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Pre-Hospital Antiplatelet Therapy for STEMI Patients Undergoing Primary Percutaneous Coronary Intervention: What We Know and What Lies Ahead

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Abstract

Early recanalization of the infarct-related artery to achieve myocardial reperfusion is the primary therapeutic goal in patients with ST-elevation myocardial infarction (STEMI). To decrease the duration of ischaemia, continuous efforts have been made to improve pre-hospital treatment and to target the early period after symptom onset. In this period the platelet content of the fresh coronary thrombus is maximal and the thrombi are dynamic, and thus more susceptible to powerful antiplatelet agents. There have been substantial advances in antiplatelet therapy in the last three decades with several classes of oral and intravenous antiplatelet agents with different therapeutic targets, pharmacokinetics, and pharmacodynamic properties. New parenteral drugs achieve immediate inhibition of platelet aggregation, and fast and easy methods of administration may create the opportunity to bridge the initial gap in platelet inhibition observed with oral $P2Y_{12}$ inhibitors. Moreover, potential future management of STEMI could directly involve patients in the process of care with self-administered antiplatelet agents designed to achieve rapid reperfusion. However, the potential anti-ischaemic benefits of potent antiplatelet agents will need to be balanced against their risk of increased bleeding. This study presents a comprehensive and updated review of pre-hospital antiplatelet therapy among STEMI patients undergoing primary percutaneous intervention and explores new therapies under development.

Keywords

- myocardial infarction
- STEMI
- pre-hospital
- coronary reperfusion
- antiplatelet therapy
- $P2Y_{12}$ inhibitors
- glycoprotein IIb/IIIa
- selatogrel
- RUC-4

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Introduction

ST-elevation myocardial infarction (STEMI) is characterized by a tear or erosion of an atherosclerotic plaque in the coronary circulation, followed by occlusive or near-occlusive arterial thrombus formation and critical reduction in blood flow to the downstream myocardial tissue.[1] Although rare, coronary artery thromboembolism is a non-atherosclerotic cause of STEMI, and may be a clinical manifestation of a hypercoagulable state.[2]

Early and complete recanalization of the infarct-related artery to achieve myocardial reperfusion significantly reduces morbidity and mortality among patients with STEMI and is the primary therapeutic goal.[3] Current practice guidelines emphasize the organization of STEMI networks since they decrease transfer time to primary percutaneous coronary intervention (PCI) centres and allow the initiation of STEMI treatment at the first medical contact by trained and equipped medical or paramedical staff.[3] Indeed there is a general consensus that early administration of antiplatelet therapy should be given early when the probability of PCI is high such as for STEMI.[4]

There have been substantial advances in antiplatelet therapy in the last three decades, with several classes of oral and intravenous (IV) antiplatelet agents with different therapeutic targets, pharmacokinetics and pharmacodynamic properties. Nevertheless, finding the optimal therapeutic regimen and the appropriate timing of drug administration remains a clinical challenge. In an effort to decrease the duration of ischaemia, the early period after symptom onset represents a golden opportunity in the management of STEMI patients. Accordingly, continuous efforts have been made to improve pre-hospital treatment to target this critical time period. This study presents a comprehensive and updated review of pre-hospital antiplatelet therapy among STEMI patients undergoing primary PCI and explores new therapies under development.

Platelet Inhibition

STEMI is a dynamic event in which platelet activation is a key step in the process leading up to thrombus formation.[5] Disruption of the cap of an atherosclerotic plaque exposes matrix proteins to which platelets adhere, leading to platelet activation and release of the platelet activators thromboxane A2 and adenosine diphosphate (ADP).[6] These mediators amplify the initial platelet response by binding to their cognate platelet receptors, including the binding of ADP to the platelet $P2Y_1$ and $P2Y_{12}$ receptors,[7] resulting in a conformational change of the αIIbβ3 (glycoprotein IIb/IIIa [GPIIb/IIIa]) receptors on platelets, binding of the plasma proteins fibrinogen and von Willebrand factor (vWF), and platelet aggregation,[8] which creates the nucleus for further thrombus formation. This mechanism occurs rapidly and progressively, thus supporting the need for pharmacotherapies that are fast acting and easily administered. Thus, instituting antithrombotic therapy in the early period after symptom onset provides the best opportunity for improving the outcome of STEMI.[9,10]

Early platelet inhibition facilitates epicardial reperfusion, reduces thrombotic burden, improves microcirculatory function, and reduces ischaemic complications such as stent thrombosis (ST).[11–14] A rapid onset of action (especially in STEMI setting where both the duration of the period of platelet-rich dynamic thrombus formation and the reperfusion benefit are time dependent) and more effective platelet inhibition seem key elements in improving thrombotic outcomes. It has been shown that patients with the highest inhibition of platelet aggregation have less residual ST-segment deviation 1 hour post-PCI.[15] Moreover, there is a significant relationship between platelet function and major adverse cardiovascular events (MACE) and early thrombosis.[15] Data from GPI dosing demonstrate a relationship between achieving at least 80% inhibition of ADP-induced platelet aggregation and clinical outcomes.[16] However, more potent platelet inhibition is associated with increased risk of bleeding. Thus, the risk-to-benefit ratio needs to be personalized to the individual patient's risk of morbidity and mortality related to thrombosis versus their risk of bleeding, especially in elderly patients.[17] However, upstream antiplatelet treatment in STEMI patients has been shown to be relatively safe in terms of major bleeding events.[18–20]

Different classes of antiplatelet drugs are currently available, including oral cyclooxygenase-1 (COX-1) inhibitors (aspirin), $P2Y_{12}$ receptor inhibitors (the oral thienopyridines clopidogrel and prasugrel, the cyclopentyl-triazolopyrimidine ticagrelor, and the IV adenosine triphosphate [ATP] analogue cangrelor), and IV GPIIb/IIIa receptor inhibitors (GPIs; abciximab, tirofiban, eptifibatide). Furthermore, novel agents under investigation include a selective antagonist of the $P2Y_{12}$ receptor developed for subcutaneous administration (Selatogrel) as well as a subcutaneous GPIIb/IIIa receptor inhibitor (RUC-4; ►**Fig. 1**; ►**Table 1**).

Oral Agents

Aspirin

Aspirin is the oldest antiplatelet drug. Aspirin functions primarily by inhibiting production of thromboxane A2 by the enzyme COX-1.[21] The ISIS-2 (Second International Study of Infarct Survival) study was the first trial to demonstrate the efficacy and safety of aspirin following acute myocardial infarction (AMI). The study showed a significant reduction in vascular death among patients who received aspirin compared with placebo (odds reduction: $23 \pm 4\%$; $p < 0.00001$), and aspirin was also associated with significant reductions in re-infarction (1.0 vs. 2.0%) and stroke (0.3 vs. 0.6%).[22] Subsequently, aspirin became the mainstay of AMI treatment, administered as early as possible in all patients with minimal contraindications. Aspirin can be administered orally, and is available in several formulations; non-enteric-coated aspirin and chewed aspirin tablets are recommended in the setting of AMI.[3] Despite the lack of clinical data on the differences among formulations, liquid formulation results in higher peak plasma levels at an earlier time point after administration.[23] Slightly different oral loading doses are recommended depending on the region: 150 to 300 mg in

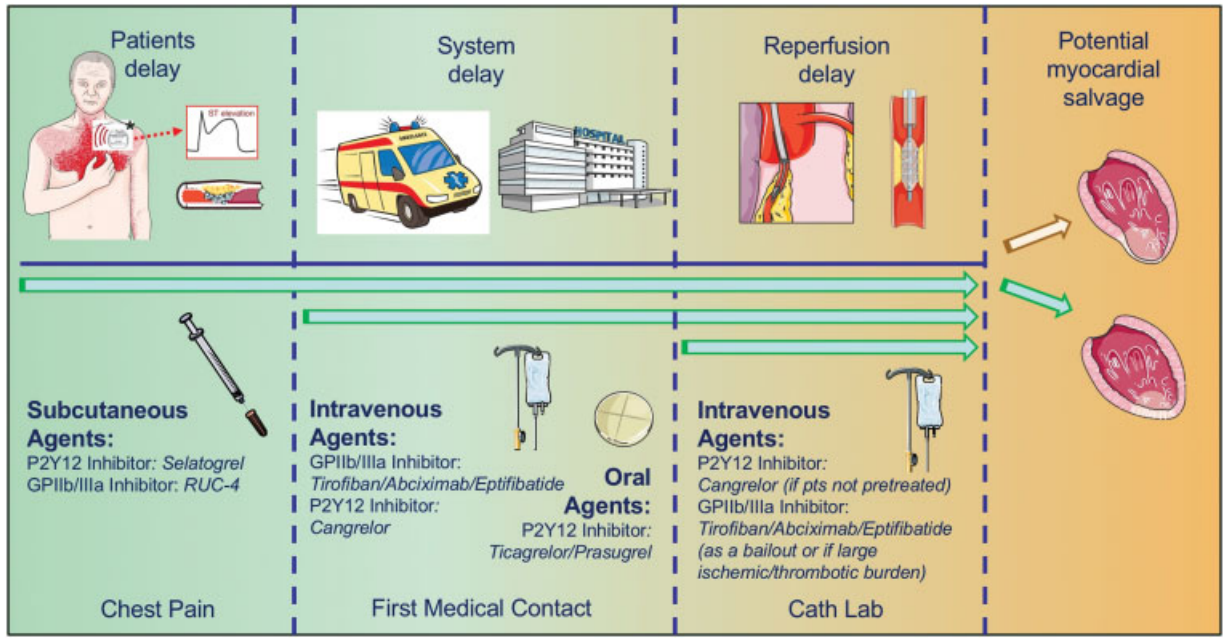

Fig. 1 Different antiplatelet drugs and potential timing of administration before PCI (Pts, patients; GPIIb/IIIa, glycoprotein IIb/IIIa; *implantable or wearable devices, may provide timely recognition of ST elevation, i.e., diagnosis of STEMI could not require the arrival of the ambulance).

Europe[3] and 162 to 325 mg in the United States.[24] IV administration is also feasible and European guidelines recommend the dosage of 75 to 250 mg IV,[3] but there are limited data on the optimal IV dosage. A single loading dose of 250 or 500 mg of IV compared with 300 mg of oral aspirin was associated with faster and more complete inhibition of thromboxane generation and platelet aggregation in a small clinical study, with no differences in bleeding complications.[25] Nevertheless, it is unclear if IV administration of aspirin results in improved clinical outcomes.

Oral $P2Y_{12}$ Receptor Inhibitors

$P2Y_{12}$ receptor inhibitors diminish platelet activation induced by ADP.[26] There is a large body of data that support a dual antiplatelet therapy (DAPT), that is, aspirin plus a $P2Y_{12}$ inhibitor, in patients with acute coronary syndrome

Table 1 Major characteristics of traditional and newer antiplatelet drugs

Antiplatelet agent	Mechanism of action	Reversibility	Onset of action	Peak effect	Duration of action	Route of administration	Trials of prehospital administration
Aspirin	Acetylation of platelet cyclooxygenase	Irreversible	30–60 min	1–2 h	10 d	PO, IV, PR	–
$P2Y_{12}$ inhibitors							
Clopidogrel	Binding to the $P2Y_{12}$ component of ADP receptors	Irreversible	2 h	6 h	5 d	PO	Zeymer et al[47]; Ducci et al[46]
Prasugrel		Irreversible	< 30 min	4 h	5–9 d	PO	Vlachojannis et al[56]
Ticagrelor		Reversible	30 min	2 h	3 d	PO	Montalescot et al[19]
Cangrelor		Reversible	2 min	30 min	1 h	IV	–
Selatogrel		Reversible	15 min	30–60 min[‡]	4–12 h	SC	In planning
Glycoprotein IIb/IIIa inhibitors							
Abciximab	Binding to glycoprotein IIb/IIIa receptors	Irreversible	< 10 min	30 min	3–5 h[a]	IV	Montalescot et al[5]; Arntz et al[66]
Eptifibatide		Reversible	< 5 min	1 h	4–8 h	IV	Hanefeld et al[73]
Tirofiban		Reversible	< 10 min	30 min	4–8 h	IV	van't Hof et al[18]
RUC-4		Reversible[b]	< 15 min	30–60 min	2–4 h[c]	SC	Ongoing (NCT04284995)

Abbreviations: ADP, adenosine diphosphate; IV, intravenous; PO, per os; PR, per rectum; SC, subcutaneous.
[a]Platelet bound antibody detected in the circulation up to 15 days after administration.
[b]Although conformational change to receptor is irreversible, drug effects are reversible.
[c]Dose dependent.

(ACS).[27] Clopidogrel, prasugrel, and ticagrelor are the three widely available oral $P2Y_{12}$ inhibitors. Compared with clopidogrel, prasugrel and ticagrelor exhibit a faster onset of action, as well as more profound and consistent platelet inhibition. The landmark trials of prasugrel and ticagrelor, the TRITON TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction)[28] and PLATO trials (Study of Platelet Inhibition and Patient Outcomes),[29] respectively, showed superior efficacy of these agents compared with clopidogrel, but at the expense of an increase in major bleeding. Recommendations have relegated the use of clopidogrel to patients who have contraindications to prasugrel and ticagrelor, and patients receiving oral anticoagulants.[3] Nevertheless, clopidogrel remains one of the primary oral $P2Y_{12}$ agents employed in real-world practice.[29] Moreover, using a CYP2C19 genotype-guided strategy, clopidogrel may be non-inferior to standard treatment with prasugrel or ticagrelor.[30]

In a comparison of prasugrel vs. ticagrelor, the RAPID trial found no difference in terms of residual platelet reactivity 2 hours after the loading dose in STEMI patients.[31] The PRAGUE-18 study, which enrolled 90% STEMI patients and was stopped early for futility, showed no significant difference in the rate of the primary end point of death, re-infarction, urgent target vessel revascularization, stroke, or serious bleeding at 30 days between hospital arrival administration of prasugrel and ticagrelor in ACS patients.[32] In the 1,653 STEMI patient subgroup of the ISAR-REACT 5 trial,[33] there was no significant difference in the primary composite end point (death, myocardial infarction [MI], or stroke) at 1 year after in-hospital randomization between prasugrel and ticagrelor.[34] With the limit of the open-label design and telephone follow-up in more than 90% of patients, ticagrelor was associated with higher risk of recurrent MI.[34] More data are needed to evaluate the difference between prasugrel and ticagrelor in STEMI patients. Moreover, in this study, STEMI patients were randomized in the hospital phase of treatment; indeed, the randomization took place as soon as possible after admission,[35] and this prevented the initiation of anti-aggregation therapy in the ambulance.

The recommended loading dose of clopidogrel is 600 mg orally, followed by a maintenance dose of 75 mg/d; for ticagrelor, the loading dose is 180 mg orally, followed by 90 mg twice a day; and for prasugrel, the loading dose is 60 mg orally, followed by 10 mg/d; however, for patients with body weight $\leq$60 kg, a maintenance dose of 5 mg/d is recommended. In patients $\geq$75 years of age, prasugrel is generally not recommended, but a dose of 5 mg/d is acceptable if treatment is deemed necessary. Prasugrel is contraindicated in patients with previous stroke or transient ischaemic attack.[3] In selected population, such as elderly or low-weight patients, a reduced dose of prasugrel, compared with the standard dose of ticagrelor, is associated with maintained anti-ischaemic efficacy while protecting these patients against the excess risk of bleeding during 12 months of follow-up.[36]

The optimal timing of DAPT is still subject to debate. Administration of antiplatelet agents at initial contact (in the ambulance or at the emergency department) leads to earlier onset of desired antiplatelet effects, and theoretically, this should translate into improved outcomes. Early administration of oral antiplatelet agents in STEMI patients is complicated by the potential for diminished drug absorption by unfavourable haemodynamic conditions and drug–drug interactions (e.g., with morphine[37]). Morphine delays clopidogrel absorption, decreases plasma levels of clopidogrel active metabolite, and retards and diminishes its effects.[38] In STEMI patients, morphine use was associated with a delayed onset of action of both prasugrel and ticagrelor (and without difference between the two drugs) even after adjusting for the propensity to receive morphine and after excluding patients who suffered regurgitation.[39] The U.S. Food and Drug Administration (FDA) recommends consideration of a parenteral antiplatelet agent in ACS patients requiring coadministration of morphine or other opioid agonists because of the opioids' impact on the absorption of oral $P2Y_{12}$ antagonists. In a recent study, a routine GPI use in morphine-treated STEMI patients undergoing primary PCI appeared to protect against ST.[40]

In observational registries[41–44] and a meta-analysis,[45] clopidogrel pre-treatment has been significantly associated with a reduction in major coronary events and death; however, two small randomized studies[46,47] did not show significant improvement with clopidogrel pre-treatment in terms of myocardial reperfusion. Despite the rationale that supports early administration of oral $P2Y_{12}$ inhibitors, ticagrelor is the only $P2Y_{12}$ inhibitor to have been evaluated in a prospective and randomized fashion in the ATLANTIC trial (Administration of Ticagrelor in the Cath Laboratory or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery). Pre-hospital administration of ticagrelor was safe and was not associated with increased bleeding; however, platelet function testing demonstrated that it produced little antiplatelet effect in the pre-hospital phase.[19] There was no significant difference between the pre- and in-hospital treatment groups in terms of ST-segment elevation resolution and TIMI flow grade 3 at the time of admission to the catheterization laboratory.[19] However, the brief time interval between the study drug administration in the ambulance and catheterization laboratory may have limited the potential benefit of pre-hospital ticagrelor administration. Indeed, because of delays in intestinal absorption, a short time from first medical contact to PCI limits the percentage of STEMI patients likely to have fully inhibited platelets at the time of PCI. In fact, the effects of pre-hospital ticagrelor became apparent after PCI, with difference in platelet reactivity and immediate post-PCI reperfusion associated with reductions in ischaemic end points, including ST, over the first 24 hours after PCI and within 30 days.[14] Whereas the short time to PCI achieved in the ATLANTIC study represents excellent practice, it may not reflect routine practice in a large part of the world. Despite remarkable improvement,[48] the time to reperfusion therapy for STEMI patients transferred for primary PCI is often prolonged, with a significant proportion of transferred patients not achieving the guideline-recommended time from diagnosis to

reperfusion.[48,49] Patients with a delay between the first medical contact and PCI are those most likely to benefit from an early loading dose, allowing more time for the drug to become biologically active.[50] Although randomized trials of pre-hospital administration of $P2Y_{12}$ inhibitors were not powered to assess the effects on clinical events, it is notable that in a nationwide cohort of STEMI patients transported by physician-staffed emergency medical system ambulances for primary PCI, pre-hospital administration of DAPT was associated with improved survival compared with administration once the patients were admitted to the hospital.[51] On the other hand, pre-treatment with $P2Y_{12}$ receptor antagonists in Sweden was safe but not associated with improved infarct-related artery patency or better clinical outcome than with in-hospital administration.[52] Beyond the mere comparison of different timings of antiplatelet treatment, the "proof of concept" that early versus delayed $P2Y_{12}$ inhibition results in a significantly reduced risk of major adverse cardiac events with no significant difference in terms of bleeding risk is supported by the results of a recent meta-analysis of seven randomized studies that compared early versus delayed $P2Y_{12}$ inhibition in 9,648 STEMI patients undergoing PCI.[20]

Administering antiplatelet drugs when the likelihood of STEMI diagnosis is low could lead to an overtreatment of patients who will not ultimately undergo stenting, potentially exposing them to an increased bleeding risk with no potential benefit, or even more deleterious consequence if, for example, urgent surgery is needed for aortic dissection. However, pre-hospital STEMI diagnosis accuracy is now high, with false-positive diagnoses now $<5\%$. As a result, the net potential benefit of pre-hospital $P2Y_{12}$ inhibition is considerable.

Potential methods to accelerate the onset of action of the antiplatelet effects of oral $P2Y_{12}$ inhibitors include crushing or chewing the tablets.[53–55] However, the increase in bioavailability of oral $P2Y_{12}$ inhibitors with these strategies appears limited.[56] In the recent FABOLUS-FASTER (facilitation through aggrastat or cangrelor bolus and infusion over prasugrel: a multicenter randomized open-label trial in patients with ST-elevation myocardial infarction referred for primary percutaneous intervention) trial, chewing prasugrel did not result in immediate inhibition of platelet aggregation in the early phase of STEMI, and the results thus support the use of IV drugs to achieve immediate inhibition of platelet aggregation and to bridge the initial gap in platelet inhibition observed with oral $P2Y_{12}$ inhibitors.

Intravenous Agents

Glycoprotein IIb/IIIa Inhibitors

GPIIb/IIIa inhibitors prevent platelet aggregation by blocking the final pathway triggered separately by each of the different platelet activators, namely the binding of fibrinogen and vWF to activated GPIIb/IIIa receptors on the platelet surface. Three agents are currently approved for use: the chimeric monoclonal antibody Fab fragment, abciximab, and the small-molecular GPIIb/IIIa inhibitors, eptifibatide and tirofiban. All three agents are administered intravenously as a bolus, followed by a continuous infusion controlled by a pump and achieve >80 to 90% reduction in platelet aggregation within 10 minutes of the initiation of infusion. The efficacy of GPIIb/IIIa inhibitor administration compared with control therapy has been demonstrated in STEMI managed with PCI although predominately before the common use of the newer oral $P2Y_{12}$ receptor inhibitors.[57] The earlier administration of GPIIb/IIIa inhibitors in AMI may improve pre-PCI perfusion rates, decrease infarct size, and improve microcirculatory function. However, it is challenging to administer these agents rapidly in the pre-hospital setting while transporting patients for PCI. The efficacy and safety of pre-hospital administration of these agents among patients with STEMI has been investigated in several clinical studies.

Abciximab

Abciximab was the first approved GPIIb/IIIa inhibitor. It was demonstrated to decrease the risk of MACE among patients presenting for both elective and urgent PCI, with or without stenting.[58–61] Timing of administration was variable in the landmark trials for abciximab, and none of these initial studies administered abciximab in the pre-hospital setting. Data regarding early administration of abciximab in the emergency department show improvement in both clinical and angiographic outcomes and is hypothesized to be due to early recanalization of the infarct-related artery,[62–64] which is supported by the study by Gold et al demonstrating an increase in coronary artery blood flow within 10 minutes in patients with MI co-treated with aspirin and heparin.[13] Additionally, data from the ADMIRAL (Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up) trial further reinforced the idea that earlier may be better. The ADMIRAL trial randomized patients presenting for STEMI to either abciximab plus PCI with stenting or placebo plus PCI with stenting. Approximately 26% of patients included in the study were randomized and treated early in the mobile intensive care unit. Analysis of this subgroup demonstrated that patients who were administered abciximab early were more likely to derive benefit.[65]

Nevertheless, clinical trials evaluating pre-hospital administration of abciximab have had inconsistent results. The REOMOBILE (prehospital versus periprocedural administration of abciximab in STEMI) study was one of the initial trials to evaluate pre-hospital administration of abciximab among patients with STEMI. The trial was small ($n = 100$) and underpowered for its efficacy end points and demonstrated only a trend towards improved ST-segment resolution at 60 to 90 minutes and marginally better angiographic outcomes.[66] Furthermore, in the MISTRAL (Myocardial Infarction with ST-elevation Treated by Primary Percutaneous Intervention Facilitated by Early Reopro Administration in Alsace) study, pre-hospital administration of abciximab compared with catheterization laboratory administration among patients presenting for STEMI undergoing PCI did not improve either ST-segment resolution or TIMI flow rate after PCI. However, it tended to improve TIMI flow pre-PCI and decreased distal embolization during procedure.[67]

Notably, early administration of abciximab was not associated with an increased risk of bleeding. Although smaller studies have demonstrated a higher rate of aborted MI and ST-segment resolution with early pre-hospital administration,[68,69] the use of abciximab in that setting remains controversial.

Despite abciximab being extensively investigated in the clinical field, it is no longer marketed in the United States, Canada, and most European countries, and this has forced the switch to other GPIIb/IIIa inhibitors, most notably tirofiban.

Eptifibatide

Eptifibatide was the second GPIIb/IIIa inhibitor approved for clinical use and the first small-molecule GPIIb/IIIa inhibitor. It was shown to reduce the risk of death or non-fatal MI among patients presenting with ACS without persistent ST elevations in the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial.[70] In addition, results of the INTAMI trial (Randomized Integrilin in Acute Myocardial Infarction) and the TITAN-TIMI 34 trial (Time to Integrilin Therapy in Acute Myocardial Infarction) provided evidence suggesting that early administration of eptifibatide among STEMI patients may be beneficial. Both trials randomized patients presenting with STEMI to early (emergency department) versus late (cardiac catheterization laboratory) administration of eptifibatide. Patients randomized to early administration of eptifibatide were more likely to have improved epicardial flow by TIMI flow grade and TIMI frame count as well as improved angiographic myocardial perfusion pre-PCI compared with patients who received eptifibatide late.[71,72] The risk of major bleeding remained comparable in both treatment strategies.

Data on the pre-hospital administration of eptifibatide, however, are limited. The Bochum Feasibility Study was an open-label study that randomized patients with typical angina and concern for ACS to receive standard-of-care therapy versus standard-of-care plus eptifibatide in the ambulance within 6 hours of symptom onset ($n = 356$). Although the primary end point of death, re-infarction, revascularization of target vessels, and major bleeding was lower in the eptifibatide arm (9.6 vs. 11.8%), the difference was not statistically significant.[73]

Tirofiban

Tirofiban is also an IV agent with rapid onset of inhibition of platelet aggregation that is rapidly reversible after discontinuation of the infusion. It has been evaluated as an adjunctive antiplatelet agent among patients presenting with ACS and undergoing PCI or medical management.[74–76] Among the three commercially available GPIIb/IIIa inhibitors, tirofiban has the most consistent data for pre-hospital use. Similar to abciximab and eptifibatide, initial evidence demonstrated that earlier use of tirofiban in STEMI (emergency department setting) was associated with improved ST-segment resolution and target vessel perfusion prior to PCI.[77] This suggested that the administration of tirofiban even earlier in the time course of infarction may be of additional benefit.

Most evidence supporting pre-hospital use of tirofiban among patients with STEMI is derived from the On-TIME (Ongoing Tirofiban In Myocardial Infarction Evaluation) 2 trial. On-TIME was a double-blind, multicentre study that randomized STEMI patients who were candidates for PCI to either high-dose bolus pre-hospital tirofiban plus standard of care versus standard of care alone ($n = 984$). The primary study demonstrated significantly better resolution of ST-segment deviation both prior to and post-PCI among patients who received high-dose bolus tirofiban. The composite of death, recurrent MI, urgent target vessel revascularization, or blinded bailout use of tirofiban at 30 days was also significantly lower among patients in the tirofiban arm (32·9 vs. 26·0%; $p = 0.02$).[18] Furthermore, additional analyses that combined that pooled data from the open-label phase and the blinded phase of the study demonstrated a significant reduction in MACE (5.8 vs. 8.6%, $p = 0.043$), with long-term follow-up showing similar results at 1 year.[78] Exploratory analyses also showed improvement in initial thrombus burden and initial patency of the infarct-related vessel among patients who were administered tirofiban compared with placebo,[79] and pre-hospital tirofiban administration was independently associated with a lower risk of high N-terminal pro-brain natriuretic peptide (NT-proBNP) level after primary PCI.[80] In the last years, the use of GPI has declined, mainly due to the perception that the ischaemic benefits are counterbalanced by bleeding risks; however, clinical data on GPI bleeding risk may overstate the current experience since it is mainly based on earlier studies that included prolonged post-bolus drug infusion and femoral access site instrumentation. Thus, a high-risk subset of patients may derive particular benefit from early tirofiban treatment in terms of reduced short- and long-term mortality, without a significant increase in bleeding complications.[81]

Intravenous $P2Y_{12}$ Inhibitors: Cangrelor

Cangrelor is the first and only IV, direct $P2Y_{12}$ inhibitor, characterized by rapid onset and offset of action. This makes it ideal for use among patients with STEMI as desired platelet inhibition occurs within minutes of administration, with complete return of platelet function within 60 minutes of discontinuation of the infusion.[82] Between 2009 and 2013, three pivotal randomized clinical trials from the CHAMPION (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) programme demonstrated that cangrelor administration reduces periprocedural ischaemic complications compared with a clopidogrel loading dose alone. This was, however, associated with an increased risk of GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) mild bleeding.[83] In the pooled dataset from these trials, only 11.6% of patients ($n = 2{,}884$) enrolled had STEMI and cangrelor was not compared with pre-hospital clopidogrel loading, neither was it compared with more potent and faster-acting $P2Y_{12}$ inhibitors. Moreover, transition from cangrelor to the thienopyridines clopidogrel and prasugrel after PCI is complicated due to a competitive effect between cangrelor and the active metabolites of the oral $P2Y_{12}$ inhibitors.[84] In STEMI patients, randomized data demonstrated that cangrelor

may be used as an adjunct to ticagrelor and provides faster and stronger periprocedural platelet inhibition compared with ticagrelor alone.[85,86] However, in the recent FABOLUS-FASTER trial, tirofiban demonstrated superior efficacy than cangrelor on inhibition of platelet aggregation in patients undergoing primary PCI, suggesting that GPI might be preferable to cangrelor to minimize the risk of acute ischaemic complications.[87] Further studies powered for clinical end points are needed.

Subcutaneous Agents

Subcutaneous $P2Y_{12}$ Inhibitor: Selatogrel

Selatogrel (ACT-246475), a highly selective and potent 2-phenylpyrimidine-4-carboxamide analogue, ushers in a novel class of reversible P2Y12 receptor antagonists.[88] The safety and early antiplatelet response to subcutaneous selatogrel has been evaluated in two phase II trials among patients with chronic coronary syndromes (CCS) and patients with AMI scheduled for an invasive strategy[89,90] (►**Table 2**). The initial study to evaluate selatogrel was a prospective, multinational, double-blind, randomized, investigation of 345 patients with CCS receiving conventional background antiplatelet therapy. Patients were randomized to receive subcutaneous selatogrel (8 mg [$n = 114$] or 16 mg [$n = 115$]) or placebo ($n = 116$) and were classified as responders if the $P2Y_{12}$ reaction unit (PRU) measurement utilizing the VerifyNow assay was <100 at 30 minutes post-dose and lasted ≥ 3 hours. At 30 minutes post-selatogrel administration, 89% of patients were responders to the 8-mg dose, 90% to the 16-mg dose, and 16% to placebo ($p < 0.0001$). PRU remained <100 for up to 8 hours for both doses, returning to pre-dose or near pre-dose levels by 24 hours post-dose. Selatogrel achieved additional platelet inhibition in patients already treated with oral $P2Y_{12}$ inhibitors.[89]

Selatogrel was also evaluated in another phase II study of 47 patients with ACS (29 of whom had STEMI) along with standard-of-care adjunctive therapy. The response to treatment (defined as PRU < 100) was evaluated 30 minutes post-selatogrel administration (8 mg [$n = 24$] or 16 mg [$n = 23$]). The proportion of responders 30 minutes post-dose was 91 and 96% with 8 and 16 mg, respectively.[90] In both studies, selatogrel was safe and well tolerated; adverse events were mild in severity, with dyspnoea reported in rates similar to those with ticagrelor. Bleeding events were mostly trivial. Thus, a single subcutaneous injection of selatogrel rapidly inhibits ADP-induced platelet aggregation and may be a promising treatment in the pre-hospital setting and in clinical scenarios where early, rapid, potent, and reversible inhibition of platelet aggregation mediated by ADP is desirable, such as patients presenting with STEMI. Randomized trials are needed to establish the efficacy and safety of subcutaneous selatogrel in such context. A phase III investigation of selatogrel is planned to start in the first half of 2021 as announced by the manufacturer.

Subcutaneous GPIIb/IIIa Inhibitor: RUC-4

RUC-4 differs from current GPIIb/IIIa drugs by its subcutaneous route of administration and its capacity to lock the receptor in its inactive state.[91] In its phase I trial, the safety of two of RUC-4 doses (0.05 and 0.075 mg/kg) were evaluated in 14 healthy volunteers and 28 patients with stable CAD (►**Table 2**). Patients in both groups achieved more than 80% platelet inhibition within 15 minutes of administration with a duration of action of ~2 hours. With regard to RUC-4's safety profile, the majority of adverse events were mild and none led to study drug discontinuation.[92] An ongoing phase II open-label study (ClinicalTrials.gov Identifier: NCT04284995) is assessing the pharmacodynamic and pharmacokinetic properties of a single subcutaneous injection of RUC-4 in patients with STEMI with planned primary PCI. The simple mode of administration of RUC-4, possibly by an auto-injector, makes it a promising candidate for the management of STEMI at first medical contact, a major unmet need in pre-hospital care that could potentially improve patient outcomes.

Other Approaches to Platelet Inhibition

Other novel approaches to platelet inhibition that target other key steps in platelet aggregation are still under investigation. Revacept is an IV platelet collagen receptor inhibitor that acts directly on the target lesion with exposed endovascular collagen, often the primary trigger of platelet aggregation. Given its mechanism of action, Revacept does not affect peripherally circulating platelets, and may potentially lead to lower risk of bleeding. It is currently under investigation in the phase II ISAR-PLASTER (intracoronary stenting and antithrombotic regimen: lesion platelet adhesion as selective target of endovenous revacept) trial among patients with stable coronary disease undergoing elective PCI.[93] ARC1779 is an antiplatelet agent that binds the A1 domain of vWF, which acts as a ligand to GP1b receptor on the surface of platelets. Early phase I studies had shown that ARC1779 is well tolerated without an increase in bleeding.[94] Moreover, the benefits of platelet inhibition may be present beyond their anti-thrombotic effect because activated platelets may contribute to ischaemia/reperfusion (I/R) injury via multiple pathways.[95] Moreover, platelet inhibition may also diminish I/R injury via multiple pathways, including reduced leukocyte recruitment and microparticle formation.[95] However, the promising results have been shown mainly in pre-clinical setting, and translation into the clinical setting is still under development.

Future Directions

Novel subcutaneous therapeutic strategies can achieve rapid, high-grade, and rapidly reversible platelet inhibition. These features have the potential to enable new pre-hospital strategies to rapidly achieve patency of the infarct-related vessel prior to PCI. This is likely to translate into decreased infarct size, a reduction in STEMI complications, and overall improvement in morbidity and mortality after MI. Prospective investigations are needed to assess the value of these novel agents, but if they are judged to be safe and efficacious, they will provide important new opportunities in pre-hospital care of ACS. Since they may be self-administered

Table 2 Studies on new subcutaneous antiplatelet agents

Drug	Mechanism of action	Study	Population	No. of patients	Objective	Findings	Safety	Study
Selatogrel	Reversible binding $P2Y_{12}$ receptor antagonist	Phase II: prospective, multinational, double-blind, randomized	CCS on background oral antiplatelet therapy	345	To compare administration of selatogrel 8 or 16 mg vs. placebo in terms of platelet aggregation: responders to treatment when the $P2Y_{12}$ reaction unit measurement was <100 at 30 min post-dose and lasted ≥3 h	At 30 min post-dose, 89% of patients were responders to 8 mg, 90% to 16 mg and 16% to placebo ($p < 0.01$)	Emergent adverse events were of mild/moderate intensity	Storey et al[89]
		Phase II: prospective, multinational, double-blind, randomized	ACS	47 (29 STEMI)	To compare administration of selatogrel 8 or 16 mg in terms of platelet aggregation: response to treatment defined as $P2Y_{12}$ reaction units <100 evaluated at 30 min	The proportion of responders 30 min post-dose was 91 and 96% with 8 and 16 mg, respectively	Emergent adverse events were of mild/moderate intensity	Sinnaeve et al[90]
RUC-4	Glycoprotein IIb/IIIa receptor inhibitor (capacity to lock the receptor in its inactive state)	Phase I	Healthy volunteers and stable CAD patients	42 (14 healthy volunteers, 28 stable CAD)	Safety of various doses (0.050 and 0.075 mg/kg) of RUC-4	Patients in both groups were able to achieve within 15 min more than 80% platelet inhibition that resolved within 2 h	Majority of adverse events were mild and none led to subject discontinuation	Late-Breaking Science Abstracts[92]
		Phase II, open-label trial	STEMI presenting to the Cath Laboratory with planned primary PCI	24	to assess the PK/PD properties and safety	Ongoing, ClinicalTrials.gov Identifier: NCT04284995		

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CCS, chronic coronary syndromes; PCI, percutaneous coronary intervention; PK/PD, pharmacokinetics/pharmacodynamic; STEMI, ST-elevation myocardial infarction.

with auto-injector, or easily administered at first medical contact, they may finally fill the gaps of pre-hospital care which has been identified as the best period to improve outcomes. Nonetheless, in addition to evaluating the agents themselves, understanding the risks and limitations of a strategy of early medical therapy is paramount. Initiating antiplatelet therapy upfront carries the risk of overtreatment, especially when diagnostic uncertainty is present. Other technologies, such as implantable or wearable devices, may complement these new agents by providing more timely recognition of ischaemic events.[96]

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Conflict of Interest

B.S.C. is an inventor of abciximab and in accord with federal law and the policies of the Research Foundation of the State University of New York, he shares in royalties for the sales of abciximab. He is also an inventor of the VerifyNow assays and receives royalties for the sales of the PRU $P2Y_{12}$ cartridge. He is also an inventor of RUC-4 and an equity holder and member of the scientific advisory board of CeleCor Therapeutics, the company that is developing RUC-4. M.G. reports research grant support from Johnson and Johnson, Apple, CSL Behring and Celecor. A.W.J.v.-H. reports unrestricted grants from Medtronic, Abbott, Boehringer Ingelheim, and AstraZeneca. The other authors declare no potential conflict of interest.

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