Rationale for Upstream Dual Antiplatelet Therapy in Non-ST-Segment Elevation Myocardial Infarction

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Abstract Non-ST-segment elevation (NSTEMI) acute coronary syndrome (ACS) is a dynamic disease in which the use of dual platelet therapy has been shown to exert positive effects on ischemic outcomes. The objective of this article is to review evidence for the use of antiplatelet therapy in the emergency department and pre-angiography inpatient setting with the proposal that upstream dosing can be beneficial if the anti-ischemic benefit outweighs both the risk of treatment-related bleeding and the risk associated with withholding treatment. There is a coherence of clinical trial data that supports the early use of antiplatelet therapy with aspirin and the adenosine diphosphate inhibitors ticagrelor

and clopidogrel in troponin-positive NSTEMI-ACS (i.e., NSTEMI) in patients without obvious bleeding risk, those who may be delayed in going to catheterization, and those who are unlikely to need immediate bypass surgery.

Keywords Acute coronary syndrome · Upstream dual antiplatelet therapy · NSTEMI patients

Abbreviations

ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AHA	American Heart Association
ASA	Acetylic Salicylic Acid
ATP	Adenosine Triphosphate
BMS	Bare Metal Stent
CABG	Coronary artery bypass surgery
CAD	Coronary Artery Disease
cAMP	Cyclic adenosine monophosphate
COX	Cyclooxygenase
CV	Cardiovascular
DES	Drug Eluting Stent
GPIIb/IIIa	Glycoprotein IIb/IIIa
NSAIDS	Nonsteroidal Anti-inflammatory Drugs
NSTEMI	Non-ST elevation Myocardial Infarction
PCI	Percutaneous coronary intervention
PGI2	Prostacyclin
PI	Phosphodiesterase inhibitors
STEMI	ST Elevation Myocardial Infarction
Type 1 NSTEMI	MI consequent to a pathologic process in the wall of the coronary artery (e.g., plaque erosion/rupture, fissuring or dissection)
TXA2	Thromboxane A2
GP	Glycoprotein
PAR	Protease activated receptor

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Introduction

This article and the two that follow reflect the collaborative work of emergency physicians (EPs) and hospitalists within the Hospital Quality Foundation (HQF), a nonprofit professional organization dedicated to improving the practice of hospital medicine. As a part of these efforts, HQF has developed the “HEMI” (Hospital-Emergency Medicine Interface) educational initiative to bring into sharp focus interventions and programs aimed at supporting the evidence basis and improving consistent delivery of “best practice” care for patients managed across the transition from emergency department to hospital medicine, and, ultimately, back out to the community (see Fig. 1).

Emergency physicians and hospitalists are responsible for much of the early assessment and management of patients with acute coronary syndrome (ACS). Their decisions have broad downstream ramifications and ideally should be based on similar interpretations of the evidence that are consistently applied. Medical care of NSTEMI-ACS managed invasively can be divided into two phases: “upstream” and “downstream.” The upstream interval encompasses all care provided prior to diagnostic angiography and there includes the risk stratification, decision making, and actions of EMS personnel, EPs, hospitalists and other internists, and non-interventional cardiologists. Downstream care is post-angiographic and, therefore, is driven by knowledge of the coronary anatomy. Downstream management decisions include the choice among PCI, CABG, and medical strategies, and are made by interventional cardiologists, hospitalists and other internists, and—to some extent—the patient’s primary care provider.

To discuss the concept of optimizing collaborative care of non-ST-segment ACS in the upstream environment, an expert panel of EPs and hospitalists met in Philadelphia, PA on 26 July 2013 to discuss their perspectives on the evidence around the continuum of care for patients who present to the emergency department (ED) with non-ST-

segment elevation myocardial infarctions (NSTEMI). The meeting was supported by an unrestricted educational grant from AstraZeneca Pharmaceuticals. In this report, the HEMI-ACS panel examined the rationale for upstream dual antiplatelet therapy in NSTEMI patients.

Among other points of interest, the panel focused on concerns about and approaches to NSTEMI patients by multiple stakeholders such as EPs, hospitalists, and cardiologists to create a seamless transition in care upon discharge to primary care physicians (PCPs). However, as practiced today, some EPs and hospitalists withhold antiplatelet therapy because of the inordinate concern that an NSTEMI patient will require coronary artery bypass graft (CABG) surgery, because of qualitative concerns about bleeding, or because the continuum of care is sufficiently fractured that they do not feel empowered to initiate this evidence-based, guidelines-supported therapy. In such cases, they tend to defer treatment decisions until they know what management path a patient will take, leaving a downstream provider (often an interventional cardiologist) to make a delayed decision [1•].

Ideally, however, EPs and hospitalists should collaborate together and with their cardiology colleagues to develop protocols for consistent, evidence-based, expeditious care of patients who are admitted to the hospital from the emergency department [2•]. With this in mind, from the moment a NSTEMI patient presents to the ED, an EP can consider that patient’s potential hospital path (e.g., admission to medical floor, catheterization, CABG), evaluate bleeding risk in response to therapy in a systematic way, and assess the potential impact of ED-administered therapies on the decisions of downstream providers.

The hospitalists’ approach to NSTEMI patients is likewise important because not only do they manage increasing numbers of these patients after admission—whatever their inpatient path may be—they also “inherit” the consequences of the EPs’ upstream treatment decisions and are in a position to initiate upstream DAPT if not done in the ED. Published guidelines call for a number of diagnostic and therapeutic actions that readily lend themselves to inclusion in a protocol that can be initiated in the ED and continued by hospitalists towards assumption of care by the cardiologist [3•].

For this report, the concept of the “upstream” setting is defined as:

- Prior to diagnostic angiography in NSTEMI patients managed by an invasive strategy and
- The first 48 h of care in NSTEMI patients who are managed medically

This report will focus on antiplatelet therapy rather than on anticoagulation therapy.

Fig. 1 Balancing ischemic efficacy and bleeding risk in NSTEMI-ACS

Fig. 2 Schematic depiction of how the risks of ischemia, bleeding or “doing nothing” are intertwined in the upstream management of NSTEMI

Although there is evidence that early, proactive anti-thrombotic treatment improves outcomes in the NSTEMI patient population, adherence to guidelines for the use of advanced antiplatelet therapies remains low for those patients who are most likely to benefit from them [4, 5•]. It is our contention that upstream initiation of dual antiplatelet therapy should be routinely considered for NSTEMI patients if the expected anti-ischemic benefits outweigh the risk for treatment-related bleeding, and that EPs and hospitalists should feel comfortable with making—and be empowered to make—that decision (see Fig. 2).

Pathophysiologic Basis for Antiplatelet Therapy

Platelets are crucial to hemostasis both directly, by adhering to injured vessel walls, and indirectly, by secreting procoagulant

agents during the formation of clots [6]. As such, they also play a central role in the pathophysiology of ACS. Collagen, thrombin, adenosine diphosphate (ADP), and thromboxane A₂ (TXA₂) are some of the principal stimuli of platelet activation that induce change in shape, secretion, and aggregation, and as such represent potential therapeutic targets in ACS (Fig. 3) [7].

As illustrated in Fig. 3, platelet activation occurs when the vascular endothelium is damaged and the underlying collagen and tissue factor from the sub-endothelial matrix (ECM) are exposed to circulating platelets. Platelets then bind directly to collagen-specific glycoprotein surface receptors and become activated. Collagen acts primarily through the GP IIb/IIIa receptor, whereas thrombin, ADP, and TXA₂ function through G-protein-coupled receptors (GPCRs). This adhesion is further strengthened by the von Willebrand factor (vWF), which is released from the endothelium and from platelets and fibrinogen (Fg); vWF forms additional links between the platelets' glycoproteins (GP) and the collagen fibrils to continue the platelet activation cascade [7]. Platelet activation by ADP is mediated by the P₂Y₁ and P₂Y₁₂ receptors; P₂Y₁₂ is the major receptor responsible for platelet activation by ADP. Activation of P₂Y₁ receptors results in an increase in intracellular calcium, which triggers platelet activation and degranulation, initiating signaling cascades that cause platelet aggregation and lead to the growth of thrombi [8].

Antiplatelet Therapies: Overview

Antiplatelet therapy has been called the “cornerstone” of treatment in ACS because platelet activation and aggregation are at the pathophysiologic root of the disease. There are several

Fig. 3 Platelet activation [8]

Fig. 4 Sites of action of different antiplatelet therapies [7] (from Kavanagh et al. [36])

modes of action for antiplatelet therapy, generally distinguished by the target platelet receptor, as highlighted in Fig. 4.

Aspirin, the foundational antiplatelet medication, irreversibly acetylates cyclooxygenase 1 (COX-1), preventing the synthesis of TXA₂, a key player in the platelet activation process. Aspirin is also thought to exert an intravascular anti-inflammatory effect that is beneficial in acute thrombosis. Thienopyridines (ticlopidine, clopidogrel, prasugrel, elinogrel) and triazolopyrimidines (ticagrelor) interfere with platelet activation by blocking the interaction of ADP with its platelet receptor (P2Y₁₂). Phosphodiesterase inhibitors (PI) such as dipyridamole are thought to act by blocking the decomposition of cyclic adenosine monophosphate (cAMP), which inhibits calcium release during platelet activation. Glycoprotein IIb/IIIa receptor antagonists block fibrinogen receptors, which are involved in the final step of the platelet aggregation pathway in which activated platelets are linked together via strands of fibrinogen [7].

Aspirin should be given as soon as possible to patients with symptoms of ACS. The preferred dose is 324 (81 × 4) or 325 mg of non-enteric-coated drug. In addition, where dual antiplatelet therapy is warranted, P2Y₁₂ receptor blockers have become the drug of choice (Table 1). The early success of ticlopidine and clopidogrel showed this receptor to be a useful target for the prevention of platelet activation. Newer

P2Y₁₂ agents, ticagrelor and prasugrel, have recently come on the market, and other such agents are in development (e.g., cangrelor, elinogrel) [9]. Ticlopidine was the first thienopyridine investigated in ACS, but its use declined due to concern for its well-documented hematologic adverse events, and it was replaced by clopidogrel in the US despite an absence of head-to-head data [10].

Prasugrel will not be examined in this review as a potential upstream agent because the evidence from the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction) [11], TRILOGY (The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) [12], and ACCOAST (A Comparison of Prasugrel at PCI or Time of Diagnosis of Non-ST Elevation Myocardial Infarction) [13] studies do not support a role for this drug in NSTEMI prior to stenting. The TRITON-TIMI 38 trial randomized 13,608 moderate- to high-risk ACS patients scheduled for PCI to receive prasugrel (60-mg loading dose and then 10-mg daily maintenance dose) or clopidogrel (300-mg/75-mg) for 6–15 months while the TRILOGY ACS trial involved 9,326 (7,243 patients < 75 years old) who were treated with prasugrel (10 mg daily) versus clopidogrel (75 mg daily) within ten days of presentation with either unstable angina or NSTEMI myocardial infarction

Table 1 Antiplatelet therapies

Drug	Type	Indication	Pros	Cons	Contraindications	Mode of dose
Clopidogrel	P2Y ₁₂ antagonist	ACS Recent MI, recent stroke, or established PAD	Familiarity from 10 years of use Lower cost Universally available	Prodrug that requires metabolism by the cytochrome P450 system, slowing onset of action Irreversible Long duration of action warrants delays for CABG/major surgery if possible Drug–drug interactions with omeprazole Boxed warning: Diminished effectiveness in poor metabolizers Not to be used upstream, based on TRITON-TIMI 38 [11], TRILOGY [12], and ACCOAST Only downstream Only after stenting Significantly higher bleeding risk than clopidogrel Boxed warnings: Do not use in patients with active pathological bleeding or a history of transient ischemic attack or stroke Generally not recommended in patients $\geq$ 75 years of age Do not use in patients likely to undergo urgent CABG surgery 14 % of patients in PLATO reported dyspnea Boxed Warning: Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial hemorrhage Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided	Active pathological bleeding, such as peptic ulcer or intracranial hemorrhage Hypersensitivity to clopidogrel or any component of the product	Oral
Prasugrel	P2Y ₁₂ antagonist	ACS (UA/NSTEMI and STEMI) patients who are to be managed with PCI	Prodrug, but rapid onset of action after oral administration Achieved greater and more consistent platelet inhibition in individual patients as compared with clopidogrel in TRITON-TIMI 38 [11]	Not to be used upstream, based on TRITON-TIMI 38 [11], TRILOGY [12], and ACCOAST Only downstream Only after stenting Significantly higher bleeding risk than clopidogrel Boxed warnings: Do not use in patients with active pathological bleeding or a history of transient ischemic attack or stroke Generally not recommended in patients $\geq$ 75 years of age Do not use in patients likely to undergo urgent CABG surgery 14 % of patients in PLATO reported dyspnea Boxed Warning: Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial hemorrhage Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided	Active pathological bleeding Prior transient ischemic attack or stroke Hypersensitivity to prasugrel or any component of the product	Oral
Ticagrelor	P2Y ₁₂ antagonist	ACS	Not a prodrug Onset of platelet inhibition is rapid and predictable Studied upstream in PLATO [25••] Benefit vs. clopidogrel independent of downstream management (medical vs. PCI vs. CABG)	Not to be used upstream, based on TRITON-TIMI 38 [11], TRILOGY [12], and ACCOAST Only downstream Only after stenting Significantly higher bleeding risk than clopidogrel Boxed warnings: Do not use in patients with active pathological bleeding or a history of transient ischemic attack or stroke Generally not recommended in patients $\geq$ 75 years of age Do not use in patients likely to undergo urgent CABG surgery 14 % of patients in PLATO reported dyspnea Boxed Warning: Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial hemorrhage Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided	History of intracranial bleeding Active pathological bleeding Severe hepatic impairment Hypersensitivity to ticagrelor or any component of the product	Oral

Table 1 continued

Drug	Type	Indication	Pros	Cons	Contraindications	Mode of dose
Abciximab	GPIIb/IIIa inhibitor	Indicated as an adjunct to PCI for prevention of cardiac ischemic complications in patients undergoing PCI In patients with UA not responding to conventional medical therapy when PCI is planned within 24 h	Binds the GP IIb/IIIa receptor with very high affinity Good results in diabetics	Associated with a significantly higher incidence of thrombocytopenia within 4 h of drug initiation than eptifibatide [37] GUSTO IV (Global Use of Strategies to Open Occluded Coronary Arteries) trial of abciximab, studying upstream and prolonged infusions of the drug, was not only negative but also associated with increasing rates of thrombotic complications with increasing durations of infusion [14] Highest cost of the GPIIb/IIIa inhibitors	Active internal bleeding Recent (within 6 weeks) gastrointestinal (GI) or genitourinary (GU) bleeding of clinical significance History of cerebrovascular accident (CVA) within 2 years, or CVA with a significant residual neurological deficit Bleeding diathesis Administration of oral anticoagulants within 7 days unless prothrombin time ≤ 1.2 times control Thrombocytopenia ($<100,000$ cells/ μL) Recent (within 6 weeks) major surgery or trauma Intracranial neoplasm, arteriovenous malformation, or aneurysm Severe uncontrolled hypertension Presumed or documented history of vasculitis Known hypersensitivity to any component of this product or to murine proteins	i.v.
Tirofiban	GPIIb/IIIa inhibitor	Indicated to reduce the rate of thrombotic cardiovascular events (combined endpoint of death, myocardial infarction, or refractory ischemia/repeat cardiac procedure) in patients with NSTEMI-ACS	Competitive blocker to fibrinogen at the platelet GP IIb/IIIa receptor Suitable for upstream or cath lab use	In TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Trial), abciximab was superior to tirofiban in a combined end point of death and MI when the original low, 10 μg bolus dose of tirofiban is used [38]	Known hypersensitivity to any component of tirofiban History of thrombocytopenia with prior exposure to tirofiban Active internal bleeding, or history of bleeding diathesis, major surgical procedure or severe physical trauma within the previous month	i.v.

Table 1 continued

Drug	Type	Indication	Pros	Cons	Contraindications	Mode of dose
Eptifibatide	GPIIb/IIIa inhibitor	Indicated for: Treatment of ACS managed medically or with PCI Treatment of patients undergoing PCI (including intracoronary stenting)	Competitive blocker to fibrinogen at the platelet GP IIb/IIIa receptor Suitable for upstream or cath lab use	EARLY-ACS suggests trade-off between efficacy and bleeding often not favorable for upstream therapy [16]	Bleeding diathesis or bleeding within the previous 30 days Severe uncontrolled hypertension (4) Major surgery within the preceding 6 weeks Stroke within 30 days or any history of hemorrhagic stroke Coadministration of another parenteral GP IIb/IIIa inhibitor Dependency on renal dialysis Known hypersensitivity to any component of the product	i.v.

who are not intended to undergo revascularization procedures. The ACCOAST trial involved 4,033 patients with non-ST-elevation ACS and a positive troponin level who were scheduled to undergo coronary angiography within 2–48 h of randomization and randomly assigned 1:1 to prasugrel 30 mg before angiography or a matching placebo. The high overall bleeding risk with prasugrel also limits its utility in a clinical setting in which the coronary anatomy is unknown.

Dual antiplatelet therapy could also be provided with ASA and an anti-aggregation antiplatelet agent. The three currently available GPIIb/IIIa inhibitors are the most potent antiplatelet therapies available to date and represent three distinct molecular entities: the monoclonal antibody abciximab (not supported in the upstream environment based on GUSTO-IV-ACS (Global Use of Strategies to Open Occluded Coronary Arteries IV-Acute Coronary Syndrome) study) [14], the non-peptide tyrosine derivative tirofiban, and the cyclic heptapeptide eptifibatide.

As a group, GPIIb/IIIa inhibitors provide a high level of platelet blockade; their principal benefit resides in their unique mechanism of action: the ability to prevent aggregation of activated platelets, thrombus formation, and distal thromboembolism because they exert their activity later in the pathway than any other antiplatelet class. Their action blocks aggregation regardless of the agonist (ADP, thrombin, collagen, etc.) that activates the platelets [15]. Although this high potency is associated with more severe bleeding events than with other types of agents, the use of parenteral GPIIb/IIIa inhibitors is well established. Guidelines continue to support their use in dual antiplatelet therapy, but the EARLY-ACS data call into question their routine utility in the upstream setting.

The EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome) trial examined the early use of eptifibatide in the setting of concurrent upstream (but not always early) clopidogrel use, both upstream (immediately after diagnosis and before coronary angiography) and downstream (peri-coronary or post-coronary angiography), and found that at 30 days, the rate of death or myocardial infarction in the earlier-eptifibatide group was about the same as compared with the delayed-eptifibatide group. These agents can also be a component of so-called “triple” therapy—ASA, a P2Y₁₂ inhibitor, and a IIb/IIIa antagonist; such therapy is reserved for patients at high ischemic risk with ongoing chest pain and low bleeding risk [16].

Advanced Anti-Platelet Therapies Suitable for Upstream Use in NSTEMI

Clopidogrel

Clopidogrel is an oral, irreversible platelet inhibitor that has been available since 1997 and has been studied

Fig. 5 Results from the CURE Trial

extensively in patients with NSTEMI. The drug works by irreversibly inhibiting the platelet P2Y₁₂ receptor, an ADP chemoreceptor on platelet cell membranes [16]. The first clinical evidence of the therapeutic benefit of clopidogrel appeared in the results of the Clopidogrel in Unstable Angina to Prevent Recurring Events (CURE) trial, in which patients with NSTEMI-ACS were randomized to receive aspirin alone or dual antiplatelet therapy (DAPT) with aspirin plus clopidogrel [17]. In this study, clopidogrel reduced the primary combined end point of death, MI, and stroke by 20 % in the overall study population (9.3 vs. 11.4 %; RR 0.80, 95 % confidence interval (CI) 0.72–0.90; $P < 0.001$); this effect persisted from 24 h following drug administration throughout the 12 months of the study [18] (see Figs. 5 and 6).

Cumulative hazard rates were for the first primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or stroke) during the 12 months of the study [17].

Since results of that landmark trial were published, results of several other trials and contemporary registries have highlighted the efficacy of clopidogrel in the ACS setting and supported the rationale for the use of DAPT. Studies such as PCI-CURE focused on a subset of CURE NSTEMI patients undergoing percutaneous coronary intervention (PCI). For those patients who were preloaded with clopidogrel and aspirin plus long-term DAPT thereafter, the relative risk of CV mortality and ischemic events was reduced by 25 % when compared with that of patients who did not receive DAPT prior to treatment and took only 2–4 weeks of DAPT post after PCI (8 vs. 6 %; $P = 0.047$) [18].

Clopidogrel is suitable as an option for EPs and hospitalists to consider for upstream DAPT. Clinical trials offer evidence that clopidogrel is effective in an upstream setting and is beneficial regardless of whether downstream care is medically, PCI-driven, or CABG-driven [18–20]. Second, clopidogrel has a real-world track-record, with more than ten years of clinical experience that has led to familiarity

Fig. 6 Primary efficacy (events prevented) and excess in life-threatening bleeding in clopidogrel group compared with placebo group. Difference between two curves shows net absolute benefit of clopidogrel [4]

with and comfort in use. Third, there are data from CURE that show ischemic benefit accruing within 24 h of dosing (Fig. 6). Given that contemporary data from ACTION indicate the median time from ED arrival to diagnostic angiography in NSTEMI is about 23 h, this speed of clinical effect—with a 300 mg loading dose that now is often doubled in order to accelerate onset of action even more—should resonate with both upstream and downstream providers. A secondary analysis of the CURE data (see Fig. 7) by Yusuf suggests that efficacy from a 300 mg loading dose may accrue as early as 24 h after administration [4]. Fourth, clopidogrel use has been associated with very few fatal bleeding events; and fifth, clopidogrel is a generic drug with low procurement cost.

There are, however, important limitations to clopidogrel as the drug of choice for upstream DAPT in NSTEMI patients. First, clopidogrel is a prodrug that must be metabolized by CYP450 enzymes (specifically CYP2C19) to produce the active metabolite that inhibits platelet activation [16]. Thus, its onset of action is slow, and platelet inhibition usually occurs 5–6 h after a single loading dose (LD) of 300 mg of oral clopidogrel is administered, and 3–5 days at the standard daily oral dose of 75 mg without a LD. Results of recent studies (e.g., ARMYDA-5) [18] have suggested that increasing the LD of clopidogrel to 600 mg may improve the drug's efficacy. This dependence on CYP450 metabolism also results in potential drug–drug interactions when clopidogrel is used concomitantly with inhibitors of the CYP450 enzyme such as proton pump inhibitors (PPIs) and has become a major concern for practitioners and the public revolving around the potential interaction.

To address concerns that have been raised about the potential for PPIs to blunt the efficacy of clopidogrel, the

Clopidogrel and Optimization of Gastrointestinal Events (COGENT) trial sought to determine whether PPI versus placebo reduced important GI events in patients on dual antiplatelet therapy [20]. The investigators randomly assigned 3,761 patients with an indication for dual antiplatelet therapy to receive clopidogrel in combination with either omeprazole or placebo, and with two primary endpoints they looked at a composite of overt gastrointestinal issues and standard cardiovascular end points and concluded that there was a lack of clinically important interaction between omeprazole and a clopidogrel-based dual antiplatelet regimen.

Second, due to the irreversible binding of clopidogrel to the ADP receptor, platelets exposed to the active metabolite of clopidogrel are affected for the remainder of their lifespan (about 7–10 days), which can increase the risk of bleeding. According to its label, clopidogrel should be discontinued five days prior to elective surgery, such as CABG procedures [16].

Finally, inter-patient metabolic variability in converting the pro-drug to the active moiety must also be considered when using clopidogrel. Multiple *in vivo* studies have shown a genetically determined lack of uniform response to the drug [21]. For instance, decreased response to clopidogrel is common among Asians (nearly 70 % in some communities) due to genetic polymorphisms associated with hypo-responsiveness, [22] and use in this population has been associated with increased risk of recurrent ischemic events [20] (see Fig. 7).

Ticagrelor

Ticagrelor, an oral platelet ADP receptor inhibitor, has been available since 2011. It is indicated to reduce the rate

of thrombotic cardiovascular events in patients with ACS. In common with the thienopyridines (e.g., clopidogrel and prasugrel), ticagrelor binds to the platelet P2Y₁₂ ADP receptor, preventing ADP-mediated activation of the GPIIb/IIIa receptor complex and thereby preventing platelet activation and, indirectly, aggregation. Unlike the thienopyridines, ticagrelor is a reversible antagonist of the P2Y₁₂ receptor and belongs to a related class of compounds, called cyclo-pentyl-triazolo-pyrimidines (CPTPs) [23]. In contrast to clopidogrel (and prasugrel), it is not a prodrug and does not depend upon metabolic activation [24].

Ticagrelor is, thus, characterized by a faster onset of action, relatively quick reversibility, and greater potency and consistency of platelet inhibition when compared with clopidogrel. Use of the drug leads to therapeutic inhibition of ADP-induced platelet activation as soon as 2–4 h following a loading dose of 180 mg; this platelet inhibition is sustained with twice-daily doses of 90 mg [20].

Although ticagrelor is a relatively new drug in the ACS space and has, thus, not established a record of use over a long period of time as has clopidogrel, some of its attributes suggest that it can be an appropriate option as an antiplatelet agent in NSTEMI patients. First, the seminal clinical trial PLATO (The Study of Platelet Inhibition and Patient Outcomes) showed a mortality benefit of ticagrelor over clopidogrel. PLATO evaluated 18,624 patients with ACS (with or without ST-segment elevation) who had an onset of symptoms during the previous 24 h. Patients were randomized to receive ticagrelor 90 mg twice daily or clopidogrel 75 mg once daily for 12 months; both groups also received aspirin up to 325 mg daily. PLATO concluded that ticagrelor reduced the primary efficacy endpoint, a composite of cardiovascular death, MI, or stroke,

Fig. 7 Cardiovascular death, MI, stroke, and severe ischemia within first 24 h after randomization. Adapted from Yusuf [4]

Fig. 8 PLATO study design
(*numbers of patients
randomized and treated:
ticagrelor 9,235; clopidogrel
9,186)

Fig. 9 Cumulative Kaplan–Meier estimates of the time to the first adjudicated occurrence of the primary efficacy end point (from Wallentin et al. [25••])

from 11.7 to 9.8 % versus clopidogrel [hazard ratio (HR), 0.84; $P < 0.0011$]. Rates of major bleeding overall were similar [25••] (see Fig. 8).

Ticagrelor significantly reduced the single endpoint of overall mortality by 22 % compared with clopidogrel (4.5 vs. 5.9 %; $P < 0.001$). Although overall bleeding rates were similar, ticagrelor was associated with increased rates of major bleeding not related to CABG (4.5 vs. 3.8 %; $P = 0.03$), dyspnea (13.8 vs. 7.8 %; $P < 0.001$), and discontinuation due to adverse events (7.4 vs. 6.0 %; $P < 0.001$) [26].

The primary endpoint—a composite of death from vascular causes, myocardial infarction, or stroke—occurred

significantly less often in the ticagrelor group than in the clopidogrel group (9.8 vs. 11.7 % at 12 months; hazard ratio, 0.84; 95 % confidence interval, 0.77–0.92; $P < 0.001$).

Notably, although ticagrelor is a reversible agent with more rapid onset of action and offset of action as clopidogrel, the Food and Drug Administration (FDA) mandated that its label carry the same information as that of the latter regarding patients who will undergo a CABG procedure, that is, a 5-day delay [23]. Notably, in PLATO, investigators sending ticagrelor-treated patients to CABG were advised to wait 48–72 h, not 5 days, prior to surgery, and those patients who underwent CABG after being randomized to ticagrelor experienced significantly lower

Table 2 EARLY ACS: key end points (adapted from Giugliano et al. [33])

End point	Routine early eptifibatide (%)	Provisional delayed eptifibatide (%)	OR (95 % CI)	<i>P</i>
Death/MI/recurrent ischemia requiring urgent revascularization/thrombotic bailout at 96 h ^a	9.3	10.0	0.92 (0.80–1.06)	0.23
Death/MI at 30 days	11.2	12.3	0.89 (0.79–1.01)	0.08
TIMI major bleed	2.6	1.8	1.42 (1.07–1.89)	0.015
TIMI minor bleed	3.6	1.7	2.14 (1.63–2.81)	<0.001

^a Primary end point

mortality than similarly managed patients who were treated with clopidogrel [27, 28].

Third, ticagrelor is not a pro-drug, so it does not require metabolic activation via liver enzymes. This attribute minimizes the effects of genetic metabolic polymorphisms and, thus, fluctuations in bioavailability. Ticagrelor is metabolized by the CYP450 pathways, but its drug–drug interactions are minimal. Prescribing information for ticagrelor suggests avoiding concomitant use of drugs that are either strong CYP3A4 inhibitors (e.g., ketoconazole, many antiviral medications) or CYP3A4 inducers (e.g., dexamethasone, antiseizure medications, St. John's wort) [23] (see Fig. 9).

Fourth, PLATO suggests that ticagrelor's efficacy advantage over clopidogrel is independent of later management approaches. In PLATO, the benefit of ticagrelor was present in medically managed, PCI-treated, and CABG-treated patients. This is an important consideration for the first providers, who cannot know for certain the subsequent course of the NSTEMI patient.

It is worth noting that the most recent European Society of Cardiology NSTEMI-ACS Guidelines [10•] suggest that ticagrelor—specifically—should be considered as the first-line antiplatelet therapy after ASA. These guidelines even suggest switching patients initially treated with clopidogrel to ticagrelor, likely referring to the mortality benefit.

Some of the potential drawbacks to the use of ticagrelor are that no generic version is currently available and procurement costs of the drug over the span of a 12-month treatment regimen are substantially higher than for generic clopidogrel. However, a substudy of the PLATO trial showed that treating a broad spectrum of ACS patients with ticagrelor was more cost-effective than treatment with generic clopidogrel [29]. In this Swedish substudy, the price of generic clopidogrel was \$0.23 per day as compared with the \$3.00 to \$4.65 per day price range of ticagrelor. Their analysis of health care costs and quality adjusted life years from PLATO found that using ticagrelor instead of clopidogrel was cost effective.

With regards to adverse events, with few exceptions, ticagrelor appears to have a similar profile as compared to

clopidogrel. In PLATO, ticagrelor was associated with a higher rate of major bleeding not related to coronary-artery bypass grafting (CABG) when compared with clopidogrel (4.5 vs. 3.8 %, respectively; *P* = 0.03). Also, ticagrelor was associated with a higher level of dyspnea than with clopidogrel (13.8 vs. 7.8 %), although few discontinued the study drug because of dyspnea (0.9 % with ticagrelor vs. 0.1 % in the clopidogrel group) [25••]. All other adverse events were similar between the two groups.

Based on results from the PLATO study, ticagrelor can significantly reduce the rate of death from vascular causes, myocardial infarction, and stroke in comparison with the leading antiplatelet therapy, clopidogrel. However, there remains a data gap regarding the use of both agents, specifically in the upstream setting, and more studies will be required to validate its recommendation as the upstream antiplatelet therapy of choice in NSTEMI patients. Clopidogrel—a drug shown to be inferior to ticagrelor in PLATO—was recently shown in a large meta-analysis to reduce cardiovascular complications in NSTEMI patients without raising the risk of major bleeding [5•]. Similar signals were found in an ACTION study that also included a few ticagrelor-treated patients [1]. Prospective validation of upstream efficacy and an acceptable risk–benefit trade-off is needed, but in the meantime there are no compelling data supporting harm from upstream use of ticagrelor or clopidogrel [30].

GPIIb/IIIa Inhibitors: Is There a Role for Them Upstream?

GPIIb/IIIa inhibitors, parenteral drugs that block the final common pathway of platelet aggregation, are used upstream with decreasing frequency in contemporary ACS care. Three intravenous GP IIb/IIIa inhibitors are available to USA physicians: abciximab, tirofiban, and eptifibatide. Abciximab is not suitable as an upstream agent in NSTEMI, based on results from the GUSTO IV-ACS study (Global Utilization of Strategies to open Occluded coronary arteries trial IV in Acute Coronary Syndromes), in which abciximab demonstrated no significant benefit over

placebo in NSTEMI patients with respect to the primary end point of death or MI at 30 days [14]; further, a trend toward higher all-cause mortality was seen with longer infusions of abciximab [31].

Glycoprotein IIb/IIIa inhibitors provide a high level of platelet blockade because they act later in the pathway than any other class of antiplatelet agent and can inhibit aggregation after activation. While this unique pharmacology provides for an advantage, their high potency has also been associated with the occurrence of more severe bleeding events. Thus, the optimal role for GP IIb/IIIa inhibitors in the upstream therapy of NSTEMI patients is unclear.

Small-molecule GP IIb/IIIa inhibitors (eptifibatide and tirofiban) are effective antiplatelet agents with rapid onset of action and a relatively short half-life. These drugs are low-molecular-weight molecules that competitively inhibit the GPIIb/IIIa receptor, resulting in a brief receptor blockade. Both drugs undergo renal clearance and require dose adjustment in patients with kidney disease [15].

Although the optimal timing for the initiation of treatment with GPIIb/IIIa inhibitors in patients with NSTEMI-ACS has not been extensively studied, some clinical data is available. In the PURSUIT trial (Platelet Glycoprotein IIb/IIIa in UA: Receptor Suppression Using Integrilin Therapy), patients with ischemic pain within the previous 24 h who also had electrocardiographic changes suggestive of ischemia or an elevated MB fraction of creatinine kinase were randomly assigned to receive a bolus and infusion of either eptifibatide or placebo for up to 72 h (96 h in patients undergoing PCI). Patients who received eptifibatide had a 1.5 % absolute reduction in incidence of the primary end-point of death or nonfatal MI at 30 days ($P = 0.04$) [32].

The EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome) trial examined the early use of eptifibatide in the setting of concurrent clopidogrel use immediately after diagnosis and before coronary angiography, as well as peri-coronary or post-coronary angiography. At 30 days, the rate of death or myocardial infarction was 11.2 % in the early-eptifibatide group, as compared with 12.3 % in the delayed-eptifibatide group; a 1.1 % absolute reduction that did not achieve statistical significance ($P = 0.08$) [33]. The researchers concluded that the early use of eptifibatide did not improve short-term ischemic outcomes but “may be associated” with a reduced 30-day ischemic risk when administered with clopidogrel. However, their suggested potential benefit was also associated with an increased rate of TIMI major bleeding [34] (see Table 2).

So how should this be interpreted in the setting before coronary angiography? GP IIb/IIIa agents such as

eptifibatide have a rapid onset. Their anti-aggregation ability trumps any single anti-activation agent, and they are highly efficacious in hyperacute patients. Further, GP IIb/IIIa agents have a secondary action of disaggregating existing coronary thrombi that works after platelet activation (as do the other agents) so they are well suited for patients with high ischemic risk and high probability to undergo CABG due to their rapid reversibility.

However, increased bleeding risk associated with their use and lack of robust clinical evidence in the upstream setting suggest that they be used with caution in the NSTEMI setting. It should be noted that for NSTEMI-ACS patients, the recommendations for GP IIb/IIIa differ between the European Society of Cardiology (ESC) [10•] and the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines [35]. Although the ESC suggest withholding GPIIb/IIIa inhibitors until post-angiography unless there is ongoing ischemia or when oral dual antiplatelet is not feasible (class IIA), the USA guidelines recommend their pre-angiographic use as an alternative to clopidogrel (class I) or with clopidogrel (class IIA) in patients beginning an initial invasive strategy [20, 21].

Conclusions

Acute coronary syndrome is a dynamic disease, and the early use of dual antiplatelet therapy has been shown to be beneficial to outcomes. The authors sought to review evidence for the upstream use of antiplatelet therapy in the emergency department and inpatient setting with the proposal that upstream dosing is beneficial if the ischemic benefits outweigh risk for bleeding or if potential benefits are better than no therapy—“doing nothing” for antiplatelet therapy beyond ASA.

The continuum of care from the ED (through either PCI or CABG if needed), to inpatient care, to discharge and outpatient care must be as seamless as possible. Emergency and hospital physicians should practice upstream with an eye towards the post-angiographic consequences (e.g., is this patient highly likely to go to CABG) management, knowing that actions they take are certain to affect future medical decisions for any given patient.

As we have highlighted throughout this report, specific factors favoring upstream use of antiplatelet therapies include: if the ischemic risk is greater than the bleeding risk, if patients are high risk (e.g., diabetic, prior stent, high TIMI score, and if patients have a planned catheterization). Specific factors that do not support upstream use of antiplatelet therapy in NSTEMI patients include obvious bleeding risk and known three-vessel disease (or other known reason for surgery).

Thus, for troponin-positive, type 1 NSTEMI patients, the authors conclude that all patients should be candidates for early antiplatelet therapy with ticagrelor or clopidogrel and recognize that the two drugs were compared in this setting in the PLATO trial. The authors reaffirm that potential benefits of this therapy must clearly outweigh risks and that no therapy beyond ASA should be given upstream if the risk for bleeding is high.

Compliance with Ethics Guidelines

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

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- Of importance
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