysis in myocardial infarction.

6.7%; p= 0.001). No differences in secondary end point of death or re-infarction were noted at 30 days (11.2 vs 12.3%; p = 0.08) [27]. A subsequent *post hoc* analysis examining the interaction between clopidogrel use and GPI demonstrated that upstream clopidogrel plus early eptifibatide did not reduce the primary end point over delayed eptifibatide; however, it was associated with a lower risk of 30-day death or MI [48].

Thus, routine use of GPI in addition to aspirin and clopidogrel is likely of limited benefit in patients with non-ST-segment elevation ACS given its significant bleeding risk. It may be beneficial in patients at highest risk such as – those with elevated troponin values in whom an invasive management strategy is planned and unfractionated heparin or low molecular weight heparin is utilized as the anticoagulant. Further, the benefit of upstream GPI may be on 30-day outcomes in patients who have been loaded early with clopidogrel, although the results of this *post hoc* analysis should be interpreted with caution [48].

Combined antiplatelet therapy utilizing next-generation antiplatelets agents

The TRITON-TIMI 38 trial investigated the use of prasugrel in patients with moderate to high-risk ACS defined as STEMI or non-ST elevation ACS (TIMI risk score of ≥3 with elevated cardiac enzymes or significant ST depression) undergoing PCI. A total of 13,608 subjects were randomized to prasugrel or clopidogrel prior to undergoing PCI. The primary end point was cardiovascular death, MI or stroke at 15 months. Prasugrel was superior to clopidogrel in reducing the primary end point (9.9 vs 12.1%; p > 0.001), but was noted to cause excess major bleeding (2.4 vs 1.8%; p = 0.03), including significant increases in fatal bleeding. The risks of prasugrel outweighed benefits in patients older than 75 years, those with prior stroke, and those with a body weight <60 kg [3]. A substudy examining PCI patients who were treated with GPI found that the benefits of prasugrel were maintained irrespective of whether or not GPI were used. In the population receiving GPI, upstream use was employed in only 14.7% of subjects. The remainder received GPI during or after PCI. Importantly, though prasugrel was noted to cause increased bleeding, this risk was not increased further by concomitant GPI use [49].

The reversible, non-dihydropyridine P2Y12 inhibitor ticagrelor was tested against clopidogrel in the PLATO study. This study enrolled 18,624 patients with ACS including STEMI and non-ST ACS. The primary end point of vascular death, MI or stroke was reduced from 11.7% to 9.8% in subjects receiving ticagrelor (p < 0.001). Significant reductions in vascular death and MI were also noted. Excess major bleeding was noted in the ticagrelor group (4.5 vs 3.8%; p = 0.03). Approximately one quarter (26%) of patients in this trial were treated with GPI. The interaction p-value testing the effect of ticagrelor among patients who did and did not receive GPI was not statistically significant (p = 0.41) indicating that the benefit of ticagrelor was independent of GPI use [4].

The results of a PLATO substudy addressing only those subjects with STEMI have been recently reported. In the 7544 patients undergoing planned primary PCI, the primary end point was nonsignificantly reduced in the ticagrelor versus clopidogrel groups (9.4 vs 10.8%; p = 0.07). GPI use (36.5% of subjects) did not influence ischemic outcomes (HR 0.95; 95% CI: 0.74–1.21). However, in the patients not receiving GPI, there was a trend towards a significant reduction in the primary end point with ticagrelor compared with clopidogrel (HR 0.83, 95% CI: 0.70–1.00) [50].

Future perspective

It has become increasingly apparent that bleeding events adversely affect mortality in ACS patients [51]. As such, antiplatelet strategies may evolve in several important ways. First, since the most benefit of triple antiplatelet therapy in ACS patients is present in those not adequately preloaded with thienopyridines prior to PCI, newer, more potent, reversible agents such as ticagrelor or the novel agent elinogrel may obviate the need for triple antiplatelet therapy in ACS [4,52]. Second, the development of tools to grade bleeding and ischemic risk may identify those subjects with the most to gain from combined antiplatelet strategies [53]. Third, advances in interventional equipment (e.g., smaller catheters and sheaths) and greater adoption of trans-radial access for PCI may lessen the bleeding risk associated with aggressive, combination antiplatelet therapies (reviewed in [54]). Future antiplatelet therapies for ACS will likely be individualized based on personalized risk profiles consisting of clinical and genetic markers.

Conclusion

In summary, the anti-ischemic benefits of triple antiplatelet therapy in ACS are limited by increased bleeding risk. For patients with STEMI, triple therapy may be beneficial at the time of PCI when heparin is used as the antithrombin and in the absence of adequate thienopyridine preloading. Similarly, the addition of GPI to dual antiplatelet therapy may be reasonable at the time of angiography when a large thrombus burden is present. In non-ST elevation ACS, there is no role for routine, upstream GPI use in the presence of adequate thienopyridine loading; this strategy is reserved for subjects at highest risk (e.g., positive tropinin or refractory symptoms). Triple antiplatelet therapy remains indicated for

bailout thrombotic complications during PCI. The role of triple antiplatelet therapy when using more potent, rapid-acting antiplatelet agents such as prasugrel and ticagrelor is even less clear. These newer agents may narrow the clinical utility for triple antiplatelet therapy even further.

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Executive summary

- Platelet activation and aggregation are the pathologic hallmarks of acute coronary syndromes (ACS).
- Combined antiplatelet therapies that target multiple pathways of platelet activity improve ischemic outcomes in patients with ACS at a cost of increased bleeding risk.
- Triple antiplatelet therapy in ST-elevation myocardial infarction is indicated in subjects receiving percutaneous coronary intervention on heparin without thienopyridine preloading or in those with large thrombus burden present on angiography.
- In non-STE elevation ACS subjects, triple antiplatelet therapy is reserved for patients with high-risk features or for bailout indications during percutaneous coronary intervention.
- Newer, more potent and rapid-acting antiplatelet agents may narrow the clinical utility for triple antiplatelet therapy even further.

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