Pretreatment With Antiplatelet Drugs in Invasively Managed Patients With Coronary Artery Disease in the Contemporary Era

Review of the Evidence and Practice Guidelines

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Antiplatelet therapy is the mainstay of pharmacological management in patients with coronary artery disease (CAD) manifestations, particularly those with an acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI).[1] In these settings, platelet inhibition with aspirin and a $P2Y_{12}$ receptor inhibitor is associated with ischemic benefit, although this may occur at the expenses of an increased risk of bleeding.[2–4] Clopidogrel is the most studied $P2Y_{12}$ receptor and still represents the most used across the globe. However, a major conundrum in clinical practice, which has been amplified during the recent years with the development of novel antiplatelet therapies, both oral (prasugrel and ticagrelor) and intravenous (cangrelor), is whether patients undergoing an invasive evaluation should be pretreated with a $P2Y_{12}$ receptor inhibitor.[5] The introduction of novel antiplatelet therapies has also led to question the role of pretreatment with glycoprotein IIb/IIIa receptor inhibitors (GPI).[6]

Although the need for adequate platelet inhibition is emphasized among invasively managed patients with CAD, the evidence supporting pretreatment, particularly with $P2Y_{12}$ inhibitors, is somewhat scarce. Indeed, changes in practice patterns in the current era of ACS management, which is typically characterized by shorter timeframes from clinical presentation to the cath-laboratory, have fueled the debate on the benefits of pretreatment. On one side, proponents of pretreatment call into question the need for safeguarding the patient from ischemic events in the early vulnerable period before and immediately after PCI.[7] On the other side, challengers of pretreatment raise concerns over the putative unnecessary excess of platelet inhibition and related bleeding risk when patients do not undergo PCI (ie, when medical management or coronary artery bypass grafting [CABG] is needed).[8] Overall, in view of the conflicting data and the newly available studies exploring the effect of pretreatment with antiplatelet drugs versus in-hospital administration, there is a clinical need for reappraising the effect of early initiation of antiplatelet therapy on clinical outcomes of patients undergoing invasive management. This article summarizes the current evidence on pretreatment with oral and intravenous antiplatelet agents administered on top of aspirin therapy in patients across the spectrum of CAD manifestations undergoing invasive management.

Pretreatment: Definitions

The term pretreatment encompasses a variety of different scenarios, in which a drug is given in the ambulance, at the referral hospital, in the medical emergency department, in the cardiac intensive care unit, or even in the cath-laboratory after coronary angiography and before PCI. For the purpose of the present review, pretreatment is intended as any treatment given before the coronary anatomy has been defined and a decision about revascularization is undertaken.

Guidelines for non–ST-segment–elevation ACS (NSTE-ACS) emphasize the need for early invasive strategies to prevent recurrent ischemia or improve short- and long-term outcomes, with the timing of angiography dependent on the risk profile of the individual patient (ie, troponin elevation, diabetes mellitus, ST-segment depression, and renal insufficiency) and the acuteness of risk.[9–12] In parallel, in recent years, there has been a substantial interest in elaborating transfer protocols and networks for minimizing delays in patients with ST-segment–elevation myocardial infarction (STEMI) undergoing primary PCI (ie, first medical contact-to-balloon time goal to 120 minutes for interhospital transfer of STEMI patients, with emphasis on the need to strive for total ischemia times <90 minutes).[10,11,13,14] As a consequence, the time from first medical contact or hospital admission to coronary angiography has substantially decreased in the past 10 years, as reflected by contemporary studies (Figure 1).[4,15–28]

Although these time quality metrics have been recently reported to be as short as ≈4 hours in NSTE-ACS and ≈40 to 50 minutes in STEMI (the latter being a timeframe where even more potent drugs than clopidogrel may have not still achieved their full antiplatelet effects), the use of pharmacological agents in patients with longer delays to coronary angiography and PCI remains intuitively attractive. This is particularly true in real-world practice where treatment delays are longer than those reported in randomized controlled trials. For instance,

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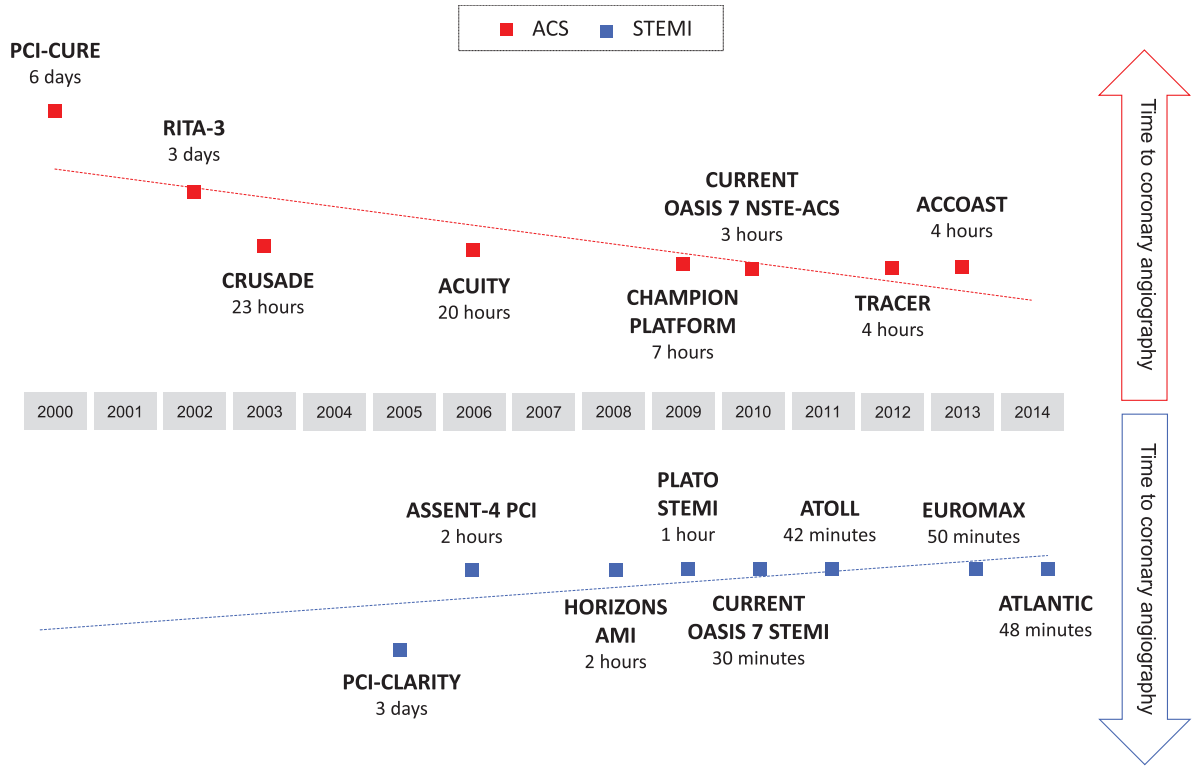

Figure 1. Time from hospital admission or first medical contact to coronary angiography in studies of acute coronary syndromes (ACS; Percutaneous Coronary Intervention Clopidogrel in Unstable Angina to Prevent Recurrent Events [PCI CURE],[15] Randomised Intervention Treatment of Angina [RITA 3],[16] Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines [CRUSADE],[17] Acute Catheterization and Urgent Intervention Strategy [ACUITY],[18] Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition [CHAMPION]-Platform,[19] Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Optimal Anti-Platelet Strategy for Interventions [CURRENT OASIS 7],[20] Thrombin Receptor Antagonist for Clinical Event Reduction [TRACER],[21] and A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients With Non–ST-Segment–Elevation Myocardial Infarction [ACCOAST][22]) and ST-segment–elevation myocardial infarction (STEMI; percutaneous coronary intervention–Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction [PCI-CLARITY],[23] Assessment of the Safety and Efficacy of a New Treatment Strategy With Percutaneous Coronary Intervention [ASSENT 4 PCI],[24] Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction [HORIZONS AMI],[25] Study of Platelet Inhibition and Patient Outcomes [PLATO],[4] CURRENT OASIS 7,[20] Angioplasty and Intravenous Lovenox or Unfractionated Heparin [ATOLL],[26] European Ambulance Acute Coronary Syndrome Angiography [EUROMAX],[27] and Administration of Ticagrelor in the Cath-Laboratory or in the Ambulance for New ST-Segment–Elevation Myocardial Infarction to Open the Coronary Artery [ATLANTIC][28]). NSTE indicates non–ST-segment elevation.

in the National Cardiovascular Data Registry, among 100 228 patients admitted for STEMI and 158 492 patients admitted for non-STEMI between October 2009 and September 2012, the rates of early $P2Y_{12}$ antagonists use (defined as documented use within 24 hours of admission) were ≈90% and ≈57% among STEMI and non-STEMI patients, respectively, with slightly decreasing trends over time.[29] However, although a comparable snapshot synthesizing the European perspective is not available, pretreatment was found to be a highly prevalent practice (≈80%) in 2585 patients with ACS from the Italian EYESHOT (Employed Antithrombotic Therapies in Patients With Acute Coronary Syndromes Hospitalized in Italian Coronary Care Units) registry.[30]

In NSTE-ACS, pretreatment is expected to address the window of vulnerability where the coronary anatomy is still unknown and revascularization has not been yet undertaken. In patients with STEMI, pretreatment aims at achieving quicker antiplatelet effects to prevent thrombotic complications during and immediately after primary PCI. In STEMI patients undergoing thrombolysis, pretreatment is intended as part of the modern definition of pharmacoinvasive strategy (ie, PCI represents an invasive back-up implying transportation to a PCI hospital for either immediate rescue PCI in case of failed fibrinolysis or nonurgent coronary angiography to determine the need for additional revascularization of the culprit lesion), whereas the term facilitated PCI (ie, decision to perform PCI is already taken before the additional pharmacological reperfusion treatment has been given) has been abandoned.[31]

Guidelines on Pretreatment With Antiplatelet Therapies

Practice guidelines have been subject to numerous changes during the past years with regard to pretreatment with oral and intravenous antiplatelet therapies. Tables 1–3 summarize the most current recommendations on timing of $P2Y_{12}$ inhibitor initiation in clinical practice guidelines from Europe and the United States.[9–14]

Stable CAD

In patients with stable CAD, aspirin is recommended before elective stenting by both the European Society of Cardiology

Table 1. Recommendations on Timing of $P2Y_{12}$ Inhibitor Initiation and Glycoprotein IIb/IIIa Inhibitors in Guidelines for Stable CAD Undergoing Elective PCI

Title	Recommendation	Class	LOE
United States			
2011 ACCF/AHA/SCAI guideline for PCI[10]	The efficacy of clopidogrel pretreatment remains controversial	…	…
	In patients undergoing elective PCI treated with UFH and not pretreated with clopidogrel, it is reasonable to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban)	IIa	B
	In patients undergoing elective PCI with stent implantation treated with UFH and adequately pretreated with clopidogrel, it might be reasonable to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban)	IIb	B
Europe			
2013 ESC guidelines on the management of stable CAD[32]	Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended	III	A
2014 ESC/EACTS guidelines for myocardial revascularization[11]	Treatment with 600-mg clopidogrel is recommended in elective patients with PCI once anatomy is known and decision to proceed with PCI preferably ≥2 h before the procedure	I	A
	Pretreatment with clopidogrel may be considered in patients with high probability for significant CAD	IIb	C
	In patients on a maintenance dose of 75-mg clopidogrel, a new loading dose of ≥600 mg may be considered once the indication for PCI is confirmed	IIb	C
	GPI should be considered only for bailout	IIa	C

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; CAD, coronary artery disease; EACTS, European Association of Cardio-Thoracic Surgeons; ESC, European Society of Cardiology; GPI, glycoprotein IIb/IIIa inhibitor; LOE, level of evidence; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Interventions; and UFH, unfractionated heparin.

(ESC) and the American College of Cardiology Foundation/American Heart Association/Society of Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI).[10,11] Pretreatment with $P2Y_{12}$ antagonists was reported as being a practice of uncertain use in the 2011 ACCF/AHA/SCAI guidelines for PCI[10] and was even contraindicated (class III) in the

Table 2. Recommendations on Timing of $P2Y_{12}$ Inhibitor and Glycoprotein IIb/IIIa Inhibitors Initiation in Guidelines for Non–ST-Segment–Elevation Acute Coronary Syndromes

Title	Recommendation	Class	LOE
United States			
2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Segment–Elevation Acute Coronary Syndromes[12]	A loading dose of a $P2Y_{12}$ receptor inhibitor should be given before the procedure in patients undergoing PCI with stenting	I	A
	In patients with high-risk features (eg, elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban) at the time of PCI	I	A
	In patients with high-risk features (eg, elevated troponin) treated with UFH and adequately pretreated with clopidogrel, it is reasonable to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban) at the time of PCI	IIa	B
2011 ACCF/AHA/SCAI guideline for PCI[10]	In patients with high-risk features (eg, elevated troponin level) not treated with bivalirudin and not adequately pretreated with clopidogrel, it is useful at the time of PCI to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban) in patients treated with UFH	I	A
	In patients with high-risk features (eg, elevated troponin level) treated with UFH and adequately pretreated with clopidogrel, it is reasonable at the time of PCI to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban)	IIa	B
Europe			
2011 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation[9]	A $P2Y_{12}$ inhibitor (should be administered) as soon as possible	I	A
2014 ESC/EACTS guidelines for myocardial revascularization[11]	Pretreatment with prasugrel in patients in whom coronary anatomy not known, is not recommended	III	B
	Pretreatment with GPI in patients in whom the coronary anatomy is not known, is not recommended	III	A

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; EACTS, European Association of Cardio-Thoracic Surgeons; ESC, European Society of Cardiology; GPI, glycoprotein IIb/IIIa inhibitor; LOE, level of evidence; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Interventions; and UFH, unfractionated heparin.

Table 3. Recommendations on Timing of $P2Y_{12}$ Inhibitor and Glycoprotein IIb/IIIa Inhibitors Initiation in Guidelines for STEMI

Title	Recommendation	Class	LOE
United States			
2013 ACCF/AHA Guideline for the Management of STEMI[14]	A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI	I	B
	It may be reasonable to administer intravenous GPI receptor antagonist in the precatheterization laboratory setting (eg, ambulance and ED) to patients with STEMI for whom primary PCI is intended	IIb	B
2011 ACCF/AHA/SCAI guideline for PCI[10]	In patients undergoing primary PCI treated with UFH, it is reasonable to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban), in patients not pretreated with clopidogrel	IIa	A
	In patients undergoing primary PCI treated with UFH, it is reasonable to administer a GPI (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban), in patients pretreated with clopidogrel	IIa	C
	Routine precatheterization laboratory (eg, ambulance or emergency department) administration of GPI as part of an upstream strategy for patients with STEMI undergoing PCI is not beneficial	III	B
Europe			
2012 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation[13]	A combination of DAPT with aspirin and an adenosine diphosphate receptor blocker as early as possible before angiography	…	…
	Upstream use of a GPI (vs in-laboratory use) may be considered in high-risk patients undergoing transfer for primary PCI	IIb	B
2014 ESC/EACTS guidelines for myocardial revascularization[11]	It is recommended to give $P2Y_{12}$ inhibitors at the time of first medical contact	I	B
	Upstream use of a GPI (vs in-laboratory use) may be considered in high-risk patients undergoing transfer for primary PCI	IIb	B

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; DAPT, dual antiplatelet therapy; EACTS, European Association of Cardio-Thoracic Surgeons; ED, emergency department; ESC, European Society of Cardiology; GPI, glycoprotein IIb/IIIa inhibitor; LOE, level of evidence; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Interventions; STEMI, ST-segment–elevation myocardial infarction; and UFH, unfractionated heparin.

2013 ESC guidelines for stable CAD.[32] The 2014 ESC myocardial revascularization guidelines now recommend administering 600-mg clopidogrel only after the coronary anatomy is known and preferably ≥2 hours before PCI (class I), whereas pretreatment with clopidogrel may be considered (class IIb) in patients with high probability for significant CAD, and reloading (class IIb) in patients on a maintenance clopidogrel dose.[11] According to the same guidelines, GPI should be reserved only for bailout use,[11] whereas the latest 2011 ACCF/AHA/SCAI guidelines for PCI states that it is reasonable (class IIa) to administer GPI in patients who are not pretreated with clopidogrel and it might be reasonable (class IIb) in those who are adequately pretreated.[10]

Non–ST-Segment–Elevation Acute Coronary Syndromes

Aspirin is recommended for all patients with NSTE-ACS without contraindications (regardless of the treatment strategy) in the 2014 ESC guidelines for myocardial revascularization and as soon as possible in the 2014 American College of Cardiology (ACC)/AHA guidelines for NSTE-ACS.[11,12] For years, pretreatment with a $P2Y_{12}$ inhibitor has consistently been given a class I strength of recommendation in both the current ESC and the former 2012 ACC/AHA guidelines for invasively managed NSTE-ACS.[9,33] Although the level of evidence for pretreatment was high in these documents, the supporting references did not relate to any randomized trial of upstream versus downstream use of $P2Y_{12}$ inhibitors at that time.[2–4,15] Notably, in the more recent 2014 ESC guidelines for myocardial revascularization and ACC/AHA guidelines for NSTE-ACS, there is no longer a specific recommendation for early initiation of $P2Y_{12}$ inhibitors in NSTE-ACS (and pretreatment with prasugrel is a class III recommendation in the ESC guidelines).[11] According to the 2011 ACCF/AHA/SCAI guidelines for PCI and the 2014 guidelines for NSTE-ACS, GPI may be used in patients with high-risk features who are (class IIa) or are not (class I) adequately pretreated with clopidogrel,[10,12] whereas pretreatment with GPI in patients in whom the coronary anatomy is unknown is contraindicated (class III) by the 2014 ESC myocardial revascularization guidelines.[11]

ST-Segment–Elevation Myocardial Infarction

Aspirin is recommended for all patients without contraindications in the 2014 ESC guidelines for myocardial revascularization and before primary PCI in the 2013 ACCF/AHA guidelines for STEMI.[11,14] In 2012, the ESC guidelines for STEMI acknowledged the lack of trials evaluating the commencement of dual antiplatelet therapy before hospital admission, rather than in hospital, nor its use before, rather than during angiography in the setting of STEMI.[13] Importantly, after publication of these guidelines, specifically designed trials of pretreatment with newer $P2Y_{12}$ inhibitors have been made available.[22,28] In the 2014 ESC guidelines for myocardial revascularization, administration of $P2Y_{12}$ inhibitors is now recommended at first medical contact in patients presenting with STEMI,[11] matching the as early as possible statement included in the class I recommendation for pretreatment included in the 2013 ACCF/AHA guidelines for STEMI.[14] Use of GPI before primary PCI, mostly driven by data using abciximab, is given a class IIb in both the 2012 ESC[13] and the 2013 ACCF/AHA guidelines for STEMI,[14] as well as in the 2014 ESC guideline for myocardial revascularization.[11] Notably, routine upstream GPI administration was not considered beneficial in STEMI by the 2011 ACCF/AHA/SCAI guideline for PCI (class III).[10]

Figure 2. Studies of pretreatment in patients with stable coronary artery disease and non–ST-segment–elevation acute coronary syndromes (Clopidogrel for the Reduction of Events During Observation [CREDO],[34] Primary Angioplasty for Patients From General Non-PCI Hospitals Transferred to PCI Units With or Without Emergency Thrombolysis [PRAGUE-8],[35] and A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients With Non–ST-Segment–Elevation Myocardial Infarction [ACCOAST][22]). ACS indicates acute coronary syndromes; CD, cardiovascular death; CVA, cerebrovascular accidents; D, death; GPI, glycoprotein IIb/IIIa inhibitors; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; Rev, revascularization; and Urev, urgent revascularization.

Pretreatment With Oral Antiplatelet Agents

Multiple studies have explored the effect of pretreatment with currently approved oral $P2Y_{12}$ inhibitors in patients undergoing elective PCI (clopidogrel) or presenting with an ACS (clopidogrel, prasugrel, and ticagrelor; Figures 2 and 3).[22,28,34–37] Study designs and key results of randomized clinical trials of pretreatment are summarized in Table 4.[22,28,34–38]

Stable CAD

There is a paucity of evidence supporting pretreatment with clopidogrel in the setting of stable CAD and elective PCI. In the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, preloading with a 300-mg clopidogrel dose was not found to reduce the incidence of ischemic events at 28 days compared with no preloading. In a prespecified subanalysis, patients who received clopidogrel loading ≥6 hours before PCI experienced a borderline nonsignificant

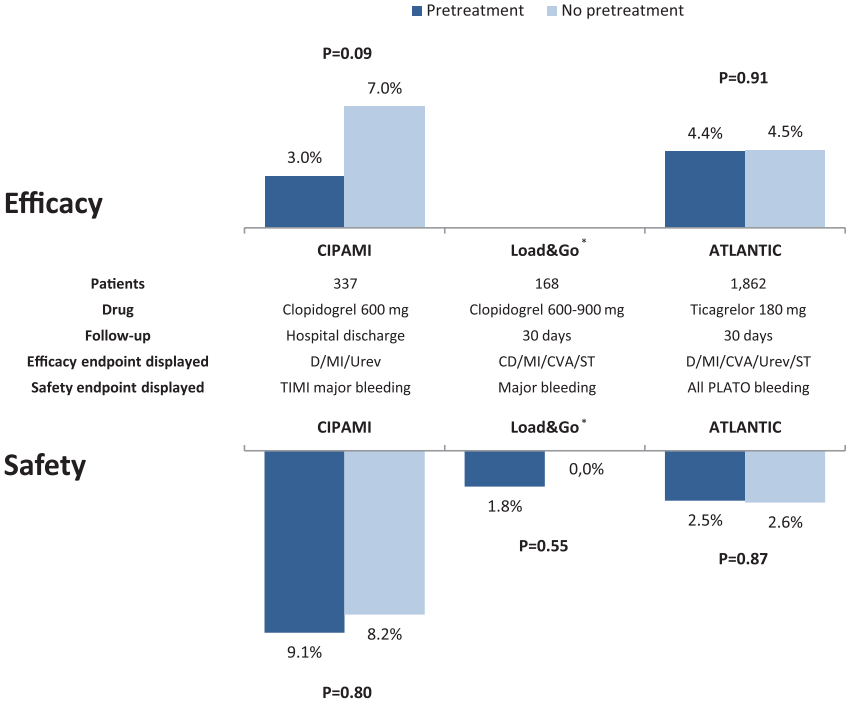

Figure 3. Studies of pretreatment in patients with ST-elevation myocardial infarction (Clopidogrel Administered Prehospital to Improve Primary PCI in Patients With Acute Myocardial Infarction [CIPAMI],[36] Load&Go,[37] and Administration of Ticagrelor in the Cath-Laboratory or in the Ambulance for New ST-Segment–Elevation Myocardial Infarction to Open the Coronary Artery [ATLANTIC][28]). CD indicates cardiovascular death; CVA, cerebrovascular accidents; D, death; MI, myocardial infarction; PLATO, Study of Platelet Inhibition and Patient Outcomes ST, stent thrombosis; TIMI, thrombolysis in myocardial infarction; and Urev, urgent revascularization. *Load&Go reported 2 deaths and 1 myocardial infarction in the overall population (*P*, nonsignificant [NS] for comparison between groups).

Table 4. Summary of Clinical Trials of Pretreatment With $P2Y_{12}$ Inhibitors Across the Broad Spectrum of CAD

Study, y	Design	Size	Summary of Findings	Comments
Stable CAD				
CREDO[39]	Patients referred for planned PCI or coronary angiography (33% stable CAD, 67% unstable angina or recent myocardial infarction) randomized to receive either a 300-mg LD of clopidogrel or placebo on top of aspirin therapy between 3 and 24 h from PCI. After PCI, both the groups received aspirin and clopidogrel 75 mg daily through 28 d, whereas clopidogrel was discontinued (and placebo resumed) thereafter in patients randomized to no preloading, or continued in patients randomized to preloading, and both the groups continued to receive aspirin until the end of the 12-month treatment period	2116	Preloading with a 300-mg clopidogrel dose was not found to reduce the incidence of death, MI, or urgent target vessel revascularization at 28 d compared with no preloading (6.8% vs 8.3%; *P*=0.23), and there was no increase in major bleeding (4.8% vs 3.8%; *P*=0.24)	Not a true pretreatment study because of inclusion of patients mostly selected not before but after a coronary angiography was available
PRAGUE-8[35]	Stable patients with CAD randomized to receive 600-mg clopidogrel ≥6 h before coronary angiography or in the cath-laboratory after coronary angiography and only in case of PCI	1028	The combined ischemic end point (death, periprocedural MI, stroke, or reintervention within 7 d) occurred in 0.8% of patients who were pretreated and 1% of those who were not (*P*=0.75). Patients who received pretreatment were more likely to experience bleeding complications (3.5% vs 1.4%; *P*=0.025)	High 600-mg LD of clopidogrel before elective coronary angiography increased the risk of minor bleeding complications, whereas the benefit on periprocedural infarction was not significant
NSTE-ACS				
ARMYDA-5[38]	Patients (39% with NSTE-ACS) randomized to receive a 600-mg clopidogrel LD 4–8 h before PCI or a 600-mg LD given in the catheterization laboratory after coronary angiography, but before PCI	409	No significant difference in the 30-d incidence of major adverse cardiac events (cardiac death, MI, or unplanned target vessel revascularization) between the pretreatment and no pretreatment groups (8.8% vs 10.3%; *P*=0.72). No increased risk of bleeding or vascular complications with pretreatment (5.4% vs 7.8%; *P*=0.42)	The small numbers and the minor proportion of patients with NSTE-ACS are limitations of this study
ACCOAST[22]	Patients with NSTE-ACS and a positive troponin level scheduled to undergo early (<48 h) invasive management were randomized to receive 30 mg prasugrel before angiography followed by additional 30 mg at the time of PCI (pretreatment group) or placebo before angiography followed by 60 mg prasugrel at the time of PCI (control group)	4033	The risk of the primary efficacy end point, a composite of cardiovascular death, MI, stroke, urgent revascularization, or unplanned use of GPIs through 7 d, was similar between the 2 groups (HR with pretreatment 1.02, 95% CI, 0.84–1.25; *P*=0.81). Patients in the pretreatment group had significant increases in the primary safety end point of all TIMI major bleeding (HR, 1.90; 95% CI, 1.19–3.02; *P*=0.006), as well as significant increases in noncoronary artery bypass grafting-related TIMI major and life-threatening bleeding	The trial was prematurely interrupted on recommendation from the data safety monitoring board when 398 of the 400 intended primary end point events had been collected, corresponding to 4033 of the ≈4100 patients originally planned
STEMI				
CIPAMI[36]	Patients with STEMI referred to primary PCI randomized to receive a LD of 600-mg clopidogrel given in the prehospital phase vs clopidogrel administered only after the diagnostic angiogram	337	The primary end point, TIMI 2/3 patency of the infarct-related artery in the diagnostic angiography immediately before PCI, was not different between the groups, whereas there was a trend (*P*=0.09) toward a reduction in the composite of death, reinfarction, and urgent target vessel revascularization in prehospital-treated patients	The study was underpowered to assess clinical differences

(*Continued*)

Table 4. Continued

Study, y	Design	Size	Summary of Findings	Comments
Load&Go[37]	Patients with STEMI randomized to 900-mg clopidogrel, 600-mg clopidogrel, or no pretreatment (followed by 300-mg clopidogrel just before primary PCI) at the first medical contact	168	TIMI perfusion grade 3, the primary end point of the trial, was not significantly different between patients randomized to prehospital loading dose (600- or 900-mg clopidogrel) and those randomized to no pretreatment (300 mg). There was also no significant difference between the 600- vs 900-mg prehospital treatment groups with regard to the primary end point	The study was underpowered to assess clinical differences
ATLANTIC[28]	Patients with STEMI lasting <6 h were randomized to receive a ticagrelor loading dose prehospital (ie, in the ambulance) vs in-hospital (ie, in the catheterization laboratory)	1862	There were no differences between the two groups in terms of the 2 coprimary surrogate end points (absence of ≥70% resolution of ST-segment elevation before PCI and absence of TIMI flow grade 3 in infarct-related artery at initial angiography)	The study was underpowered to assess clinical differences

ACCOAST indicates A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients With Non–ST-Segment–Elevation Myocardial Infarction; ARMYDA, Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty; ATLANTIC, Administration of Ticagrelor in the Cath-Laboratory or in the Ambulance for New ST-Segment–Elevation Myocardial Infarction to Open the Coronary Artery; CAD, coronary artery disease; CI, confidence interval; CIPAMI, Clopidogrel Administered Prehospital to Improve Primary PCI in Patients With Acute Myocardial Infarction; CREDO, Clopidogrel for the Reduction of Events During Observation; GPI, glycoprotein IIb/IIIa inhibitors; HR, hazard ratio; LD, loading dose; MI, myocardial infarction; NSTE-ACS, non–ST-segment–elevation myocardial infarction acute coronary syndrome; PCI, percutaneous coronary intervention; PRAGUE-8, Primary Angioplasty for Patients From General Non-PCI Hospitals Transferred to PCI Units With or Without Emergency Thrombolysis; STEMI, ST-segment–elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction.

(*P*=0.051) 39% relative risk reduction for the primary end point, and no interaction was observed between the effect of clopidogrel preloading and the clinical presentation (ACS versus no ACS).[34] In addition, a post hoc analysis suggested that longer intervals (>15 hours) between the 300-mg loading dose of clopidogrel and PCI significantly reduced the incidence of cardiac events compared with placebo.[34,39] Although informative, the CREDO study cannot be considered a true pretreatment study because of inclusion of patients mostly selected not before but after a coronary angiography was available.

Pharmacodynamic studies have shown that a 600-mg loading dose of clopidogrel achieves faster antiplatelet effect and better clinical outcomes than a 300-mg loading dose in patients undergoing PCI.[40,41] Single loading doses of clopidogrel >600 mg are associated with only modest or no additional significant suppression of platelet function likely due to limited drug absorption.[42,43] Although not supported by large-scale randomized clinical trials until years after these earlier investigations, these findings led to changes in clinical practice, in which 600-mg clopidogrel loading dose regimens had become the standard of care and the use of 300 mg essentially abandoned by most practitioners. Later, the benefit of doubling the loading dose of clopidogrel, particularly in patients undergoing PCI, has been well established,[20,44] resulting in an interest shift in understanding the effect of pretreatment with a high clopidogrel loading dose regimen. Although not a trial of pretreatment versus no pretreatment as all patients were pretreated with a 600-mg loading dose, an analysis from the Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT) trial conducted in 2159 patients with PCI showed no incremental benefit at 30 days for durations of pretreatment >2 hours.[45] In the Primary Angioplasty for Patients From General Non-PCI Hospitals Transferred to PCI Units With or Without Emergency Thrombolysis (PRAGUE-8) trial, the combined ischemic end point was not reduced by pretreatment with 600-mg clopidogrel and was associated with a higher risk of minor bleeding complications.[35] A meta-analysis from the Academic Research Organization (ACTION) group found no differences in mortality with clopidogrel pretreatment versus no pretreatment in 1636 elective patients with PCI from randomized clinical trials (odds ratio [OR], 1.12; 95% confidence interval [CI], 0.17–7.27; *P*=0.91) and 5919 patients from observational analyses of randomized clinical trials (OR, 1.34; 95% CI, 0.77–2.34; *P*=0.31).[46] Notably, significant decreases in major coronary events were found with pretreatment when pooling observational studies but not when pooling randomized clinical trials.

Overall, the available evidence suggests that pretreatment might have a role only if a 300-mg loading dose of clopidogrel is used. However, this no longer represents the standard of care. The use of pretreatment with a 600-mg loading dose of clopidogrel is not supported by a specifically designed randomized trial, whereas the ACTION meta-analysis found no difference in mortality and conflicting results on secondary end points. Prasugrel and ticagrelor are not approved for

Table 5. Pharmacological Characteristics of $P2Y_{12}$ Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Group	Thienopyridine	Thienopyridine	CPTP	ATP analog
Administration	Oral	Oral	Oral	IV
Receptor blockade	Irreversible	Irreversible	Reversible	Reversible
Onset of action	2–8 h	30 min–4 h	30 min–2 h	seconds
Offset of action	7–10 d	7–10 d	3–5 d	≈60 min
Delayed onset in STEMI	Yes	Yes	Yes	No

CPTP indicates cyclopentyl triazolo-pyrimidines; and STEMI, ST-segment–elevation myocardial infarction.

patients with stable CAD and their effect with pretreatment remains unknown in this setting.

Non–ST-Segment–Elevation Acute Coronary Syndromes

Similarly to stable CAD and elective PCI, the evidence supporting pretreatment with oral $P2Y_{12}$ receptor inhibitors in NSTE-ACS is also poor. At difference of patients with stable CAD, in the NSTE-ACS setting, in addition to clopidogrel, the novel $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor have also been studied (Table 5).

Clopidogrel

In patients with NSTE-ACS on oral aspirin therapy from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, dual antiplatelet therapy with clopidogrel for ≤12 months (300-mg loading dose, followed by 75 mg once daily) was found to determine a 20% relative reduction in the risk of the composite primary end point (death from cardiovascular causes, nonfatal myocardial infarction, or stroke) compared with placebo, at the price of a 38% increase in major bleeding.[2] The benefits of clopidogrel emerged within 24 hours of initiation of treatment, with lower rates of the primary outcome in combination with refractory or severe ischemia, and continued throughout the 12 months of the study.[47] Patients undergoing CABG in the CURE trial (16% of the overall study population) received treatment with the study drug for a median of 26 days and experienced consistent treatment effects (ie, ischemic benefit with increased bleeding, the latter particularly among patients who continued the study drug ≤5 days before surgery).[48] Conversely, patients undergoing PCI (21% of the overall study population) received treatment with the study drug (clopidogrel or placebo) for a median of 10 days (PCI-CURE substudy).[15] About a quarter of patients in PCI-CURE received open-label thienopyridines before PCI (typically in case of expected stent implantation), and >80% received them thereafter for a median of 4 weeks (typically in case of stent implantation), followed by reinitiation of the study drug for a mean of 8 months. Compared with placebo, clopidogrel was found to reduce the risk of death from cardiovascular causes or myocardial infarction by 30%, with ischemic benefits consistently noted in the period before PCI, in the subsequent 4 weeks, and in the months afterward.[15] Notably, the benefit of clopidogrel could be even an underestimate of the true treatment effect because of the abovementioned proportion of patients also receiving open-label thienopyridines in both the groups, with the potential for a diluting effect. In fact, the primary outcome was reduced by 42% after exclusion of patients who received open-label drugs before PCI. The PCI-CURE study, therefore, supports the hypothesis that an effective antiplatelet regimen with clopidogrel started before PCI will reduce clinical events for a relatively long period. However, the long pretreatment period makes this study outdated in view of the shorter contemporary times to the cath-laboratory in invasively managed NSTE-ACS (Figure 1), although a subsequent post hoc analysis showed significant ischemic benefits irrespective of the timing of PCI, with the greatest treatment effect observed in patients undergoing PCI <48 hours after randomization.[49] Because of the post hoc nature of this smaller subgroup, however, the true effect of pretreatment with clopidogrel in patients with NSTE-ACS who undergo early invasive management remains elusive.

The small Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA)-5 trial, which included 39% of patients with NSTE-ACS, showed no significant difference in the primary ischemic end point between pretreatment and no pretreatment, and no increased risk of bleeding or vascular complications was noted with pretreatment.[38] In 1041 patients with NSTE-ACS included in a nonrandomized observational study, pretreatment with clopidogrel (chronic 75-mg clopidogrel therapy or a 300- to 600-mg clopidogrel loading dose before angiography) was associated with similar short-term ischemic and bleeding outcomes, coupled with a similar long-term adjusted risk of mortality compared with in-laboratory 600-mg clopidogrel loading (ie, immediately before or after PCI).[50] The meta-analysis from the ACTION group found no differences in mortality with clopidogrel pretreatment versus no pretreatment in 4774 patients with NSTE-ACS from randomized clinical trials (OR, 0.93; 95% CI, 0.63–1.36; P=0.69) and 5026 patients from observational analyses of randomized clinical trials (OR, 0.92; 95% CI, 0.65–1.3; P=0.65), although a potential reduction of major coronary events with pretreatment was suggested in analyses restricted to randomized clinical trials (OR, 0.78; 95% CI, 0.66–0.91; P=0.002), coupled with a trend in increasing the risk of major bleeding (OR, 1.28; 95% CI, 0.98–1.67; P=0.07).[46]

In patients with NSTE-ACS undergoing PCI from the Acute Catheterization and Urgent Intervention Strategy (ACUITY) trial, there was a trend (P=0.08) toward an interaction effect of bivalirudin monotherapy versus unfractionated heparin plus GPIs and the timing of thienopyridine administration.[18] In particular, the incidence of 30-day composite ischemic events tended to be higher with bivalirudin monotherapy in patients receiving a thienopyridine after PCI and in those who did not receive a thienopyridine at all, whereas there were no differences compared with unfractionated heparin plus GPIs when thienopyridines were administered before PCI. Conversely, the effect of bivalirudin in reducing bleeding was irrespective of timing of thienopyridine administration (P for interaction=0.56).[18] Given the number of subgroups examined in the ACUITY-PCI study, and the borderline significance of the interaction for the composite ischemic end point, these results may reflect a chance finding, and caution is needed to avoid the risk of overinterpretation.

Finally, in the Early Glycoprotein IIb/IIIa Inhibition in Patients With Non–ST-Segment–Elevation Acute Coronary Syndrome (EARLY ACS) trial, routine preangiography eptifibatide was not found to be superior to delayed provisional use but led to more bleeding.[51] Randomization to early eptifibatide versus placebo was stratified by the intent to use upstream clopidogrel, enabling a meaningful analysis on the benefit:risk ratio of intensive platelet inhibition with combined early use of antiplatelet agents. After multivariable adjustment, intended upstream clopidogrel use was not found to differentially influence the effect of early eptifibatide on the primary ischemic end point (P for interaction=0.988).[52]

In aggregate, the available evidence coming from clinical trials (PCI-CURE and ARMYDA-5), observational analyses from randomized clinical trials (ACUITY-PCI and EARLY ACS), registries and the ACTION meta-analysis cannot be considered conclusive on the issue of pretreatment with clopidogrel. With the possible exception of PCI-CURE, a trial no longer reflecting current practice of NSTE-ACS management, the available data do not seem to highlight a clear clinical benefit of clopidogrel loading before PCI versus in-laboratory use.

Prasugrel

In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), the primary end point, a composite of cardiovascular death, nonfatal myocardial infarction or stroke, was significantly decreased by 19% in invasively managed NSTE-ACS and STEMI patients treated with prasugrel compared with those treated with clopidogrel, a benefit that came at the price of increased bleeding.[3] The study protocol did not allow any study drug administration before angiography in the 10 074 patients with NSTE-ACS (74% of the overall study population) included in the trial.[3] Twenty-two percent of patients with NSTE-ACS in the TRITON-TIMI 38 received the loading dose after coronary angiography and before PCI, whereas the vast majority (78%) received it during or after PCI.[3] Interestingly, in patients referred to CABG after coronary angiography, prasugrel was shown to be associated with a significant reduction of mortality compared with clopidogrel (adjusted OR, 0.26; 95% CI, 0.08–0.85; P=0.025), despite significant increases in bleeding.[53]

Because of the evidence gap about pretreatment in TRITON-TIMI 38, a specific trial on this topic was undertaken. In the A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients With Non–ST-Segment–Elevation Myocardial Infarction (ACCOAST) trial, the median time from the loading dose to coronary angiography was ≈4 hours.[22,54] The risk of the primary efficacy end point was similar between the 2 groups, but patients in the pretreatment group had a 90% increase in the key safety end point of all thrombolysis in myocardial infarction (TIMI) major bleeding, as well as significant increases in non-CABG–related TIMI major and life-threatening bleeding. The primary findings from the ACCOAST trial were consistent in multiple prespecified subgroups, including patients undergoing PCI,[55] who represented 69% of the overall population, and patients stratified by the median of time from the first loading dose to coronary angiography. Notably, when patients were stratified into quartiles of time from the first loading dose to coronary angiography, there was again no evidence of a significant interaction effect with the primary end point, whose estimate remained neutral even in patients with longer (>14 hours) duration of pretreatment (Eli Lilly/Daiichi Sankyo, data on file). An accompanying pharmacodynamic substudy showed that at the time of arterial access, there was greater platelet inhibition in the pretreatment group than in the control group, suggesting that unnecessary platelet inhibition may partly account for the excess of bleeding noted with pretreatment.[22] Overall, the above data and considerations do not support pretreatment with prasugrel in NSTE-ACS.

Ticagrelor

Compared with clopidogrel, ticagrelor was found to reduce by 16% the composite of death from vascular causes, myocardial infarction, or stroke in patients with NSTE-ACS and STEMI enrolled in the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial.[4] Differently from the TRITON-TIMI 38 trial, patients in PLATO were randomized to treatment with ticagrelor versus clopidogrel before coronary angiography, when the coronary anatomy was unknown, and inclusion of patients pretreated with clopidogrel was allowed. Thus, although patients randomized in the TRITON-TIMI 38 trial were mostly referred to PCI, those enrolled in the PLATO trial were more representative of an all-comers population of patients with ACS, including patients referred to invasive or noninvasive management.[45–49] In PLATO, the ischemic and bleeding risks were not different with ticagrelor versus clopidogrel in patients who were already on aspirin and clopidogrel at study entry, which represented nearly half of the overall trial population. The study design of PLATO, as well as the lack of a significant statistical interaction with antiplatelet pretreatment somehow supports the current broad practice of administering ticagrelor before the coronary anatomy is defined. However, it should be noted that no studies have explored the comparative effectiveness of ticagrelor pretreatment versus in-laboratory administration for patients with NSTE-ACS. Ongoing pharmacodynamics studies are currently evaluating the effects of ticagrelor administered in the cath-laboratory among $P2Y_{12}$ receptor naive patients with ACS undergoing PCI after defining coronary anatomy (NCT01603082 and NCT02052635).

ST-Segment–Elevation Myocardial Infarction

Patients with ACS have more activated and hyper-reactive platelets than patients with stable CAD.[56] This is particularly accentuated in STEMI, were a longer onset of action has been reported with $P2Y_{12}$ inhibitors compared with the delays usually described in patients with stable CAD.[57–61] Indeed, even prasugrel and ticagrelor, whose onset of action is ≈30 minutes in stable CAD, require ≈4 to 6 hours for achieving full antiplatelet effects in STEMI.[58–61] On this background, the short contemporary time from first medical contact to PCI does not allow the majority of patients with STEMI to have fully inhibited platelets at the time of PCI. Similarly to NSTE-ACS, pretreatment with oral $P2Y_{12}$ receptor inhibitors is a broad practice in STEMI, despite the lack of compelling data. Clinical data on pretreatment with clopidogrel, prasugrel, and ticagrelor are described below.

Clopidogrel

Evidences on the benefit of clopidogrel pretreatment in STEMI are controversial. A prospectively planned analysis of the Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28), a randomized, double-blind, placebo-controlled trial of 300-mg clopidogrel loading in patients receiving fibrinolytics for STEMI, investigated the benefit of clopidogrel pretreatment before PCI compared with in-laboratory administration

(PCI-CLARITY study).[23] The median number of days from fibrinolysis to PCI was 3. For patients undergoing stenting, the protocol recommended open-label clopidogrel (including a loading dose) to be administered after coronary angiography. The primary outcome, the 30-day composite of cardiovascular death, recurrent myocardial infarction, or stroke, was significantly reduced with clopidogrel pretreatment both before and after PCI and without a significant increase in major or minor bleeding.[23] The role of clopidogrel in STEMI was further supported by the results of the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) trial, which showed a significant 9% reduction in death, reinfarction, or stroke with clopidogrel compared with placebo in a wide range of patients with acute myocardial infarction.[62] However, there is not data available on the effect of clopidogrel pretreatment from COMMIT on outcomes of patients undergoing PCI.

As the evidence of the benefit of primary PCI over fibrinolytic therapy continued to grow and thus the broader use of mechanical reperfusion for patients with STEMI, the question on the benefits of pretreatment with a $P2Y_{12}$ receptor inhibitor also emerged. Two small randomized trials of primary PCI focused on surrogate end points and ended with negative findings.[36,37] On the contrary, several registries support the benefit of clopidogrel preloading in the setting of primary PCI. In the larger one (n=5955), Dörler et al[63] concluded that clopidogrel pretreatment before arrival at the PCI center is associated with reduced mortality. From a pool of patients with STEMI undergoing primary PCI (n=2014) in a regional STEMI network, Larson et al[64] compared patients who had received earlier pretreatment with a 600-mg loading dose of clopidogrel with those with pretreatment duration >60 minutes before PCI, and found that patients who received earlier pretreatment had less ischemic complications without increased bleeding or mortality. In the smaller study from Fefer et al[65] (n=383), clopidogrel loading before primary PCI was associated with a lower incidence of the primary composite end point. Consistently, a small registry from Lev et al[66] reported a higher adjusted chance of TIMI perfusion grade 3 and less reinfarction at 30 days with clopidogrel pretreatment. The ACTION meta-analysis, pooling 2198 STEMI from PCI-CLARITY and Clopidogrel Administered Prehospital to Improve Primary PCI in Patients With Acute Myocardial Infarction (CIPAMI), suggested a significant relative risk reduction in mortality (OR, 0.50; 95% CI, 0.26–0.96; *P*=0.04) and major coronary events with pretreatment, and no increase in major bleeding.[46] The accompanying meta-analysis of the 2 observational studies from Dörler et al[63] and Fefer et al[65] (n=6338) showed a consistent reduction in major adverse events with clopidogrel pretreatment, but no significant difference in mortality, and no increase in major bleeding.[46]

Overall, the available evidence supporting pretreatment with clopidogrel in STEMI is conflicting. Two small randomized studies excluded significant benefits with pretreatment in terms of myocardial reperfusion. Conversely, clopidogrel pretreatment has been associated with higher rates of reperfusion and ischemic events at 30 days in multiple nonrandomized studies and a significant mortality reduction in a meta-analysis, although these results cannot be considered conclusive because of the limitations of these studies themselves (ie, clopidogrel loading-balloon time was unknown in most registries; patients on chronic clopidogrel before STEMI were not analyzed separately but considered as part of the pretreatment group; the ACTION meta-analysis does not adequately reflect contemporary practice of clopidogrel pretreatment and reperfusion for STEMI).

Prasugrel

In TRITON-TIMI 38, the study protocol did not allow any study drug administration before angiography in patients with STEMI presenting from 12 hours to 14 days after symptoms onset, whereas pretreatment was permitted in patients with STEMI presenting within 12 hours with intent to undergo primary PCI.[67] Even though the study drug could be given immediately in the majority of patients with STEMI, it was usually delayed until during or after the PCI similar to the mandatory delay in patients with NSTE-ACS and late STEMI presenters. Only 32% of patients with STEMI undergoing primary PCI (≤12 hours) and 20% of those undergoing secondary PCI (>12 hours) in the TRITON-TIMI 38 trial received the loading dose before PCI.[68] As such, the value of pretreatment with prasugrel has not been specifically demonstrated in STEMI. However, in line with the TRITON-TIMI 38 design, the use of prehospital prasugrel is allowed in patients with STEMI undergoing primary PCI who present within 12 hours from symptoms.

Ticagrelor

Differently from prasugrel, a specifically designed trial has investigated the effect of pretreatment with ticagrelor in STEMI. In the phase IV Administration of Ticagrelor in the Cath-Laboratory or in the Ambulance for New ST-Segment–Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) study, the median time difference in the administration of the loading dose between the 2 strategies was only 31 minutes.[28] There were no differences between the 2 groups in terms of the 2 coprimary surrogate end points (absence of ≥70% resolution of ST-segment elevation before PCI and absence of TIMI flow grade 3 in infarct-related artery at initial angiography). The trial was not powered for clinical end points, and the finding of a significant reduction of stent thrombosis in the pretreatment group (0% versus 0.8% in the first 24 hours; 0.2% versus 1.2% at 30 days), albeit intriguing, should be regarded as exploratory only.[28] A small pharmacodynamic substudy showed platelet reactivity to be reduced significantly after the administration of ticagrelor in both the study groups. Notably, there was no significant difference in platelet reactivity between prehospital and in-hospital administration of ticagrelor at any time point, with the maximum numeric difference between the treatment groups being observed 1 hour after PCI.[28] Reassuringly, there were no differences in bleeding between the 2 strategies according to several classifications, and the bleeding rates were generally low.

Overall, the use of prehospital ticagrelor is allowed in patients with ACS, resembling the design of the PLATO trial. The ATLANTIC trial provides the first contemporary evidence that pretreatment with ticagrelor is safe in STEMI, although this strategy was not found to improve pre-PCI reperfusion.

Pretreatment With Intravenous Antiplatelet Agents

Although oral antiplatelet agents are inevitably associated with a delayed onset of action, particularly in the setting of STEMI, intravenous compounds are clinically available (GPI's: abciximab, tirofiban, and eptifibatide) or have been recently investigated in clinical trials (cangrelor) that may have the potential to ameliorate the clinical outcomes of patients undergoing PCI by achieving fast and potent antiplatelet effects.

Glycoprotein IIb/IIIa Inhibitors

Stable CAD and Elective PCI

Several noncontemporary studies support the use of GPI in patients with PCI on anticoagulation with unfractionated heparin who have not been adequately pretreated with clopidogrel[69–71] or even those who have been adequately pretreated.[72,73] This is in line with the recommendation from current ACCF/AHA/SCAI guidelines for PCI.[10] However, whether this recommendation is still relevant to current practice is debatable, and it is notable that the recent 2014 ESC guidelines on myocardial revascularization recommend using GPI as a bailout only.[11]

Non–ST-Segment–Elevation Acute Coronary Syndromes

Guidelines from the United States and Europe currently differ with regard to recommendation on upstream administration of GPI in NSTE-ACS. In fact, in both the ACCF/AHA/SCAI 2011 guideline for PCI and the ACC/AHA 2014 guideline for NSTE-ACS, in-laboratory use of GPI is not contraindicated, particularly if patients receive unfractionated heparin and have not been adequately pretreated with clopidogrel.[10,12] Differently, the 2014 ESC guidelines for myocardial revascularization do not recommend using GPI upstream.[11] A potential explanation for this discrepancy is that the American guidelines stem on sensibly older studies.[69,72,74–78] Conversely, the European guidelines include evidence from more contemporary studies.[18,51,79,80] As previously noted, the ACUITY trial found a significant benefit of bivalirudin alone with respect to the primary 30-day composite end point of ischemic and bleeding complications, driven by a reduction in major bleeding complications, regardless of whether GPI were administered downstream or upstream.[18] Similarly, the more recent ISAR-REACT 4 trial did not find a significant benefit of unfractionated heparin with abciximab in patients with non-STEMI, compared with bivalirudin alone.[79] As noted above, the EARLY ACS study compared a strategy of early administration of eptifibatide with delayed, provisional administration in 9492 patients with NSTE-ACS undergoing an invasive strategy.[51] Routine use of eptifibatide for ≈21 hours before angiography was not found to be superior to provisional use after angiography, and was associated with an increased risk of bleeding. Among patients with moderate- and high-risk NSTE-ACS undergoing an invasive treatment strategy in the ACUITY-Timing trial, deferred versus ≈5 hours of routine upstream administration of GPIs resulted in a numeric increase in composite ischemia with deferred use, which was offset by a significant reduction in major bleeding.[80] Overall, the evidence for additional benefit of routine upstream use of GPI inhibitors in patients with NSTE-ACS scheduled for coronary angiography is weak.

ST-Segment–Elevation Myocardial Infarction

In STEMI, American and European guidelines agree that pretreatment with GPI cannot be recommended on a routine basis. However, the ACCF/AHA guidelines consider reasonable the in-laboratory use of GPI in patients treated with unfractionated heparin, whether pretreated with clopidogrel, whereas the ESC guidelines suggest that GPI may be considered in high-risk patients undergoing transfer for primary PCI. Overall, the data on GPI use in STEMI are conflicting. Early administration of abciximab was found to reduce the composite ischemic end point in the outdated Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-Up (ADMIRAL) trial, with no bleeding excess.[81] Similarly, positive findings were observed with prehospital initiation of GPIs in more contemporary STEMI settings.[82–85] However, negative results for pretreatment with GPIs came from studies with relatively lower-risk STEMI populations, including Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) and Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE).[86,87] Therefore, the individual risk profile may play a role in determining which patients may benefit from early GPI initiation in STEMI.

Cangrelor

Cangrelor is the first $P2Y_{12}$ inhibitor that can be administered via the intravenous route and is associated with fast onset and offset of action.[88] Importantly, although no data on pretreatment with cangrelor are available, in-laboratory use of the drug itself may be considered an alternative to pretreatment. Cangrelor has been investigated into 3 large phase III randomized clinical trials that are part of the Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) program.[19,89,90] All trials were designed to investigate whether a treatment strategy with intravenous cangrelor started in the cath-laboratory at the time of PCI followed by transition to oral clopidogrel is more effective than clopidogrel or placebo given at the beginning or at the end of PCI. The CHAMPION-PCI and CHAMPION-Platform failed to show any significant ischemic difference at 48 hours between the 2 treatment arms and were terminated for futility before completion after interim analyses. Reasons for both CHAMPION-PCI and Platform trials failing to meet their primary end point include an unusually short time from admission to PCI (≈6–8 hours), which may have made difficult to discern ongoing myocardial infarction from periprocedural myocardial infarction.[91] This set the basis for A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require PCI (CHAMPION-PHOENIX), using the universal definition of periprocedural myocardial infarction, in which cangrelor significantly reduced the primary composite ischemic end point at 48 hours compared with clopidogrel administered immediately before or after PCI in ≈11 000 patients undergoing PCI for stable angina, NSTE-ACS, and

STEMI, with the treatment effect of cangrelor being consistent in both the patients who received clopidogrel before or after PCI (*P* for interaction=0.99).[89] The lack of a significant interaction between the treatment effect of cangrelor and the timing of clopidogrel intake was confirmed in a patient-level meta-analysis of the 3 CHAMPION trials, where no increase in major bleeding occurred, although there was an increase in minor bleeding.[92]

Overall, although none of the CHAMPION trials specifically investigated a prehospital treatment strategy with cangrelor versus in-laboratory use, early potent and fast platelet inhibition with intravenous cangrelor was associated with a significant reduction in periprocedural PCI complications, a finding that was not offset by major bleeding complications. Given its effective platelet inhibitory effects and fast offset of action, cangrelor also offers the potential advantage of bridging patients while awaiting surgery.[93,94] Although approval from regulatory authorities is pending, cangrelor for investigational use will be part of the pharmacological cocktail used together with aspirin and bivalirudin in patients with STEMI enrolled into the upcoming large Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS)-2 trial.

Practical Considerations

Overall, the evidence on the balance between safety and efficacy of pretreatment with antiplatelet agents should be viewed in the perspective of the contemporary era of early access to coronary angiography and revascularization where appropriate (Figure 1). In that perspective, it should be considered that a gradient exists in the severity of CAD from stable manifestations to NSTE-ACS and STEMI, which is paralleled by the more rapid access to coronary angiography and the likelihood of being treated with PCI and coronary stents. Also, it should be noted that the onset of antiplatelet effects of $P2Y_{12}$ inhibitors varies according to the drug (ie, cangrelor>prasugrel and ticagrelor>clopidogrel) and the clinical setting (ie, stable CAD>NSTE-ACS>STEMI; Table 5).

On this background, one may argue that the earlier the initiation of antiplatelet therapy, the earlier the antiplatelet effect occurs, thus translating into improved clinical outcomes particularly in settings at high thrombotic risk. Conversely, considerations that make deferring administration of a $P2Y_{12}$ receptor inhibitor until coronary anatomy is defined a reasonable option include the following: (1) the need for CABG still occurs in a non-negligible proportion of patients. In particular, in-hospital CABG is performed in 7% to 13% of patients hospitalized with NSTE-ACS in whom the avoidance of exposure to a $P2Y_{12}$ receptor inhibitor would enable a both timelier and safer (ie, less bleeding) surgical procedure.[12]; (2) pretreatment could correspond to overtreatment, particularly in patients who are not finally found to have CAD; (3) the risk of an ischemic complication before angiography is low; (4) the currently available literature does not show a compelling benefit associated with early initiation of $P2Y_{12}$ inhibitors before knowing coronary anatomy; and (5) important changes have occurred in clinical care since the publication of the CURE trial over a decade ago, in particular that of an early invasive strategy with patients going to the cardiac catheterization within hours rather than days (Figure 1) and the introduction of more potent and faster acting $P2Y_{12}$ receptor inhibitors. These observations are now reflected in most recently updated practice guidelines, which have down-played the need for early initiation of $P2Y_{12}$ receptor inhibiting therapy (Tables 1 and 2).[11,12] However, practice patterns vary across the globe, which may not reflect how patients are being managed in the setting of a clinical trial, which set the foundation for guideline recommendations. Therefore, for certain local practice standards, pretreatment with antiplatelet therapy may be perceived as clinically useful, particularly if timing to invasive evaluation is prolonged. Moreover, the above considerations on deferring initiation of $P2Y_{12}$ inhibiting therapy until coronary anatomy is defined are not in contrast with the sound rationale for long-term use of $P2Y_{12}$ inhibiting therapy among patients who present with an ACS but who do not undergo PCI, including those who are either medically managed or undergoing CABG.

In low-risk patients with stable CAD, there is no evidence of benefit of preloading with a high loading dose regimen of clopidogrel (PRAGUE-8).[35] In NSTE-ACS, there is a paucity of rigorous studies supporting pretreatment. Although PCI-CURE showed some evidences of benefit with pretreatment, this reflects a practice pattern that is now outdated.[15] Pretreatment with clopidogrel was not shown to be superior to in-laboratory platelet inhibition when using a high clopidogrel loading dose regimen (particularly in case of a short admission-to-needle delay) after coronary angiography (ARMYDA-5).[38] The only specifically designed study on this topic with novel therapies (ie, prasugrel) showed no ischemic benefit and increased bleeding (ACCOAST).[22] Moreover, in a recent meta-analysis of patients presenting with NSTE-ACS, pretreatment with thienopyridines was associated with no significant reduction of mortality but with a significant excess of major bleeding regardless of the strategy adopted (invasive or conservative).[95,96] Whether the negative results of pretreatment with thienopyridines also apply to ticagrelor is a matter of debate.[7,8] Finally, evidence supporting clopidogrel pretreatment in patients with STEMI undergoing primary PCI are weak and data are conflicting. ATLANTIC, the first randomized trial of pretreatment with a novel $P2Y_{12}$ inhibitor in STEMI, showed no evidence of improved reperfusion with ticagrelor pretreatment, and was not powered for clinical end points.[28] Similarly to ACCOAST in NSTE-ACS, one may argue that the results seen with ATLANTIC in STEMI may potentially also apply to prasugrel because these trials compared different strategies rather than different drugs. Indeed, if primary PCI is performed with short medical contact-to-balloon times, residual platelet reactivity before PCI is considerably high even in patients treated with new faster acting and more potent antiplatelet agents than clopidogrel, such as prasugrel or ticagrelor. In-laboratory, the use of GPI or cangrelor (when available) has the potential to bridge the necessary delay to full antiplatelet effect of oral $P2Y_{12}$ inhibitors.

Conclusions

Overall, the existing literature does not strongly support pretreatment with antiplatelet agents in patients with CAD who are invasively managed in the contemporary era. Indeed, contemporary times to coronary angiography are short, and the

risk of an ischemic complication before angiography low. Pretreatment has the potential to expose unnecessarily to aggressive antiplatelet medications and potentially causes avoidable bleeding complications in patients in whom CABG is needed, or without document CAD. Also, with newer antiplatelet drugs, it may be no longer necessary to consider pretreatment as part of a routine strategy to achieve fast antiplatelet effect. Nevertheless, results of clinical trial data do not always reflect the real world clinical setting, with variations in local practice standards where pretreatment with antiplatelet therapy may be perceived as clinically useful. Indeed, the broad armamentarium of antiplatelet therapies available and under development will allow clinicians to wisely choose among available strategies with the goal of reducing ischemic and bleeding complications.

Disclosures

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