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CORONARY HEART DISEASE (E GIANOS AND B SHAH, SECTION EDITOR)

Use of Novel Antiplatelet Agents in Acute Coronary Syndromes

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Abstract Acute coronary syndromes (ACS) encompass a broad spectrum of clinical presentations based on underlying pathology that results in myocardial ischemia and/or infarction. Despite advancements in invasive management and secondary preventive therapies, recurrent atherothrombotic coronary events remain a prevalent cause of death and recurrent cardiac events after ACS and, in those who survive, the root of long-standing cardiac comorbidities. Antiplatelet drug therapy has proven beneficial in the reduction of these events, and novel antiplatelet agents have resulted in significant improvement in clinical outcomes over the last decade. However, the balance of optimal platelet inhibition with minimal bleeding complications remains a clinical challenge. This review focuses on more recent advances in antiplatelet therapies used in the treatment of ACS.

Keywords Acute coronary syndrome · Antiplatelet therapy · Pharmacology · Platelet · Percutaneous coronary intervention

Introduction

Acute coronary syndromes (ACS) include a spectrum of three distinct clinical presentations: unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI). Although atherosclerotic plaque instability is the underlying biologic pathology that translates clinically to both ST segment elevation and non-ST segment elevation ACS, these syndromes can vary dramatically in their initial presentation and more importantly in their long-term outcomes. Recent updated guidelines use the term non-ST segment elevation ACS to convey the continuum of biology between UA and NSTEMI [1••]. The discovery of the platelet's integral role in the pathophysiology of ACS has led to its centrality as a therapeutic target [2]. Aspirin was the first such therapy, shown to have favorable profiles in secondary prevention as well as in saphenous vein graft patency following coronary artery bypass grafting (CABG) [3–5].

The impetus to develop new and more potent antiplatelet therapies was driven by the substantial cardiovascular risk that remained following treatment of ACS with aspirin therapy with or without an early invasive strategy [6, 7]. Given its principal role in platelet activation and aggregation, the adenosine diphosphate (ADP) $P2Y_{12}$ receptor became the prominent target for drug development (Fig. 1). Ticlopidine was the first of a new class of antiplatelet drugs, the thienopyridines, which possess antagonistic effects on the $P2Y_{12}$ receptor; however, it was soon replaced by a second-generation thienopyridine, clopidogrel, due to a more favorable safety profile [8, 9]. Although the addition of clopidogrel reduced the rates of recurrent cardiovascular events, there was no associated improvement in survival [7, 9]. Additionally, the benefit of clopidogrel therapy came at the expense of increased major bleeding events. These early clopidogrel data set the stage for the major challenge that would face this field, which is to maximize antithrombotic effects while minimizing bleeding. Recent advances in this field have tried to overcome this challenge and will be reviewed in detailed here.

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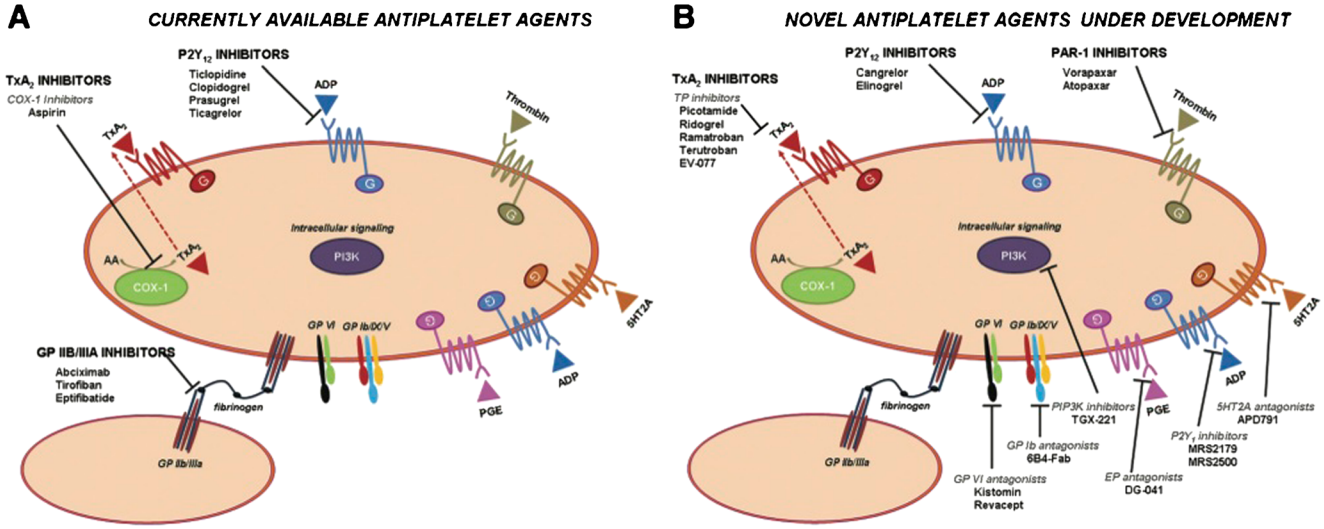

Fig. 1 Site of action of antiplatelet agents. **a** Currently available agents for acute coronary syndromes or percutaneous coronary intervention. **b** Novel antiplatelet agents under development. *5HT2A* serotonin, *AA* arachidonic acid, *ADP* adenosine diphosphate, *COX-1* cyclooxygenase-1, *EP* prostaglandin receptor, *G* g-protein, *GP* glycoprotein, *PG* prostaglandin, *PAR-1* platelet protease-activated receptor-1, *PI3K* phosphatidylinositol 3-kinase, *TP* thromboxane receptor, TxA_2 thromboxane A_2. Reproduced with permission from [27]

Intensive Antiplatelet Therapy in ACS

Prasugrel is the most contemporary thienopyridine currently available for clinical use in patients with ACS. Like clopidogrel, prasugrel is a prodrug that requires hepatic biotransformation into an active metabolite (Table 1). However, unlike clopidogrel, prasugrel's oxidative process in the liver is a more efficient one, requiring only a single cytochrome P450 (CYP)-dependent step which allows for a more rapid onset of action and a more profound inhibition of platelets [10]. Ticagrelor is the most recently FDA-approved antiplatelet agent available for use in ACS. This is the first of a newly developed class of antiplatelet drugs, cyclopentyltriazolopyrimidines, that is not a prodrug but rather directly inhibits the $P2Y_{12}$ receptor. Although ticagrelor reversibly inhibits the $P2Y_{12}$ receptor, there is no therapy currently available to reverse its effects [11••]. The pivotal trials that led to the FDA's approval of prasugrel and ticagrelor were the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) and Platelet Inhibition and Patient Outcomes (PLATO) trials, respectively. In each, the active comparator was clopidogrel; however, important differences between the two trials preclude a direct comparison of the two novel agents.

Table 1 Pharmacologic profiles of currently approved $P2Y_{12}$ receptor inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Nucleoside analogue
Prodrug	Yes	Yes	No
Receptor blockade	Irreversible	Irreversible	Reversible (no current method of reversing effects)
Administration	Oral	Oral	Oral
Dose	300–600 mg load; 75 mg daily	60 mg load; 10 mg daily; 5 mg if <60 kg	180 mg load; 90 mg twice daily
Onset of action	2–8 h	30 min–4 h	30 min–2 h
Half-life of active metabolite	30 min	7 h	9 h
Offset of action	7–10 days	7–10 days	3–5 days
Side effects	Bleeding, rash, neutropenia, TTP (rare)	Bleeding	Bleeding, dyspnea, bradycardia
Contraindications	Hypersensitivity, active bleeding, hepatic impairment, cholestatic jaundice	Hypersensitivity, active bleeding, history of TIA or stroke, patients >75 years of age	Hypersensitivity, active bleeding, hepatic impairment, history of intracranial hemorrhage, concomitant use of strong CYP34A inhibitors

Prasugrel

The TRITON-TIMI 38 trial compared the safety and effectiveness of prasugrel to clopidogrel in 10,074 patients presenting with non-ST segment elevation ACS and 3534 patients presenting with ST segment elevation ACS, where the intent was to pursue an invasive strategy [12••]. Patients were randomized to either prasugrel (60 mg loading dose and 10 mg per day maintenance dose) or clopidogrel (300 mg load and 75 mg daily maintenance dose). The protocol mandated the definition of coronary anatomy with angiography in patients presenting with non-ST segment elevation ACS prior to randomization; however, in patients presenting with ST segment elevation, ACS randomization could occur prior to percutaneous coronary intervention (PCI). Administration of study drug was allowed up to 24 h prior to PCI, but patients pretreated with clopidogrel were excluded from the study. The primary efficacy endpoint was a composite of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke during a follow-up period of up to 6 to 15 months. Stent thrombosis, defined according to the Academic Research Consortium, was a prespecified secondary endpoint [13]. Key safety endpoints included non-CABG-related TIMI major bleeding, non-CABG-related TIMI life-threatening bleeding, and TIMI major or minor bleeding.

In the overall TRITON-TIMI 38 cohort, the primary endpoint occurred in 9.9 % of the patients in the prasugrel group as compared to 12.1 % of patients in the clopidogrel group, translating into a 19 % relative risk reduction in favor of prasugrel (hazard ratio 0.81; 95 % confidence interval (CI) 0.73 to 0.90; $p<0.001$). This benefit was shown early, with an 18 % relative risk reduction present at 3 days and that persisted throughout the follow-up period. The benefit associated with prasugrel was primarily driven by a significant reduction in MI (prasugrel 7.4 % vs. clopidogrel 9.7 %; hazard ratio 0.76; 95 % CI 0.67 to 0.85; $p<0.001$) and observed in both types of ACS presentations. Definite and probable stent thrombosis was also significantly reduced, 1.1 % in the prasugrel group and 2.4 % in the clopidogrel group (hazard ratio 0.48; 95 % CI 0.36 to 0.64; $p<0.001$). This event reduction was present irrespective of whether a bare metal or drug-eluting stent was implanted. These benefits, however, existed at the expense of greater bleeding with prasugrel. The key safety endpoint, non-CABG-related bleeding, occurred in 2.4 % of the patients receiving prasugrel and in 1.8 % of the patients receiving clopidogrel (hazard ratio 1.32; 95 % CI 1.03 to 1.68; $p=0.03$) and included excessive life-threatening bleeding (1.4 vs. 0.9 %; hazard ratio 1.52; 95 % CI 1.08 to 2.13; $p=0.01$).

A prespecified analysis of net clinical benefit that included the endpoints of death from any cause, nonfatal MI, nonfatal stroke, and TIMI major bleeding still favored prasugrel over clopidogrel in the overall cohort (12.2 vs. 13.9 %; hazard ratio 0.87; 95 % CI 0.79 to 0.95; $p=0.004$). However, post hoc subgroup analyses identified three groups associated with a suggested net harm with prasugrel: (1) patients with prior stroke or transient ischemic attack (TIA) (hazard ratio 1.54; 95 % CI 1.02 to 2.32; $p=0.04$); (2) patients ≥75 years old (hazard ratio 0.99; 95 % CI 0.81 to 1.21; $p=0.92$); and (3) patients weighing <60 kg (hazard ratio 1.03; 95 % CI 0.69 to 1.53; $p=0.89$). Although the FDA approved prasugrel for use in patients with ACS, a black-box warning was placed against use in patients with prior stroke or TIA and in patients ≥75 years old and/or <60 kg.

Ticagrelor

The PLATO trial compared the safety and effectiveness of ticagrelor to clopidogrel in 11,067 patients presenting with non-ST segment elevation ACS and 7026 patients presenting with ST segment elevation ACS [11••]. The patients were randomized to either ticagrelor (180 mg loading dose and 90 mg twice daily maintenance dose) or clopidogrel (300 mg loading dose and 75 mg maintenance dose). Unlike in TRITON-TIMI 38, coronary angiography was not mandated prior to randomization, and patients pretreated with clopidogrel were eligible for randomization. In fact, 46 % of patients in each study arm received clopidogrel prior to randomization. Ticagrelor therapy was shown to significantly reduce the rate of the primary endpoint, which consisted of death from vascular causes, nonfatal MI, and nonfatal stroke, at 12 months follow-up (9.8 vs. 11.7 %; HR 0.84; 95 % CI 0.77 to 0.92; $p=0.0001$). Similar to prasugrel, ticagrelor also reduced the rate of definite and probable stent thrombosis compared to clopidogrel (2.2 vs. 3.0 %; HR 0.73; 95 % CI 0.57 to 0.94; $p=0.014$). Furthermore, the overall benefit with ticagrelor was also driven by a reduction in MI. Unlike prasugrel, however, ticagrelor was associated with a statistically significant reduction in vascular death (4.0 vs. 5.1 %; HR 0.79; $p=0.001$) and death from any cause (4.5 vs. 5.9 %; $p<0.001$) when compared to clopidogrel.

Many studies have demonstrated that, compared to aspirin monotherapy, the combination of aspirin and clopidogrel reduces adverse event rates among patients with ACS and in those undergoing PCI [6, 14]. This benefit is largely due to a reduction in the rate of nonfatal MI. Only the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) showed an improvement in survival with clopidogrel use compared to placebo (7.5 vs. 8.1 %; $p=0.03$) [6]. Ticagrelor is the first antiplatelet agent to show any survival benefit in a randomized study with an active comparator, and the benefit appears to be greater than when clopidogrel was compared to placebo. Indeed, if valid, the absolute reduction in mortality of 1.4 % represents an advance in the treatment of ACS not seen since the introduction of fibrinolytic therapy. Although the study investigators have proposed that the mortality

benefit may be due to prevention of recurrent ischemic events without associated increased bleeding, this may not be a plausible explanation. First, ticagrelor did cause increased bleeding compared to clopidogrel among the patients who did not undergo CABG surgery (PLATO definition—4.5 vs 3.8 %; p=0.03; TIMI definition—2.8 vs. 2.2 %; p=0.03). Second, the relative benefit for mortality is greater than the relative benefit for nonfatal ischemic events. Finally, there is no precedent by which such a marked mortality benefit has been observed in trials comparing different degrees of platelet inhibition.

Double-Dose Clopidogrel

The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-Oasis 7) trial randomized 25,086 patients with ACS and planned early invasive therapy to double-dose (600 mg on day 1, 150 mg on days 2–7, then 75 mg daily) versus standard dose (300 mg on day 1 then 75 mg daily) clopidogrel, and high-dose (300–325 mg daily) versus low-dose (75–100 mg daily) aspirin [15•]. The rate of the primary composite endpoint of cardiovascular death, MI, or stroke at 30 days in the prespecified group of over 17,000 patients who underwent PCI was significantly lower with the double-dose clopidogrel regimen (3.9 vs. 4.5 %; adjusted hazard ratio 0.86, 95 % CI 0.74–0.99, p= 0.039), as was definite stent thrombosis (0.7 vs. 1.3 %; 0.54 [0.39–0.74], p=0.0001). Major bleeding, however, was also more common with double-dose than with standard dose clopidogrel (1.6 vs. 1.1 %; 1.41, 1.09–1.83, p=0.009). The primary endpoint and major bleeding did not differ between the high-dose and low-dose aspirin groups.

Summary

Table 2 summarizes the three trials in which more intensive antiplatelet therapy were compared with standard clopidogrel regimens in patients with ACS. All three trials demonstrated lower rates of recurrent MI and stent thrombosis and higher rates of non-CABG bleeding with more intensive $P2Y_{12}$ inhibition. Although an outlier is the mortality benefit observed with ticagrelor in the PLATO trial, this does not fit the established paradigm, and a plausible biological mechanism has yet to be fully elucidated. The side effect profile of ticagrelor, particularly dyspnea and ventricular pauses, suggests a possible role for adenosine. Both dyspnea and ventricular pauses have been noted in patients treated with clopidogrel but to a lesser degree than with ticagrelor. Furthermore, the Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 versus Clopidogrel in NSTEMI 2 (DISPERSE 2) trial demonstrated a dose-response with the rates of both dyspnea and ventricular pauses in patients treated with two different doses of AZD6140 (now ticagrelor) [16]. Increases in uric acid levels, which have not been described with thienopyridines, also support an adenosine-mediated pathway [17].

Intensive Antiplatelet Therapy in Medically Managed ACS

Although practice guidelines support an early invasive approach in the management of moderate to high-risk patients with non-ST segment elevation ACS, there are many such patients that are not referred for coronary angiography and revascularization [18, 19]. Because benefit has been shown with the addition of clopidogrel to aspirin monotherapy in medically managed ACS and because prasugrel has outperformed clopidogrel in ACS patients managed with PCI, the logical question that remained was whether prasugrel added additional cardiovascular benefit over clopidogrel in the medically managed ACS cohort [20].

The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes

Table 2 Hazard ratios [95 % confidence intervals] for clinical outcomes in three trials comparing more intensive $P2Y_{12}$ inhibition with standard dose clopidogrel

Endpoint	TRITON-TIMI 38 (prasugrel)	PLATO (ticagrelor)	CURRENT-Oasis 7 (double-dose clopidogrel)
Cardiovascular death/MI/stroke	0.81 (0.73–0.90)	0.84 (0.77–0.92)	0.86 (0.74–0.99)
Stent thrombosis	0.48 (0.36–0.64)	0.67 (0.50–0.91)	0.54 (0.39–0.74)
Major bleeding	1.32 (1.03–1.68)	1.19 (1.02–1.38)	1.41 (1.09–1.83)
Cardiovascular death	0.89 (0.70–1.12)	0.79 (0.69–0.91)	0.96 (0.77–1.19)
All-cause death	0.95 (0.78–1.16)	0.78 (0.69–0.89)	N/A

(TRILOGY ACS) trial enrolled patients with a non-ST segment elevation ACS within 10 days of the index event and an intent to treat medically [21•]. Although angiography was not required for enrollment, 41 % of patients in each study arm did undergo angiography, and those who did were required to have coronary artery stenosis of >30 % or prior PCI/CABG. Patients randomized within 72 h without prior clopidogrel therapy were randomized to receive a loading dose of either prasugrel 30 mg or clopidogrel 300 mg, while those on stable clopidogrel therapy were randomized to receive maintenance doses of prasugrel or clopidogrel. Patients randomized after 72 h of the index event were treated with clopidogrel before randomization to maintenance doses of prasugrel or clopidogrel, while those not pretreated with clopidogrel were excluded. The maintenance dose of prasugrel was 5 mg daily for patients ≥75 years of age or those who weighed <60 kg and 10 mg daily for all others. The maintenance dose of clopidogrel was 75 mg daily. Patients with TIA or stroke were excluded. Although there was a greater antiplatelet effect with prasugrel, there were also higher rates of minor or moderate bleeding with prasugrel compared to clopidogrel. After 30 months of follow-up, there was no difference between the two groups with respect to the primary endpoint, the composite of cardiovascular death, nonfatal MI, or nonfatal stroke. Thus, prasugrel did not add a meaningful cardiovascular benefit greater than clopidogrel in medically managed patients with non-ST segment elevation ACS.

There is no dedicated study evaluating use of ticagrelor in medically managed patients ACS. However, of the more than 18,000 patients enrolled in the PLATO trial, 11,080 were classified as non-ST segment elevation ACS. During the first 10 days, 46 % of these patients were treated with PCI and 5 % with CABG; the remaining patients were treated medically without revascularization. A retrospective analysis of these patients demonstrated a reduction in the primary endpoint (cardiovascular death, MI, and stroke) with ticagrelor therapy as compared to clopidogrel (10.0 vs. 12.3 %; HR 0.83; 95 % CI 0.74 to 0.93) [22•]. Consistent with the overall trial results, significant reductions in cardiovascular and all-cause death were observed with ticagrelor therapy but at a cost of increased non-CABG-related bleeding.

Together, these data have led to the most recent American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline recommendations to support the use of clopidogrel, prasugrel, or ticagrelor as the second oral antiplatelet agent in invasively managed ACS and the use of clopidogrel or ticagrelor (not prasugrel) as the second oral antiplatelet agent in medically managed non-ST segment elevation ACS [1••].

Upstream Oral Dual Antiplatelet Therapy in Invasively Managed ACS

Upstream oral dual antiplatelet therapy (DAPT) with aspirin and clopidogrel has become a common practice in the management of patients with non-ST segment elevation ACS. This pattern stems from data that is more than a decade old, during an era when time to angiography and PCI were more prolonged than is common today [14, 23].

More recent data have challenged this paradigm. The A Comparison of Prasugrel at PCI or Time of Diagnosis of Non-ST Elevation Myocardial Infarction (ACCOAST) trial was the first randomized study to address the question of whether upfront therapy with both aspirin and a $P2Y_{12}$ inhibitor, in this case prasugrel, offered improved cardiovascular outcomes in patients managed invasively [24••]. More than 4000 patients with NSTEMI who were to undergo angiography plus possible PCI within 2 to 48 h of randomization were assigned to receive a 30-mg loading dose of prasugrel or placebo prior to angiography; at the time of PCI, the upstream prasugrel arm would then receive an additional 30 mg of prasugrel while the upstream placebo arm would receive 60 mg of prasugrel. There was no difference between the two groups with respect to the primary endpoint (composite of cardiovascular death, MI, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor bailout) both at 7 and 30 days. However, upstream prasugrel was associated with higher CABG and non-CABG-related bleeding. More importantly, 30 mg of prasugrel therapy prior to angiography led to greater life-threatening CABG-related bleeding by a factor of 6. Due to this signal towards harm, the trial was terminated early after recruitment of 4033 of the goal 4100 patients. Thus, prasugrel is not recommended for upstream use prior to PCI in the management of non-ST elevation ACS [1••].

Recent data from the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial evaluated the use of upstream ticagrelor in 1862 patients with STEMI within 6 h of presentation and with qualifying EKG-to-balloon time of under 120 min [25]. Patients were randomized to 180 mg of ticagrelor in the ambulance versus in the cardiac catheterization laboratory, then a maintenance dose of 90 mg twice daily. There was no significant difference in the coprimary endpoints of percentage of patients without at least 70 % resolution of ST segment elevation (odds ratio prehospital to in-lab 0.93; 95 % CI 0.69 to 1.25; $p=0.63$) and percentage of patients without TIMI grade 3 flow in the infarct-related artery prior to PCI (0.97; 95 % CI 0.75 to 1.25; $p=0.82$). Major adverse cardiac events and major bleeding did not differ between the groups, but stent thrombosis, both in-hospital and at 30 days (0.2 versus 1.2 %, $p=0.02$), was significantly lower in the prehospital group.

Current rates of in-hospital CABG in patients presenting with NSTEMI range from 11 to 13 % [26]. Thus, given the concerning bleeding data from ACCOAST and the negative findings from the ATLANTIC trial, the relatively rapid referral to angiography in contemporary ACS management, and the more rapid onset of action of newer antiplatelet agents, the use of oral DAPT prior to defining coronary anatomy in patients with ACS should be considered carefully. If a delay to angiography can be predicted early in the hospitalization, one could consider upstream use clopidogrel or ticagrelor.

Evaluation of Cangrelor

Cangrelor is an intravenous nonthienopyridine adenosine triphosphate analogue which directly and reversibly inhibits the $P2Y_{12}$ receptor [27]. The plasma half-life of the drug is 3–6 min and within 30–60 min of discontinuing the infusion, platelet function returns to normal. The phase II US trial evaluating cangrelor in patients referred for PCI demonstrated dose-dependent platelet inhibition that was comparable to abciximab. However, cangrelor was associated with a faster return of platelet function and less prolongation of bleeding time [28]. This promise of an intravenous, reversible $P2Y_{12}$ inhibitor with quick onset and offset held great clinical appeal to physicians. However, the clinical trial program suffered many challenges, all of which offer insight into the evaluation of such agents in the future.

The first two large randomized trials of cangrelor versus clopidogrel in patients undergoing PCI were the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PCI [29] (n=8877) and CHAMPION PLATFORM [30] (n=5362) trials. Only the CHAMPION PCI trial included patients with STEMI. Both trials randomized patients to clopidogrel and cangrelor (IV bolus of 30 μg/kg followed by a 4-μg/kg infusion), which was started 30 min prior to PCI and continued for at least 2 h or to the completion of PCI, or clopidogrel and placebo. In the CHAMPION PCI trial, patients randomized to the cangrelor group received 600 mg of clopidogrel at the completion of the cangrelor infusion, while patients randomized to the placebo group received 600 mg of clopidogrel 30 min prior to PCI. In the CHAMPION PLATFORM trial, patients in the cangrelor group received 600 mg of clopidogrel at the completion of the cangrelor infusion, while those in the placebo group received 600 mg of clopidogrel at the end of PCI. Both trials failed to show a significant difference in the primary efficacy endpoint of all-cause death, MI, and ischemia-driven target lesion revascularization at 48 h; however, there was a significantly higher rate of minor bleeding with cangrelor. The CHAMPION PLATFORM trial showed a significantly higher rate of stent thrombosis and death at 48 h in the placebo group, as this group had undergone PCI without pretreatment with a second antiplatelet agent. Both trials were stopped early after an interim analysis revealed that they were unlikely to demonstrate superiority of cangrelor. Given that 50 to 60 % of patients in the two trials presented with elevated cardiac biomarkers, questions arose regarding accurate ascertainment of MI as an endpoint in this setting. Subsequently, two further analyses suggested increased benefit of cangrelor in these two trials when the universal definition of MI was utilized [31, 32], with adjudication of periprocedural MIs incorporating baseline abnormality of enzymes and magnitude and trend of biomarker change [33].

The CHAMPION PHOENIX trial sought to evaluate IV cangrelor with the utilization of the universal definition of MI [34]. The trial randomized 11,145 patients undergoing PCI for stable angina (56.1 %), NSTEMI (25.7 %), and STEMI (18.2 %) to cangrelor or clopidogrel load in a placebo-controlled setting similar to CHAMPION PCI [35••]. Patients in the cangrelor group received 600 mg of clopidogrel at the end of the cangrelor infusion, while those in the clopidogrel group received 300 mg (25.6 %) or 600 mg (74.4 %) of clopidogrel after coronary angiography, with 63.4 % receiving the drug prior to PCI. The primary efficacy endpoint of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 h was significantly lower with cangrelor versus clopidogrel load (4.7 vs. 5.9 %, adjusted odds ratio 0.78; 95 % confidence interval, 0.66 to 0.93; p=0.005). Both the unadjusted analysis and the logistic regression model adjusted for baseline cardiac biomarkers (normal versus abnormal) and loading dose of clopidogrel demonstrated similar results. The benefit of cangrelor on the primary endpoint was largely driven by a reduction in the rate of periprocedural MI. Stent thrombosis, which was defined as a composite of the Academic Research Consortium definite stent thrombosis or intraprocedural new or worsening thrombosis adjudicated by an angiographic core lab, was also significantly lower with cangrelor versus clopidogrel (0.8 vs. 1.4 %, odds ratio 0.62; 95 % CI 0.43 to 0.90; p=0.01), as was the use of bailout glycoprotein IIb/IIIa inhibitor (2.3 vs. 3.5 %; odds ratio 0.65; 95 % CI 0.52 to 0.82; p=0.03). There was no significant difference in bleeding endpoints, and, therefore, the overall net adverse clinical event rate favored cangrelor.

The FDA advisory panel voted against the approval of cangrelor for the indication of PCI in February 2014 for several reasons. These concerns included the lack of benefit on outcomes in the first two trials, the suboptimal timing and/or dose of clopidogrel in the comparator arm in the three studies, the efficacy benefit in CHAMPION PHOENIX primarily related to periprocedural MI events (although this included significant reductions in intraprocedural stent thrombosis), and the increase in minor bleeding rates with cangrelor. In the end, despite the favorable results seen in the CHAMPION PHOENIX trial, the FDA panel felt that the overall

risk/benefit ratio associated with cangrelor in comparison to appropriately timed and dosed $P2Y_{12}$ inhibitors did not merit approval.

Other Antiplatelet Agents

Ongoing development of antiplatelet therapy continues due to limitations in currently approved agents, including the lack of availability of intravenous formulation for patients unable to take oral medication, rapid onset and offset pharmacokinetics, and thromboxane A_2 (TXA_2) inhibition for patients with aspirin allergy or inadequate response (Fig. 1). Previous evaluation of elinogrel (Novartis), a reversible $P2Y_{12}$ inhibitor with an intravenous and oral formulation, was evaluated in the INNOVATE-PCI trial of 652 patients with ACS [36••]. This trial demonstrated increased TIMI major and minor bleeding, dyspnea, and hepatic transaminase elevation with elinogrel compared to clopidogrel and the development of the drug was halted. This perhaps further demonstrated that optimal pharmacokinetic profiles in antiplatelet agents do not necessarily translate into improved clinical outcomes.

Inhibition of the thromboxane receptor may offer additional benefits beyond blocking the effect of TXA_2 on platelets, including blocking platelet activation by other ligands. Additionally, some TXA_2 pathway inhibitors also inhibit TXA_2 synthase, thus reducing intracellular signaling. Picotamide and ridogrel are combined thromboxane receptor and TXA_2 synthase inhibitors. Picotamide was evaluated in a randomized trial of diabetic patients with peripheral arterial disease and compared to aspirin resulted in a significant reduction in mortality but no significant difference in the combination of death and nonfatal vascular events [37]. Ridogrel was evaluated in patients with STEMI undergoing fibrinolysis and demonstrated no significant benefit compared to aspirin therapy [38].

Conclusions

Antiplatelet agents remain a central therapy in the treatment of ACS. Continued recurrent cardiovascular events after ACS have sparked ongoing research and development of novel antiplatelet agents. The agents prasugrel and ticagrelor represent a clear advancement in cardiovascular outcomes in patients with ACS. An ongoing clinical need exists for an intravenous agent that would allow a faster onset and offset of antiplatelet therapy. Additionally, optimizing the balance of optimal platelet inhibition to reduce cardiac events while minimizing associated bleeding events remains a challenge. Lastly, clinical trials of new antiplatelet agents will need to address the issues of patient selection, timing and dose of drug delivery in study and comparator arms, and appropriate clinical endpoints.

Compliance with Ethics Guidelines

Conflict of Interest Michael Luna and Elizabeth M. Holper declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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