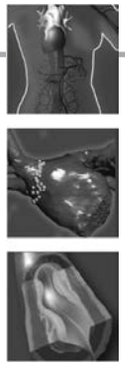

Use of antiplatelet therapies during primary percutaneous coronary intervention for acute myocardial infarction

Inhibition of platelet function is necessary to achieve successful and long-lasting primary percutaneous coronary intervention (PCI) for acute myocardial infarction. For many years, antiplatelet therapy in the setting of primary PCI consisted of two drugs that inhibit platelet activation (aspirin and clopidogrel) and an intravenous blocker of platelet aggregation (abciximab). The development of new, more potent oral antiplatelet drugs (prasugrel and ticagrelor) as well as new data on clopidogrel dosing regimens limited the use of abciximab after pretreatment with aspirin and clopidogrel. Thus, intracoronary administration of abciximab and the use of small molecule glycoprotein IIb/IIIa blockers (tirofiban or eptifibatide) challenge the contemporary schemes of antiplatelet treatment in primary PCI. We review recently published data with particular attention on patients and drug characteristics and propose an update of existing recommendations.

KEYWORDS: acute myocardial infarction ■ antiplatelet therapy ■ aspirin ■ cilostazol ■ clopidogrel ■ glycoprotein IIb/IIIa blockers ■ prasugrel ■ primary percutaneous coronary intervention ■ ticagrelor

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Rupture of the vulnerable atherosclerotic plaque in the coronary artery wall leading to activation and aggregation of platelets to form an artery occluding thrombus is the most frequent cause of acute myocardial infarction (AMI) [1–3]. Cessation of blood flow in the infarct-related artery (IRA) launches the processes of irreversible myocardial injury, which can be stopped by prompt opening of the occluded artery. Primary percutaneous coronary intervention (PCI) defined as stented angioplasty without prior or concomitant fibrinolytic therapy is a preferred method of restoring IRA patency in ST-elevation MI (STEMI) [4,5]. The beneficial effect of primary PCI can be limited by complications related to thrombus defragmentation and distal macroembolization and/or by microembolization caused by aggregates of platelets and inflammatory cells [6]. Therefore, in order to reduce the thrombotic burden and prevent complications of primary PCI such as inadequate reperfusion (also known as no reflow or slow flow) and/or stent thrombosis it is crucial to provide high peri- and post-procedural platelet inhibition [4,5]. Various antiplatelet drugs have been shown to reduce the reperfusion injury and to help maintain patency of the culprit vessel after the procedure [4,7], which results in reduction of the infarct size and recurrent ischemic events as well as its consequences (death, recurrent MI and chronic heart failure). For many years, antiplatelet therapy in the setting of primary PCI included two oral antiplatelet drugs, which irreversibly block platelet activation (aspirin and clopidogrel) together with an inhibition of platelet aggregation by intravenous glycoprotein (Gp) IIb/IIIa blockers (preferably abciximab) [8]. For a long time, the only changes in this standard regimen involved modifications of dosing and timing of antiplatelet therapy. During the last 3 years, we have been witnessing a major change in the schemes of antiplatelet treatment for primary PCI comparable with the introduction of clopidogrel over a decade ago. The most important modifications of antiplatelet therapy presented in this manuscript are related to the development of new, more potent and fast-acting antiplatelet drugs, decreasing evidence for the use of Gp IIb/IIIa blockers, individualization of antiplatelet therapy based on patients and drug characteristics and the growing ability to overcome drug resistance.

Aspirin

Aspirin acts by irreversible blockade of COX-1, a platelet enzyme responsible for the conversion of archidonic acid into thromboxane A_2, which is one of the main stimulators of platelet activation (Figure 1). Aspirin was a cornerstone of antiplatelet therapy in AMI for a long time before the introduction of primary PCI [8]. Over two decades ago, it was demonstrated

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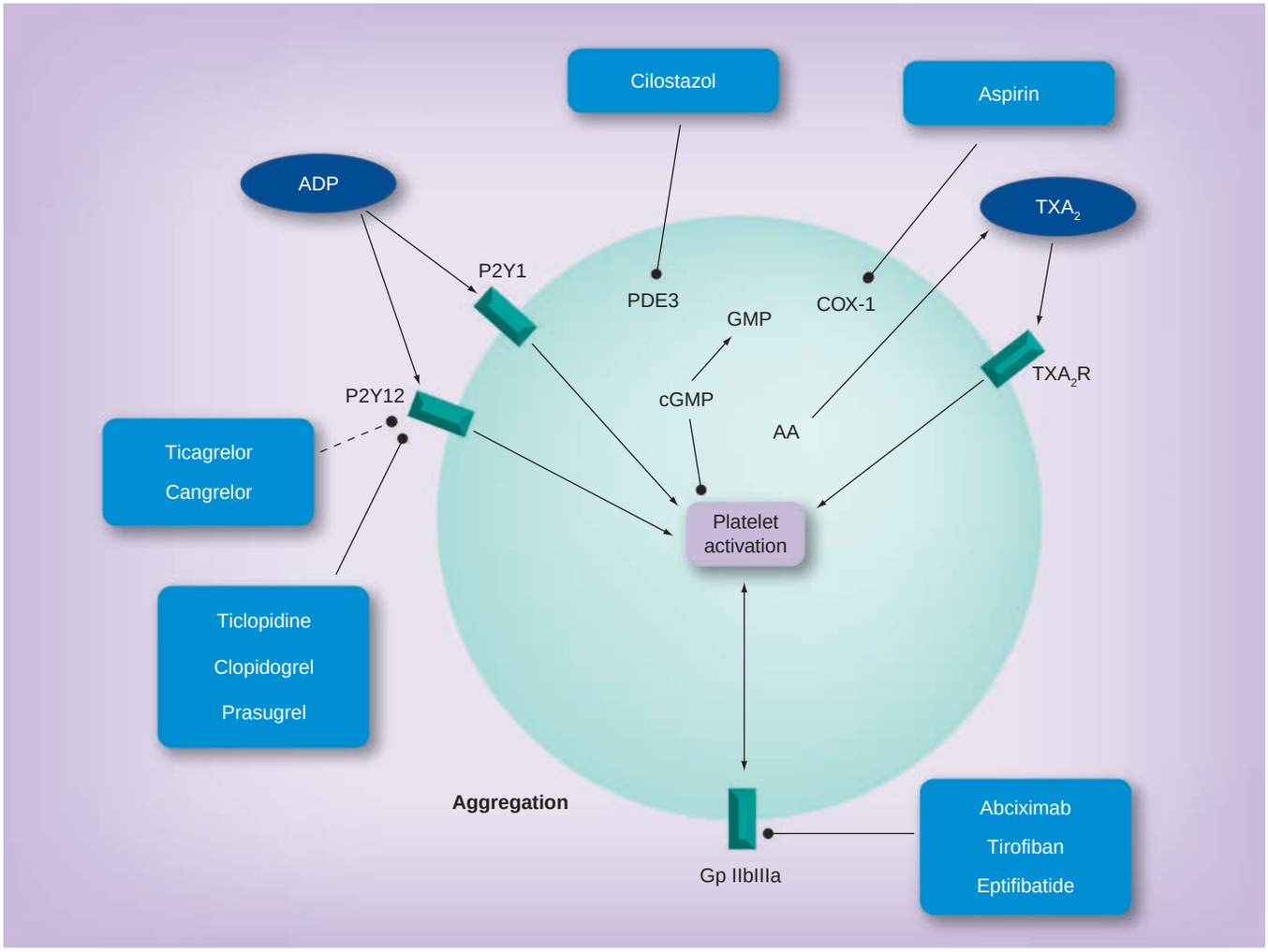

Figure 1. Antiplatelet drugs that have completed Phase III of clinical testing and their targets. Dashed line signifies reversible blockade.
AA: Arachidonic acid; Gp: Glycoprotein; PDE3: Phosphodiesterase 3; TXA_2: Thromboxane A_2; TXA_2R: Thromboxane A_2 receptor.

that aspirin 160 mg daily is almost as efficacious as the fibrinolytic drug, streptokinase [9], leading to 23% relative reduction of cardiovascular mortality at 5 weeks from MI. The undisputable benefit of aspirin treatment in AMI makes it impossible to test the efficacy of this drug in the era of mechanical reperfusion.

The antiplatelet effect of aspirin is observed after 15–30 min from the oral administration of a single 81 mg dose and owing to the irreversible nature of inhibition, the effect lasts for the lifetime of the platelets. The time to the onset of antiplatelet effect is longer for enteric-coated formulations of aspirin. In STEMI, it is recommended to initiate the treatment with a loading dose of 150–325 mg and to continue with a low maintenance dose of 75–160 mg (Table 1). If oral administration of aspirin is not possible, an intravenous bolus injection of 250–500 mg should be used. Higher maintenance doses of aspirin do not cause a more potent antiplatelet effect, but increase the risk of gastrointestinal bleeding [10]. However, recently announced results of the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS) 7 trial (discussed in detail later) demonstrated that the highest anti-ischemic effect of treatment with high doses of clopidogrel (600 mg loading dose, 150 mg/day as a maintenance dose for 7 days and 75 mg/day thereafter) are observed in patients who received a high dose of aspirin (300–325 mg/day) instead of a low dose of aspirin (75–100 mg/day) [11]. The significant interaction between high doses of clopidogrel and aspirin is not well understood and will require more detailed analyses. So far, it has been postulated that high doses of aspirin potentiate the antiplatelet effect of clopidogrel.

Clopidogrel

Clopidogrel is an oral thienopyridine drug that irreversibly blocks the platelet P2Y12 receptor for ADP, which is a stimulator of platelet activation (Figure 1). Clopidogrel is a prodrug that requires hepatic biotransformation to its active metabolite with cytochrome P450 enzymes. The onset of platelet inhibition depends on the initial dose of clopidogrel and ranges from 6 h for a 300 mg loading dose to 2 h for a 600 mg loading dose [12]. For many years, clopidogrel has been the thienopyridine of choice in STEMI as an addition to aspirin despite the lack of randomized trials showing the efficacy of such treatment performed in patients undergoing primary PCI. Only one subanalysis of patients treated primarily with fibrinolysis and subsequently with angioplasty proved that clopidogrel pretreatment reduced ischemic complications before and after PCI [13]. In addition, only one large-scale registry confirmed that adjunctive therapy with clopidogrel is associated with the reduction of 1-year mortality after reperfusion therapy [14]. The recommendation for the use of clopidogrel in the setting of primary PCI is therefore based on the results of clinical trials in patients undergoing PCI in the course of unstable angina or non-STEMI (UA/NSTEMI) such as the Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) trial or the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, which demonstrated an approximate 20% reduction of ischemic events after 1 year [15,16].

According to current guidelines, treatment with clopidogrel before primary PCI should be initiated as soon as possible after the first medical contact and consists of a loading dose of 300–600 mg and a maintenance dose of 75 mg/day (Table 1). However, recent studies demonstrate that the high loading dose of clopidogrel (600 mg) and double maintenance dose (150 mg/day) may be more effective than traditionally recommended doses [11,17]. Higher loading doses of clopidogrel lead to a stronger and more rapid antiplatelet effect, shortening the gap between initiation of treatment and beginning of platelet inhibition. This strategy together with higher maintenance doses of clopidogrel helps to overcome clopidogrel resistance (described later).

In the CURRENT-OASIS 7 trial, more than 25,000 patients (29.2% with STEMI and 70.8% with UA/NSTEMI) with planned early (<72 h) invasive management with intended PCI were randomized to either double dosing of clopidogrel (600 mg loading dose then 150 mg/day for 7 days and 75 mg/day thereafter) or standard dosing (300 mg loading dose then 75 mg/day) [11,18]. A double-dosing strategy led to the reduction of primary end points of cardiovascular death, MI and stroke at 30 days in comparison with standard dosing (3.9 vs 4.5%, respectively), but only in patients who underwent PCI procedure. There were no benefits of the new strategy in patients who did not have PCI owing to lack of significant stenosis on coronary angiogram or the need of coronary artery bypass grafting

Table 1. Summary of current ESC and ACC/AHA/SCAI guidelines on antiplatelet therapy for primary percutaneous coronary intervention.

Drug	ESC 2008	Class of recommendation and level of evidence	ACC/AHA 2004–2009	Class of recommendation and level of evidence
Aspirin	150—325 mg p.o. or 250–500 mg iv.† initially and 75–160 mg p.o. daily	IB	162–325 mg chewed p.o. initially and 75–162 mg p.o. daily	IA or C
Thienopyridines	Clopidogrel 300 and preferably 600 mg loading dose and 75 mg daily	IC	Clopidogrel: 300–600 mg loading dose as soon as possible or at the time of primary PCI and 75 mg daily as maintenance dose Prasugrel: 60 mg loading dose and 10 mg daily as a maintenance dose‡	IC
Gp IIb/IIIa inhibitors	Abciximab iv.	IIA	Abciximab or tirofiban or eptifibatide iv. at the time of primary PCI in selected patients	IIA

†*If oral ingestion is not possible.*
‡*Contraindicated in patients with prior stroke or transient ischemic attack.*
ACC: American College of Cardiology; AHA: American Heart Association; ESC: European Society of Cardiology; iv.: Intravenous; PCI: Percutaneous coronary intervention; p.o.: Per os*; SCAI: Society for Cardiovascular Angiography and Interventions.*
Data taken from [4,27].

(CABG). The reduction of primary end points was mainly related to the decreased frequency of MI (2.0 vs 2.6%) and definite stent thrombosis (0.7 vs 1.2%) with no difference in the rates of cardiovascular deaths or strokes. The reduction of recurrent MI and stent thrombosis was higher in the subgroups of patients with STEMI, in females and smokers and in patients treated with higher doses of aspirin (as previously discussed). Double-dosing strategy was related to modest excess in major bleeding, but there was no difference in thrombolysis in myocardial infarction (TIMI) major bleeding, intracranial bleeding, fatal bleeding or CABG-related bleeding. Therefore, double-dosing strategy may become a routine regimen at least for the first 7 days of treatment in acute coronary syndromes and especially in patients undergoing primary PCI.

Other recently addressed issues regarding clopidogrel treatment in patients undergoing PCI confirmed that those who are already on long-term clopidogrel treatment benefit from reloading (with 300–900 mg) at least in terms of reduction of residual platelet inhibition [19]. However, single loading dose escalation above 600 mg is not superior to a 600 mg loading dose because it does not lead to additional significant suppression of platelet function mostly due to limited absorption of clopidogrel [20].

New P2Y12 receptor inhibitors

The leading position of clopidogrel as a second antiplatelet drug in patients undergoing primary PCI has been recently challenged with the announcement of the results of clinical trials on new, more potent and fast-acting P2Y12 receptor inhibitors (Figure 1).

■ Prasugrel

Prasugrel is an orally administered thienopyridine prodrug requiring hepatic biotransformation to an active metabolite. It irreversibly inhibits platelet P2Y12 receptor and is currently registered for clinical use. Contrary to clopidogrel hepatic biotransformation of prasugrel is mostly dependent on esterases and less on cytochrome P450 enzymes, which results in less variable and faster response to the 60 mg loading dose of a drug in comparison with both 300 and 600 mg loading doses of clopidogrel [21–23]. The maintenance dose of prasugrel 10 mg/day also results in a stronger platelet inhibition than maintenance doses of clopidogrel 75 or 150 mg. The onset of action of prasugrel after administration of 60 mg loading dose can be observed after 30 min.

The TRITON-TIMI 38 trial randomized 13,608 patients with acute coronary syndromes and scheduled PCI procedure to treatment with prasugrel (60 mg loading dose and a 10 mg/day maintenance dose) or clopidogrel (300 mg loading dose and 75 mg/day maintenance dose) [24]. After 6–15 months of treatment the primary efficacy end points of cardiovascular death, MI or stroke occurred in 12.1% of patients on clopidogrel and 9.9% patients on prasugrel making a highly significant difference. Prasugrel therapy resulted in the marked reduction of individual end points such as MI (7.3 vs 9.5%), the need of urgent revascularization (2.5 vs 3.7%) and definite or probable stent thrombosis (1.1 vs 2.4%). The cost of more potent platelet inhibition consisted of more frequent TIMI major bleeding (2.4 vs 1.8%, respectively), life-threatening bleeding (1.4 vs 0.9%) and fatal bleeding (0.4 vs 0.1%) particularly in the setting of CABG. However, the net clinical benefit favored prasugrel. It has been calculated that treatment with prasugrel prevented 138 ischemic events, but provoked 35 additional non-CABG-related major bleeding events in the whole studied population. The net clinical benefit was more pronounced in a subgroup of patients with diabetes [25]. Owing to the particularly high risk of bleeding events prasugrel is contraindicated in patients with a history of transient ischemic attack or stroke. It is not recommended in patients over 75 years of age, in patients under 60 kg of bodyweight and in patients likely to undergo CABG.

A subanalysis of 3534 patients with STEMI from the TRITON-TIMI 38 trial revealed a higher 3.0% absolute risk reduction of the primary end point without an increase of TIMI major bleeding unrelated to CABG surgery and fatal or life-threatening bleeding in comparison with the whole studied population [26]. The only increase in bleeding events was observed for TIMI major and TIMI major/minor bleeding after CABG surgery. The anti-ischemic effect of prasugrel was higher in patients who received Gp IIb/IIIa inhibitors and in patients with anterior MI. Surprisingly, the benefits of prasugrel over clopidogrel treatment in STEMI were only observed in 1094 patients enrolled between 12 h and 14 days after symptom onset (secondary PCI). In 2438 patients who had primary PCI (enrolled within 12 h from the onset of symptoms), there was no significant difference in the frequency of recurrent ischemic events in comparison with clopidogrel both at 30 days and at 15 months. On the contrary, the reduction of

stent thrombosis at 30 days and 15 months was observed in patients undergoing primary PCI, but not in those undergoing secondary PCI.

Criticism of the TRITON-TIMI 38 trial was mainly related to the fact that anatomy of coronary arteries was known before randomization and therefore, future administration of prasugrel in the prehospital phase may lead to more bleeding events caused by eventual CABG surgery. Second, prasugrel was compared with 300 mg loading dose and 75 mg/day maintenance dose of clopidogrel – a regimen that is no longer optimal in the setting of acute coronary syndromes. The confirmation of a stronger platelet inhibition observed with prasugrel in comparison with a 900 mg loading dose of clopidogrel or 150 mg/day maintenance dose does not necessarily need to translate into significant reductions of recurrent ischemic events [22]. Therefore, we will have to wait for the results of the prospective clinical trial comparing clinical efficacy of the treatment with prasugrel or higher does of clopidogrel to adequately compare those two drugs. Based on the results of the TRITON-TIMI 38 trial, prasugrel is the only new P2Y12 receptor inhibitor to receive class I, level of evidence B recommendation for the use in primary PCI in the new American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions guidelines (Table 1) [27]. From a practical point of view, it seems reasonable to consider prasugrel treatment in selected patients undergoing primary PCI such as those at the highest risk of recurrent ischemic events, patients at higher risk of developing stent thrombosis or its consequences (patients with left main coronary artery stenting or after stenting of the last patent coronary artery), patients with known or suspected clopidogrel resistance, patients who developed stent thrombosis when on clopidogrel therapy or in patients with diabetes (although higher doses of clopidogrel may be an attractive alternative in all those clinical situations).

■ Ticagrelor

The second of the new drugs is ticagrelor, it is the first oral, reversible, direct-acting (without biotransformation) compound that blocks platelet signaling through activation of the P2Y12 receptor. It leads to faster and stronger platelet inhibition compared with 600 mg loading dose and 75 mg maintenance dose of clopidogrel (Figure 1) [28]. Owing to the reversible nature of platelet inhibition its offset after drug discontinuation is faster than observed for clopidogrel. Platelet inhibition on days 3 and 5 after the last dose of ticagrelor is comparable with platelet inhibition after 5 and 7 days from discontinuation of clopidogrel, respectively [28].

The Phase III PLATO trial randomized 18,624 patients with a broad range of acute coronary syndromes to treatment with ticagrelor (180 mg loading dose and 90 mg twice daily thereafter) or clopidogrel (300 mg or 600 mg loading dose in patients undergoing PCI and 75 mg daily thereafter) [29]. The primary end point of death from vascular causes, MI or stroke at 12 months occurred less often in patients receiving ticagrelor (9.8%) in comparison with patients on clopidogrel (11.7%). Ticagrelor markedly reduced the frequency of cardiovascular death (4.0 vs 5.1% for clopidogrel), death from any cause (4.5 vs 5.9%) and definite stent thrombosis (1.3 vs 1.9%), MI (5.8 vs 6.9%), but not strokes alone (1.5 vs 1.3%). Treatment with ticagrelor did not result in higher rate of major bleeding (11.6 vs 11.2% for clopidogrel) or overall incidence of fatal bleeding (0.3 vs 0.3%), but it was associated with a higher rate of major bleeding not related to CABG surgery (4.5 vs 3.8% for clopidogrel) including more cases of fatal intracranial bleeding (0.1 vs 0.01%) and fewer of fatal bleeding of other types. Ticagrelor therapy was related to a higher rate of dyspnea during the first week of therapy and to a more frequent occurrence of ventricular pauses on Holter ECG monitoring, which were however rarely associated with symptoms. The Study of the Onset and Offset of Antiplatelet Effects Comparing AZD6140, Clopidogrel, and Placebo With Aspirin (ONSET/OFFSET) analyzed potential causes of dyspnea with ECG assessment of left ventricular ejection fraction, serum N-terminal prohormone brain natriuretic peptide and comprehensive pulmonary function tests and found no differences in any of the measures between the ticagrelor group and either the clopidogrel or the placebo arm [28]. However, the side effects might have been responsible for the significantly higher discontinuation rate observed with ticagrelor in comparison with clopidogrel (1.4% absolute difference).

Subanalysis of 8430 patients with STEMI and onset of symptoms during the previous 24 h in whom primary PCI was planned presented at the AHA Scientific Sessions in 2009 in Orlando (FL, USA) confirmed the significant difference in the frequency of the primary end point (9.3% in the ticagrelor group and 11.0% in the clopidogrel arm) [30]. In contrast to prasugrel, there was no significant difference in primary

efficacy end point when STEMI patients were divided according to the time from index event to therapy (<12 h in 72% of patients and ≥12 h in 28% of patients). Furthermore, there were statistically significant reductions in several secondary end points, including MI and all-cause mortality. Academic research consortium definite and definite or probable stent thrombosis rates were also lower with ticagrelor. The rate of major bleeding events, the need for blood transfusion and fatal bleeding rates were not different between the two groups. Dyspnea-related study drug discontinuation was relatively infrequent, but occurred more often in the ticagrelor group (0.5 vs 0.1%).

In summary, due to its favorable clinical profile and clinical evidence of benefit in patients undergoing primary PCI, ticagrelor may become an attractive alternative to clopidogrel once it is made available for clinical use. The main indications for the use of ticagrelor will be similar to those described for prasugrel, but this drug may have additional advantages in patients with unclear revascularization strategy or those who may need surgery in a short time, but not urgent surgery as it still takes 3–5 days to fully reverse the action of the drug. Potential disadvantages of ticagrelor include the twice daily administration regimen and higher rates of drug discontinuation in comparison with clopidogrel due to dyspnea and ventricular pauses on Holter monitoring.

The comparison of the main results of the recently announced trials on P2Y12 receptor inhibitors in patients with acute coronary syndromes is presented in Table 2.

■ Cangrelor

The third of the recently studied drugs is cangrelor; an intravenous, direct-acting nonthienopyridine formulation, which selectively and reversibly blocks the ADP receptor P2Y12 (Figure 1). It has a plasma half-life of 3–6 min and platelet function after discontinuation of treatment normalizes within only 30–60 min [31].

The Phase III Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PCI trial included a total of 8877 patients with stable angina, unstable angina, NSTEMI or STEMI (996 patients) randomized to treatment with cangrelor or placebo (30 µg/kg bolus and 4 µg/kg/min infusion) beginning within 30 min before PCI and continued for at least 2 h or until conclusion of the index procedure, whichever was longer [32]. Patients in the placebo arm received clopidogrel 600 mg at the time of infusion and those in the cangrelor arm at discontinuation of infusion. The duration of clopidogrel therapy after the procedure was left to the discretion of the treating physician. The study demonstrated that cangrelor is not superior to clopidogrel with respect to primary end point of death from any cause, MI or ischemia-driven revascularization assessed at 48 h (7.5 vs 7.1%). Similar results were observed at 30 days. There was a trend towards a higher incidence of major bleeding with cangrelor (3.6 vs 2.9% for clopidogrel), but this was not the case for major bleeding assessed with the TIMI scale or severe/life-threatening bleeding in the Global Utilization of Streptokinase and Tissue

Table 2. Comparison of the main results of the recently announced trials on P2Y12 receptor inhibitors in patients with acute coronary syndromes.

Parameter	TRITON-TIMI 38 (n = 13,608) [24]	CURRENT-OASIS 7 (n = 17,232) [11]	PLATO (n = 18,624) [28]
Studied group	STEMI: 26% UA/NSTEMI: 74%	STEMI: 29.2% UA/NSTEMI: 70.2%	STEMI: 37.5% UA/NSTEMI: 59.5%
Compared regimen	ASA: 75–162 mg Clopidogrel: 300 mg/75 mg	ASA: low dose (75–100 mg) or high dose (300–325 mg) Clopidogrel: 300 mg/75 mg	ASA: 325 mg/75 mg Clopidogrel: 300–600 mg (with PCI)/75 mg
Time of follow-up	6–15 months	30 days	12 months
CV death, MI and stroke at 30 days	-19%	-15% -21% with high-dose ASA	-16%
Definite stent thrombosis	-58%	-42% -51% with high-dose ASA	-33%
TIMI major bleeding	+32	No increase	No increase
CABG-related bleeding	Fourfold increase	No increase	No increase
Fatal bleeding	Fourfold increase	No increase	No increase

ASA: Acetylsalicylic acid; CABG: Coronary artery bypass graft; CV: Cardiovascular; MI: Myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis in myocardial ischemia.
Data taken from [11].

Plasminogen Activator for Occluded Coronary Arteries (GUSTO) scale. The results were similar in the small subset of patients with STEMI, but patients undergoing primary PCI were not analyzed separately.

In summary, negative results of the CHAMPION PCI trial demonstrate that at least for now there is no use for cangrelor in the setting of primary PCI. An ongoing Maintenance of Platelet Inihibition With Cangrelor After Discontinuation of Thienopyridines in Patients Undergoing Surgery (BRIDGE) study is trying to assess the clinical utility of cangrelor as a bridge before surgery in patients with acute coronary syndrome after discontinuation of clopidogrel treatment [101]. Another potentially interesting but unstudied application of cangrelor refers to unconscious patients who are unable to receive oral P2Y12 inhibitors (e.g., clopidogrel and prasugrel).

■ Elinogrel

The last of the new drugs is elinogrel; a selective, direct acting and reversible P2Y12 inhibitor available in both intravenous and oral forms. Intravenous administration of elinogrel results in immediate onset of action and oral administration has a potential for less interpatient variability. The drug is administered as an intravenous bolus and then continued orally twice a day. Elinogrel is currently being tested in a Phase II trial on patients requiring nonurgent PCI, but positive safety results may open the field for drug testing in patients with acute coronary syndromes [102].

Phosphodiesterase inhibitors

Cilostazol is an oral drug with antiplatelet effects and acts on platelet activation via the selective inhibition of phosphodiesterase (PDE) 3 (Figure 1). The drug is not included in the contemporary guidelines for STEMI but several studies recently performed in Asia demonstrate interesting results. In a large retrospective analysis of 4203 patients undergoing primary PCI in Korea triple antiplatelet therapy (aspirin: 200 mg loading dose and 100 mg/day maintenance dose; clopidogrel: 300–600 mg loading dose and 75 mg/day maintenance dose; and cilostazol: 200 mg loading dose and 100 mg/day maintenance dose twice daily for at least 1 month) was related to lower incidence of in-hospital and 8-month mortality compared with dual antiplatelet therapy (aspirin and clopidogrel) with similar frequency of major bleeding events [33]. Subgroup analysis demonstrated more benefits from triple antiplatelet therapy in patients over 65 years of age, in females and in diabetics. These results are in agreement with observations from a randomized study on 1212 patients with acute coronary syndrome undergoing PCI (36% with STEMI) where triple antiplatelet therapy significantly reduced the incidence of major adverse cardiac or cerebral events without excess of bleeding at 30 days and at 1 year [34]. Cilostazol was found to have not only antiplatelet but also vasodilatory and antimitogenic effects, which may limit the rate of in-stent restenosis and the need of repeat vascularization [35]. However, it should be noted that up to 15% of patients discontinued the treatment with cilostazol owing to side effects (e.g., gastrointestinal symptoms, skin rash and headaches).

Antiplatelet drug resistance

Resistance to antiplatelet drugs has been a matter of debate for almost a decade and is presented in detail in other reviews and meta-analyses [36–40]. Although this phenomenon was shown to impact patients prognosis in most situations there is no recommendation on screening for antiplatelet drug resistance with means of platelet function testing. However, it seems accepted that patients who are found to be clinically or biochemically resistant require modification of antiplatelet therapy. Currently, there are several alternative treatment options available. First, it was demonstrated that repeated loading doses of clopidogrel (up to 2400 mg) and/or high maintenance dose (150 mg/day) may almost eliminate the resistance to this drug [41,42]. Recently, it has been also shown that the response to clopidogrel and prognosis in patients with AMI are worse in carriers of the genetic variant 681 G>A (*2) of cytochrome P450 (*CYP2C19*), which is involved in biotransformation of clopidogrel [43–47]. This polymorphism does not affect active drug metabolite levels, inhibition of platelet aggregation or clinical cardiovascular event rates in patients treated with prasugrel [48]. An ability to overcome clopidogrel resistance was also demonstrated for two direct-acting drugs (not requiring hepatic biotransformation) – ticagrelor [49] and elinogrel [50]. Another strategy proven to limit clopidogrel resistance is adjunctive use of cilostazol in combination with dual antiplatelet therapy with aspirin and clopidogrel [51]. It was also shown that patients undergoing elective PCI who were poor responders to aspirin and/or clopidogrel benefit from the administration of Gp IIb/IIIa blocker as demonstrated by a study using a high-dose bolus of tirofiban [52].

Gp IIb/IIIa blockers

The rationale for the use of most potent antiplatelet drugs is that Gp IIb/IIIa blockers in patients with STEMI improve coronary perfusion after reopening of the occluded IRA (Figure 1 & Table 1). It has been established that suboptimal reperfusion caused by distal macro- or microembolization is a strong and independent risk factor of worse left ventricular function and affects prognosis [53]. Meta-analyses including data from the ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT), Intracoronary Stenting and Antithrombotic Regimen (ISAR)-2, Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC), The Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up (ADMIRAL), The Abciximab and Carbostent Evaluation (ACE) and other smaller trials demonstrated that the use of abciximab in patients with STEMI undergoing primary PCI leads to the reduction of short- and long-term mortality [54–56]. It should be noted however that those trials were performed before the wide introduction of clopidogrel treatment [57–61]. Moreover, baseline antiplatelet therapy consisted of ticlopidine treatment 250 mg twice daily or clopidogrel 75 mg daily without a loading dose. It was subsequently proven that blood concentration of the active form of ticlopidine or clopidogrel reaches therapeutic level after a few days of treatment and that a loading dose of clopidogrel leads to faster onset of action and improves prognosis [12]. Before that era, most patients had inadequate platelet inhibition in the periprocedural phase, which might have worsened the prognosis. The addition of Gp IIb/IIIa blockers before or during primary PCI was filling the time gap between the initiation of therapy with thienopyridines and acquisition of adequate platelet inhibition.

Recent data question the value of Gp IIb/IIIa inhibitors in primary PCI in the era of prehospital treatment with high loading doses of aspirin and clopidogrel and an offspring of new potent and fast-acting antiplatelet and anti-thrombin drugs. There are at least three clinical trials and one large registry that address this issue. First, the Bavarian Reperfusion Alternatives Evaluation (BRAVE)-3 trial randomized patients with STEMI undergoing PCI within 24 h from the onset of pain to receive either intravenous abciximab or placebo in a catheterization laboratory in addition to a loading dose of clopidogrel 600 mg and a loading dose of aspirin 500 mg [62]. The primary end point of infarct size measured by means of SPECT at 5–7 days postrandomization was similar in both study groups. There was also no difference in relation to single or combined secondary end points of 30-day mortality, stroke, nonfatal MI or urgent target vessel revascularization between two treatment strategies. At the same time abciximab infusion more frequently caused thrombocytopenia and tended to increase minor bleeding events. The authors of the study concluded that in patients with STEMI treated with primary PCI who received pretreatment with high loading dose of clopidogrel, the addition of abciximab does not reduce the infarct size.

Another large trial on the use of abciximab in primary PCI – the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial – randomized 3602 patients to receive either unfractionated heparin (UFH) plus a Gp IIb/IIIa blocker (abciximab or high-dose bolus of tirofiban) or bivalirudin with provisional IIb/IIIa blockers [63]. Patients in both groups received a loading dose of aspirin (324 mg chewed or 500 mg intravenous) and clopidogrel (300 or 600 mg). At 1-year cardiac and noncardiac mortality and major (non-CABG)-related bleeding rates were higher among patients treated with Gp IIb/IIIa blockers and UFH than among those who received bivalirudin. However, it should be noted that the occurrence of acute stent thrombosis (≤24 h), but not subacute stent thrombosis was significantly higher in patients treated with bivalirudin. This fact raised serious concerns and might have been related to ADP-induced platelet activation before maximal thienopyridine blockade of the P2Y12 receptor or to residual thrombin activity after the discontinuation of bivalirudin [63]. Those concerns have led to the ongoing BRAVE-4 trial evaluating combination of UFH and clopidogrel in comparison with bivalirudin and the more potent, fast-acting P2Y12 inhibitor, prasugrel, in patients with AMI undergoing emergency catheterization and coronary intervention [103].

The findings of those trials are supported by the large real-life STEMI registry comprising 7193 patients undergoing primary PCI [64] in which all patients received pretreatment with aspirin 300 mg and various regimens of other antiplatelet drugs. There were four possible scenarios: treatment with Gp IIb/IIIa blockers alone, a loading dose of clopidogrel 300 mg alone, combination of Gp IIb/IIIa blockers and clopidogrel or no other antiplatelet

therapy. Propensity-adjusted survival analysis showed no additive effect on 1-year survival for combination therapy with Gp IIb/IIIa blockers and clopidogrel in comparison to treatment with clopidogrel alone or Gp IIb/IIIa blockers alone.

Therefore, current ACC/AHA 2009 STEMI and PCI guidelines state that the use of Gp IIb/IIIa blockers as an addition to dual-antiplatelet therapy with UFH or bivalirudin may be useful at the time of primary PCI but only in selected patients and not as a routine therapy [27]. An example of patients who may still benefit from therapy with Gp IIb/IIIa blockers come from the recent update meta-analysis of trials on adjunctive Gp IIb/IIIa blocker use in primary angioplasty [65]. The study was based on 16 trials (including newer studies such as BRAVE-3, HORIZONS-AMI, Ongoing Tirofiban In Myocardial infarction Evaluation [on-TIME 2] and Primary Percutaneous Coronary Angioplasty With and Without Eptifibatide in ST-segment Elevation Myocardial Infarction [ASSIST]) on 10,085 patients and demonstrated that Gp IIb/IIIa blockers did not reduce 30 day mortality or re-infarction rates and were associated with higher risk of major bleeding. However, there was a significant relationship between a patient's risk profile and benefits from adjunctive Gp IIb/IIIa blockers in terms of death, but not reinfarction. Therefore, patients at the highest risk of negative outcomes as assessed, for example, with the use of TIMI risk score remain as good candidates for adjunctive Gp IIb/IIIa blocker administration in catheterization laboratory in addition to prehospital aspirin and clopidogrel. This form of therapy may be still valuable in patients who did not receive preprocedural thienopyridine therapy as demonstrated another analysis of previously published trials [66].

There is an ongoing debate on the timing of Gp IIb/IIIa blocker administration for primary PCI. In the ADMIRAL trial, 300 patients with STEMI scheduled for primary PCI with stenting were assigned to early or periprocedural abciximab or placebo [58]. Treatment with abciximab improved coronary patency before stenting, the success rate of stenting procedure, the rate of coronary patency at 6 months and left ventricular function and clinical outcomes at 30 days and at 6 months. The benefits of abciximab were observed only in the subgroup of patients (26%) in whom treatment with abciximab was initiated before or during transportation to the catheterization laboratory (in the ambulance or emergency department), but not in those who were randomized in the hospital phase (in the intensive care unit or in the catheterization laboratory). It should be noted however that the antiplatelet cotherapy included aspirin and ticlopidine (250 mg twice daily) initiated after stenting, which due to the fact of long latency between the initiation of treatment with ticlopidine and onset of platelet inhibition, limits the value of those results in the current era. More recent trials analyzing the issue of timing of Gp IIb/IIIa blockers do not support the findings of the ADMIRAL trial. In the Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) trial patients scheduled for primary PCI were randomized to prehospital combination of half-dose fibrinolytic agent plus abciximab, prehospital abciximab alone or abciximab at the time of PCI [67]. None of the studied facilitation strategies significantly improved clinical outcomes compared with abciximab administered at the time of primary PCI. Based mainly on the results of this trial, the 2009 ACC/AHA guidelines on STEMI retained the previous recommendation on uncertain benefit of the use of Gp IIb/IIIa inhibitors before primary PCI (class IIB, level of evidence B) [27]. This recommendation is supported by another study in which treatment with eptifibatide plus heparin versus heparin alone initiated before cardiac catheterization on top of aspirin 160 mg and clopidogrel 600 mg did not improve clinical outcomes and was associated with more bleeding complications at 30 days [68]. In fact, only one of the recent large trials, the on-TIME 2 study, comparing early, prehospital administration of high-dose of tirofiban versus placebo in addition to clopidogrel 600 mg and aspirin 500 mg showed a marked 1-year improvement of survival in the tirofiban arm in the subset of patients undergoing primary PCI [69].

For many years abciximab has been the preferred agent for patients undergoing primary PCI due to the largest set of randomized trials [57–61]. However, several recently published clinical trials [70–72] and their meta-analysis [73] demonstrated no difference in outcomes between abciximab and small-molecule Gp IIb/IIIa blockers (e.g., tirofiban and eptifibatide) in terms of short-and long-term mortality, re-infarction, strokes or major bleeding. Based on the results of those trials current 2009 ACC/AHA guidelines on STEMI upgraded the recommendation on the use of small molecule Gp IIb/IIIa inhibitors at the time of primary

Table 3. Proposed modification of existing recommendations for antiplatelet treatment in primary percutaneous coronary intervention including drugs registered for clinical use.

Drug	When	Loading dose	Maintenance dose
Aspirin	As soon as possible	Oral chewable, nonenteric-coated 150–325 mg iv. 250–500 mg if p.o. not possible	75–100 mg daily (300–325 mg for 30 days in patients on clopidogrel?)
Clopidogrel or prasugrel	As soon as possible	Clopidogrel: 600 mg Prasugrel: 60 mg	Clopidogrel: 150 mg for 7 days, then 75 mg daily possible Prasugrel: 10 mg daily
Abciximab, eptifibatide or tirofiban	At the time of primary PCI in selected patients	Abciximab: standard bolus dose (iv. or ic.) then iv. infusion Eptifibatide: double bolus (iv. or ic.) then iv. infusion Tirofiban: higher bolus dose (iv. or ic.) then iv. infusion	N/A

ic.: Intracoronary; iv.: Intravenous; N/A: Not applicable; p.o.: Per os.

PCI (with or without stenting) in selected patients (as described above) from class IIb to IIa (level of evidence B) [27].

The drawback of Gp IIb/IIIa inhibitors as a recommended strategy accompanying primary PCI in STEMI may be reduced by recent communications suggesting that intracoronary instead of intravenous bolus of abciximab resulting in high local drug concentrations may be more effective [74]. In the randomized trial, Thiele *et al.* demonstrated that the new regimen consisting of intracoronary bolus and 12 h intravenous infusion resulted in the significant reduction of infarct size, the extent of microvascular obstruction as assessed with cardiac magnetic resonance as well as improvement in perfusion and a trend towards lower rates of major adverse cardiac events. It has been shown that the advantages of intracoronary bolus administration of abciximab may be related to more powerful anti-inflammatory effects of the drug as evidenced by a larger reduction of the inflammatory reaction marker sCD40L compared with the standard intravenous bolus [75]. Several clinical trials has been initiated to further analyze the potential benefits of local, intracoronary bolus administration of abciximab in primary PCI either as sole therapy [76,104] or when accompanied by thrombus aspiration [76,77]. The benefits of the new administration strategy may be also seen with the use of small-molecule Gp IIb/IIIa blockers as shown in the recently published ICE (with eptifibatide) trial [78] or a nonrandomized study on tirofiban [79].

Future perspective

The field of antiplatelet therapy adjunctive to primary PCI is undergoing a fast evolution, which in the near future will result in tailoring of therapy based on patients and drug characteristics. The decision on administration of antiplatelet drugs in the prehospital phase and/or in catheterization laboratory will be based on the history of previous antiplatelet treatment and its complications including drug resistance or stent thrombosis (potent platelet inhibition preferred: high doses of clopidogrel, prasugrel and ticagrelor), time to beginning of primary PCI (fast-acting drugs preferred if short: prasugrel, ticagrelor and Gp IIb/IIIa blockers), the risk of bleeding complications and the possibility of surgery in the short term (reversible drugs with favorable safety profile preferred: ticagrelor and cangrelor), the overall risk of recurrent ischemic events (potent platelet inhibition preferred: prasugrel, ticagrelor, high doses of clopidogrel and Gp IIb/IIIa blockers), the risk of distal embolization (potent platelet inhibition in the IRA: intracoronary Gp IIb/IIIa blockers) or patients condition (intravenous drugs: cangrelor and possibly elinogrel in unconscious patients). The suggested changes in recommendations for antiplatelet therapy in primary PCI implementing the results of recently published clinical trials are presented in Table 3.

There are several other potentially interesting targets of antiplatelet therapy at the advanced phase of clinical testing [105], which may further expand the choice of antiplatelet drugs for primary PCI. The most promising drugs include platelet PAR-1 receptor inhibitors for thrombin such as SCH 530348 now in Phase III testing (TRA-CER trial in patients with NSTEMI [105]) or E5555 now in Phase II testing in patients with acute coronary syndromes [106] and antibodies against von Willebrand factor – now in Phase II testing in patients with stable/unstable coronary artery or NSTEMI undergoing PCI [107].

Executive summary

Aspirin

- Main antiplatelet drug for primary percutaneous coronary intervention (PCI).
- 300–325 mg loading dose administered as early as possible before the procedure with a maintenance dose of 75 mg daily.
- Possible higher efficacy of higher maintenance dose (300–325 mg) when administered with clopidogrel.

Clopidogrel

- Main antiplatelet drug for primary PCI.
- 600 mg loading dose administered as early as possible before the procedure.
- Higher clinical efficacy demonstrated for 150 mg maintenance dose over standard 75 mg maintenance dose.

New P2Y12 receptor inhibitors

- Higher clinical efficacy over clopidogrel in acute coronary syndrome shown for two drugs – prasugrel (oral, selective, irreversible and nondirect acting) and ticagrelor (oral, selective, reversible and direct acting).
- Lack of higher clinical efficacy over clopidogrel in acute coronary syndrome demonstrated for cangrelor (intravenous, selective, reversible and direct acting).

Phosphodiesterase inhibitors

- Higher clinical efficacy in primary PCI demonstrated for combination of cilostazol, aspirin and clopidogrel over aspirin and clopidogrel alone.

Drug resistance

- Clinical efficacy of aspirin and clopidogrel reduced by drug resistance.
- Drug resistance limited/eliminated with high doses of clopidogrel, prasugrel, ticagrelor, elinogrel, cilostazol or Gp IIb/IIIa inhibitors.

Glycoprotein IIb/IIIa blockers

- Main antiplatelet cotherapy in primary PCI.
- Evidence of reduced utility when used on top of prehospital treatment with high loading doses of aspirin and clopidogrel.
- Similar clinical efficacy of all Gp IIb/IIIa blockers (abciximab, eptifibatide and high-dose tirofiban).
- Possible higher clinical efficacy demonstrated for 150 mg maintenance dose over standard 75 mg maintenance dose for 7 days after primary PCI.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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