

Parenteral Antiplatelet Drugs in ST-Elevation Myocardial Infarction

Citation for published version (APA):

Rikken, S. A. O. F., Storey, R. F., Andreotti, F., Clemmensen, P., & Ten Berg, J. M. (2023). Parenteral Antiplatelet Drugs in ST-Elevation Myocardial Infarction: Current Status and Future Directions. *Thrombosis and Haemostasis*, 123(02), 150-158. <https://doi.org/10.1055/s-0042-1753479>

Document status and date:

Published: 07/02/2023

DOI:

[10.1055/s-0042-1753479](https://doi.org/10.1055/s-0042-1753479)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Parenteral Antiplatelet Drugs in ST-Elevation Myocardial Infarction: Current Status and Future Directions

Sem A. O. F. Rikken^{1,2}  Robert F. Storey³ Felicita Andreotti⁴ Peter Clemmensen^{5,6}
Jurriën M. ten Berg^{1,2}

¹ Department of Cardiology, St. Antonius Hospital, Nieuwegein, The Netherlands

² School for Cardiovascular Diseases, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Maastricht, The Netherlands

³ Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom

⁴ Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

⁵ Department of Cardiology, University Heart and Vascular Center, Hamburg, Germany

⁶ Department of Medicine, Nykøbing F Hospital, Nykøbing Falster, Denmark

Address for correspondence Jurriën M. ten Berg, MD, PhD, FACC, FESC, Department of Cardiology, St Antonius Hospital Nieuwegein, Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands (e-mail: jurtenberg@gmail.com).

Thromb Haemost

Abstract

Oral inhibitors of the platelet P2Y₁₂ receptor are indispensable in the treatment of ST-elevation myocardial infarction (STEMI), improving outcomes and even reducing mortality in some studies. However, these drugs are limited by delayed absorption and suboptimal platelet inhibition at the time of primary percutaneous coronary intervention. Despite efforts to achieve faster and more sustained platelet inhibition, strategies such as prehospital administration, higher loading doses, and crushed formulations have not led to improved coronary reperfusion. Parenteral glycoprotein IIb/IIIa inhibitors act sooner and are more potent than oral P2Y₁₂ inhibitors, but their use has been limited by the increased risk of major bleeding and thrombocytopenia. Hence, there is a clinical need to refine drugs that deliver rapid, effective, yet safe platelet inhibition in the setting of STEMI. Novel parenteral antiplatelet drugs, such as cangrelor, selatogrel, and zalunfiban, have been recently developed to achieve rapid, potent antiplatelet effects while preserving hemostasis. We provide a description of currently available parenteral antiplatelet agents and of those in clinical development for prehospital administration in STEMI patients.

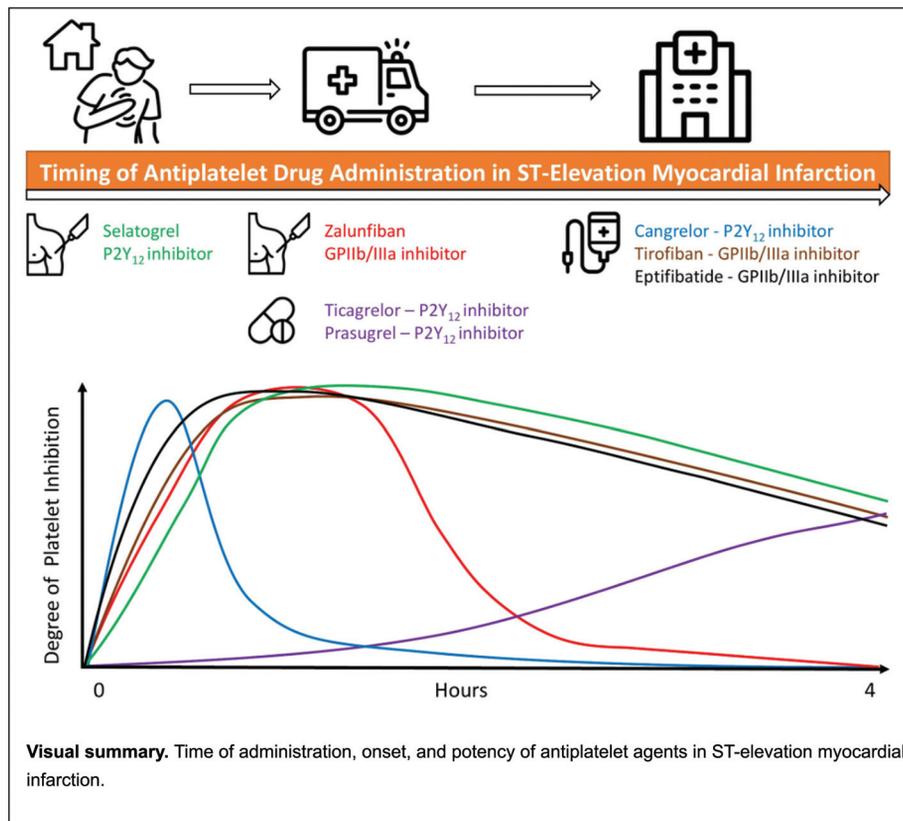
Keywords

- ▶ prehospital administration
- ▶ antiplatelet drugs
- ▶ ST-elevation myocardial infarction
- ▶ cangrelor
- ▶ selatogrel
- ▶ zalunfiban

received
March 31, 2022
accepted after revision
June 10, 2022

© 2022. Thieme. All rights reserved.
Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI <https://doi.org/10.1055/s-0042-1753479>.
ISSN 0340-6245.



Introduction

Atherothrombotic disease constitutes a major health care problem and accounts for one in four deaths globally.¹ ST-elevation myocardial infarction (STEMI) is a clinical manifestation of atherothrombotic disease within the coronary arteries and is characterized by intraluminal thrombus formation after atherosclerotic plaque rupture or erosion. In fact, thrombus formation due to platelet activation forms the pharmacological basis for the institution of antiplatelet therapy in STEMI. The management of STEMI is primarily aimed to achieve rapid restoration of coronary artery blood flow in the infarct-related vessel to ensure myocardial salvage. Hence, timely initiation of appropriate reperfusion and antiplatelet therapy is essential since a longer ischemic time is associated with increased myocardial necrosis and mortality.² Despite temporal trends showing significant reductions in total ischemic time and subsequent improvements in clinical outcomes over the past decades, mortality rates among STEMI patients have stagnated in recent years.³

Consequently, physicians have focused on new antiplatelet strategies to improve clinical outcomes. Current European guidelines recommend treating STEMI patients undergoing primary percutaneous coronary intervention (pPCI) with dual antiplatelet therapy consisting of aspirin and an oral P2Y₁₂ inhibitor at first medical contact to prevent recurrent thrombotic events.^{4,5} Ticagrelor and prasugrel are preferred over clopidogrel because of their faster onset, greater potency, and lower interindividual variability.^{6,7} However, both prasugrel and ticagrelor display suboptimal platelet inhibition during

the first hours in STEMI patients undergoing pPCI. In fact, high on-treatment platelet reactivity (HPR), i.e., insufficient pharmacodynamic response to antiplatelet therapy, is observed up to 6 hours after administration of prasugrel and ticagrelor in STEMI.^{8–13} HPR before pPCI correlates with a greater thrombotic burden, lower pre-PCI vessel patency, and worse clinical outcomes.^{14–16} Opioids further increase HPR due to delayed absorption of all oral P2Y₁₂ inhibitors.^{10,17}

On the other hand, the antithrombotic effect of oral P2Y₁₂ inhibitors comes at the expense of bleeding complications, and major bleeding is associated with an increased risk of death to the same extent as ischemic events.¹⁸ Given the irreversibility of all oral antiplatelet agents, except ticagrelor (which however may take up to 20 hours to be fully cleared from the circulation of healthy subjects), the slow pharmacodynamic offset of oral agents may have deleterious consequences, including bleeding during urgent major invasive procedures such as coronary artery bypass grafting, or procedural delays because of unacceptably high bleeding risk.^{19,20} Given the limitations of all oral P2Y₁₂ inhibitors, several strategies have been investigated to improve the efficacy of these drugs.

Strategies Investigated in the Past to Accelerate Platelet Inhibition

Prehospital use of oral P2Y₁₂ inhibitors was first investigated in the ATLANTIC (Administration of Ticagrelor in the Cath Laboratory or in the Ambulance for New ST-Elevation

Myocardial Infarction to Open the Coronary Artery) trial, which randomized 1,862 patients with ongoing STEMI and symptom onset within 6 hours to prehospital versus in-hospital administration of ticagrelor.²¹ The ATLANTIC trial showed no significant difference in terms of thrombolysis in myocardial infarction (TIMI) flow grade 3 and ST-segment elevation resolution assessed at initial ECG monitoring, nor in platelet reactivity between treatment arms. However, the median time difference in treatment administration between the prehospital and in-hospital groups was only 31 minutes, which may have attenuated any benefit of earlier antiplatelet treatment. Subgroup analysis according to treatment with morphine suggested a potential benefit of prehospital ticagrelor in those who did not receive morphine but not in those who did, consistent with prior studies showing delayed onset of action of prasugrel and ticagrelor in morphine-treated patients.^{10,21,22} Notably, prehospital treatment in the ATLANTIC trial did significantly reduce definite early stent thrombosis (0% vs. 0.8%, $p=0.008$ in the first 24 hours) and did not lead to increased bleeding risk.

More recently, prehospital treatment with crushed versus integral oral prasugrel was assessed in the COMPARE CRUSH (COMPARison of pre-hospital CRUSHed versus uncrushed Prasugrel tablets in patients with STEMI) trial,^{8,23} which randomized 727 STEMI patients within 6 hours of symptom onset. The COMPARE CRUSH showed no significant benefit of crushed prasugrel in terms of TIMI 3 flow in the infarct-related artery at initial coronary angiography, nor any significant difference in complete ST-segment resolution 1-hour post-PCI. Regarding safety, there was no increase in major bleeding, which was in accordance with the ATLANTIC trial. Interestingly, the COMPARE CRUSH trial showed a significant reduction in platelet reactivity at the beginning of coronary angiography in the crushed prasugrel arm (median time after

loading administration: 45 minutes). However, a considerable proportion still exhibited HPR at the beginning of angiography (crushed 43.3% vs. integral 62.6%, $p<0.01$), underscoring the need for faster and more potent agents to improve early platelet inhibition.

Parenteral antiplatelet agents may provide a bridging alternative to achieve optimal platelet inhibition and to prevent ischemic complications in the early phase of STEMI. It is known that parenteral antiplatelet agents achieve faster and greater platelet inhibition in comparison to oral P2Y₁₂ inhibitors.²⁴ In fact, only intravenous glycoprotein IIb/IIIa inhibitors (GPIs) have shown to improve pre-PCI myocardial reperfusion, while oral P2Y₁₂ inhibitors did not.^{21,23,25} Currently available parenteral antiplatelet agents include the intravenously administered GPIs eptifibatide and tirofiban and the recently approved intravenous P2Y₁₂ inhibitor cangrelor. Novel agents under clinical development are the subcutaneous P2Y₁₂ inhibitor selatogrel and the subcutaneous GPI zalunfiban. This article aims to summarize the current evidence on parenteral antiplatelet agents for STEMI patients.

Currently Available Parenteral Antiplatelet Agents

Intravenous Glycoprotein IIb/IIIa Inhibitors

Eptifibatide and tirofiban are both reversible, small molecules that competitively prevent fibrinogen and/or von Willebrand factor from binding to the platelet glycoprotein IIb/IIIa receptor (→Table 1). Eptifibatide is a cyclical heptapeptide with a KGD (Lys-Gly-Asp) binding motif, whereas tirofiban is a nonpeptide tyrosine derivative with an RGD (Arg-Gly-Asp) binding motif. Both agents require an intravenous bolus followed by continuous infusion, exhibit fast

Table 1 Traditional and novel parenteral antiplatelet drugs in clinical development

Feature	Cangrelor	Eptifibatide	Tirofiban	Zalunfiban	Selatogrel
Class	P2Y ₁₂ inhibitor	GPIIb/IIIa inhibitor	GPIIb/IIIa inhibitor	GPIIb/IIIa inhibitor	P2Y ₁₂ inhibitor
Description	Adenosine triphosphate analog	Cyclical KGD-containing heptapeptide	Nonpeptidic RGD mimetic	Displaces the Mg ²⁺ ion in the metal-ion-dependent adhesion site thereby locking the GPIIb/IIIa receptor in an inactive state	2-Phenyl-pyrimidine-4-carboxamide analog
Reversibility	Yes	Yes	Yes	Yes	Yes
Onset of action	2 min	<5 min	<10 min	<15 min	15 min
Duration of action	30–60 min	4–8 h	4–8 h	90–120 min	4–12 h
Plasma half-life	3–9 min	2–2.5 h	2–2.5 h	Unknown	Unknown
Dose	Bolus: 30 µg/kg Infusion: 4 µg/kg/min (2 h)	Bolus: double bolus of 180 µg/kg (in 10 min) Infusion: 2 µg/kg/ min (24–48 h)	Bolus: 25 µg/kg (30 min) Infusion: 0.10 µg/kg/ min (48 h)	T.B.D.	T.B.D.
Renal adjustment	No	Yes	Yes	Unknown	Unknown

Abbreviations: GP, glycoprotein; T.B.D., to be determined.

onset of action, and have a plasma half-life of 2 to 2.5 hours.²⁶ Abciximab, a chimeric monoclonal antibody irreversibly directed at the glycoprotein IIb/IIIa receptor, with a shorter double phase half-life, albeit a long functional half-life, was withdrawn from the market in 2019.

Early administration of GPI improves patency of the infarct-related vessel PCI, reduces infarct size, and improves clinical outcomes in STEMI patients.^{25,27–30} Greater efficacy was observed with earlier administration and this is in part explained by the relatively high platelet content during the first hours of thrombus formation, which makes antiplatelet therapy particularly effective in this early stage.^{31–33} The ON-TIME 2 (Ongoing Tirofiban in Myocardial Evaluation ON-TIME 2) trial, which randomized 984 STEMI patients to prehospital high bolus dose of tirofiban or placebo, showed that early, prehospital initiation of tirofiban improved ST-segment resolution before angiography and improved clinical outcomes without an increase in major bleeding at 30 days and 1 year.^{25,34}

In contrast, there were also studies that reported negative results with early administration of GPIs.^{35–37} However, these findings likely reflect an attenuated antiplatelet effect due to a longer median time from symptom onset to study drug administration, which was more than twice as long as in the ON-TIME 2 trial (median time from symptom onset to study drug administration: 76 minutes vs. 150 minutes).^{25,36,37} Despite the observed ischemic benefit of early administration of a GPI in several trials, pretreatment is currently not recommended due to bleeding risk concerns and the development of alternative safer strategies.^{5,38} However, it must be considered that this recommendation is based on evidence from trials that randomized patients late, often within the hospital, using prolonged postbolus GPI infusion and femoral access during PCI. Notably, post-pPCI infusion of a GPI offers a potential strategy for addressing delayed absorption of oral P2Y₁₂ inhibitors in opiate-treated patients, with observational data on a 6-hour infusion of tirofiban suggesting that this may reduce the risk of acute stent thrombosis.³⁹

Intravenous P2Y₁₂ Inhibitors

Cangrelor is a rapid-acting, reversible analog of adenosine triphosphate that inhibits the platelet P2Y₁₂ receptor (►Table 1). It requires continuous intravenous infusion given its half-life of 3 to 9 minutes and platelet function rapidly recovers within 1 hour after administration.⁴⁰ Cangrelor has been investigated in three large randomized controlled trials that assessed different strategies of cangrelor infusion in the catheterization laboratory compared with (oral) clopidogrel administration in both stable and acute coronary syndrome (ACS) patients.^{41–43} A patient-level meta-analysis of these three trials, which included 24,910 patients of which 11.6% were STEMI patients, reported that cangrelor significantly reduced thrombotic complications at 48 hours after PCI including stent thrombosis without an increase in major bleeding.⁴⁴ However, cangrelor was combined with or tested against clopidogrel, which has been replaced in the most recent guidelines by ticagrelor and prasugrel. Ergo, the

CANTIC study (Platelet Inhibition with Cangrelor and Crushed Ticagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention) was initiated to provide information on the use of cangrelor in combination with crushed ticagrelor in STEMI patients undergoing pPCI.³⁸ Patients were randomized in-hospital to a blinded 2-hour infusion of either cangrelor or placebo and platelet reactivity was measured with the VerifyNow assay. Cangrelor led to prompt and more potent antiplatelet effects compared with crushed ticagrelor alone, with significant differences in platelet reactivity apparent as early as 5 minutes with no patients demonstrating HPR during cangrelor infusion. These findings are in line with other studies and suggest that cangrelor might be used for bridging until ticagrelor achieves its full antiplatelet effect.⁴⁵

Prehospital use of cangrelor in STEMI may be able to achieve rapid onset of platelet inhibition after symptom onset, possibly leading to improvements in vessel patency in the infarct-related artery and a reduction in thrombotic complications. However, it is currently unknown whether prehospital treatment of cangrelor can improve pre-PCI myocardial reperfusion and clinical outcomes, in part because cangrelor is only indicated in P2Y₁₂ inhibitor-naïve patients undergoing PCI.⁴⁶ Moreover, cangrelor requires continuous infusion with an electronic pump which cannot be performed universally by ambulance services. Another potential issue concerns the transition from cangrelor to oral P2Y₁₂ inhibitors since cangrelor blocks the binding of thienopyridine-active metabolites to the P2Y₁₂ receptor, so timing of the prasugrel (or clopidogrel, but not ticagrelor) loading dose relative to timing of cangrelor cessation is critical.^{47,48} Notably, in a randomized head-to-head comparison, tirofiban showed superior inhibition of platelet aggregation compared with cangrelor at 30 minutes after infusion measured with light transmission aggregometry (LTA) in response to 20 μmol/L adenosine diphosphate (ADP; 95.0 ± 8.9 vs. 34.1 ± 22.5%; *p* < 0.001), suggesting that GPI might be preferable over cangrelor in STEMI to reduce thrombotic risk.²⁴

Parenteral Agents under Clinical Development

Zalunfiban

Zalunfiban (RUC-4) is a novel, reversible, subcutaneously administered, small-molecule GPI that is being developed for prehospital administration in STEMI (►Table 1). At the molecular level, zalunfiban binds to both the αIIb and β3 subunits of platelet glycoprotein IIb/IIIa receptor and displaces the Mg²⁺ ion from the metal ion-dependent adhesion site of the β3 subunit required for binding to fibrinogen and von Willebrand factor; this locks the β3 subunit of the receptor in its inactive state without exposing neoepitopes.⁴⁹ It is postulated that this mechanism may reduce the likelihood of GPI-induced thrombocytopenia because evidence suggests that much of the thrombocytopenia caused by GPI results from presence of auto-antibodies to newly formed epitopes induced by a conformational change after ligand binding.

Following preclinical studies, zalunfiban has been investigated in a phase I clinical trial in 14 healthy volunteers and in 28 patients with chronic coronary syndrome (CCS) on a background of aspirin to assess the safety, tolerability, pharmacodynamics, and pharmacokinetics of escalating doses of subcutaneous zalunfiban (0.04, 0.05, and 0.075 mg/kg) until a weight-adjusted biologically effective dose was identified, as determined by LTA in response to 20 $\mu\text{mol/L}$ ADP.^{50,51} Zalunfiban was well tolerated, and no serious adverse events or severe bleeding complications occurred. Bleeding events were uncommon (7%), mild, limited to the injection site, and did not lead to study drug discontinuation. All three tested doses showed rapid (<15 minutes), dose-dependent inhibition of platelet aggregation, and platelet function resolved to normal within 90 to 120 minutes.

More recently, a phase IIa open-label clinical study was conducted in 27 STEMI patients (mean age: 62 years) to assess the tolerability, pharmacodynamics, and pharmacokinetics of even higher escalating, weight-adjusted doses of subcutaneous zalunfiban.⁵² The primary pharmacodynamic endpoint was defined as $\geq 77\%$ or greater inhibition of iso-thrombin receptor activating peptide (iso-TRAP)-induced platelet aggregation measured at 15 minutes after zalunfiban administration in the cardiac catheterization laboratory with the VerifyNow assay. In comparison, 77% inhibition after stimulation with 3 to 4 $\mu\text{mol/L}$ iso-TRAP corresponds to approximately 80% inhibition with LTA stimulated by 20 $\mu\text{mol/L}$ ADP, the value that has been most closely correlated with antithrombotic effects in vivo using other GPIs.⁵³ Single zalunfiban doses (0.075, 0.090, and 0.110 mg/kg) demonstrated potent platelet inhibition, i.e., $\geq 77\%$ inhibition of the iso-TRAP-induced response in 3/8 subjects treated with 0.075 mg/kg, 7/8 subjects treated with 0.090 mg/kg, and 7/8 subjects treated with 0.110 mg/kg. The mean (min–max) inhibition of platelet aggregation at 15 minutes after administration was 77.5% (65.7–90.6%), 87.5% (73.8–93.1%), and 91.7% (76.4–99.3%, p for trend = 0.002), respectively. A 50% recovery of platelet function was established after 89.1, 104.2, and 112.4 minutes in the three cohorts, respectively. Zalunfiban was well tolerated by all STEMI patients, with injection site bruising (11/27) and vascular access site hematoma (6/27) representing the most frequently reported adverse events of interest. Both hemoglobin levels and platelet counts remained stable as did kidney and liver function tests.

Selatogrel

Selatogrel (ACT-246475) is a novel, subcutaneously administered, reversible, 2-phenylpyrimidine-4-carboxamide analogue that rapidly inhibits the platelet P2Y₁₂ receptor (► **Table 1**).⁵⁴ Preclinical studies compared ticagrelor with selatogrel infusions in a rat thrombosis model and reported that both P2Y₁₂ antagonists fully prevented FeCl₃-induced thrombus formation in the carotid artery. Interestingly, selatogrel caused 2.6 times less blood loss than ticagrelor at doses of equivalent antithrombotic efficacy.⁵⁵ Also, it was observed that selatogrel did not influence vascular tone, while ticagrelor caused vasodilation, which may explain the higher blood loss.

Following these results, subcutaneous selatogrel was investigated in a first-in-human randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics.⁵⁶ Six escalating doses (1, 2, 4, 8, 16, or 32 mg) were evaluated in healthy male subjects ($N=8$ per dose). Selatogrel showed rapid (<30 minutes), dose-dependent inhibition of platelet aggregation and dose-dependent duration to at least 12 hours in the 32 mg group. Selatogrel was well tolerated, with no injection-site reactions and no bleeding complications.

Later, two phase II trials have been conducted to assess the safety, pharmacodynamics, and pharmacokinetics of subcutaneous selatogrel in CCS and ACS patients.^{57,58} In the first phase II study, 345 CCS patients on aspirin were randomized in a 1:1:1 ratio to selatogrel 8 mg, 16 mg, or placebo. Pharmacodynamics were assessed with the VerifyNow assay and with ADP-induced LTA. Both doses showed potent inhibition within 30 minutes after administration in approximately 90% of patients. Inhibition of platelet aggregation was observed for up to 8 hours with both doses and platelet reactivity to ADP returned to normal or near-normal within 24 hours, with similar results using VerifyNow assay and LTA. Concerning safety, minor bleeding complications occurred in 9.6 and 4.3% with 8 and 16 mg, respectively.⁵⁷ No major bleeding complications nor deaths occurred during the study period. However, transient dyspnea occurred in 5.3 and 8.7% with selatogrel 8 and 16 mg, respectively, versus none with placebo. Interestingly, selatogrel provided an additive effect in patients already receiving oral P2Y₁₂ inhibitors.

In the other phase II study, 47 patients (median age: 69 years) with type 1 acute myocardial infarction (62% STEMI) were randomized to 8 or 16 mg selatogrel within the hospital.⁵⁸ Similarly to the phase II trial in CCS patients, selatogrel showed consistent, rapid, dose-dependent platelet inhibition, was well tolerated, and did not cause major bleeding complications. However, it is difficult to appreciate the contribution of selatogrel to the observed platelet inhibition, as a placebo arm was not included and patients were concomitantly treated with a loading dose of ticagrelor or clopidogrel. As with cangrelor, care needs to be taken when switching from selatogrel to thienopyridines in view of the potential negative interaction between selatogrel and the thienopyridine-active metabolites.⁵⁹

Discussion

Rapid restoration of epicardial flow is cardinal to reduce the extent of myocardial necrosis and improve early and late survival of STEMI patients. It is well established that prolonged ischemic time is associated with worse outcomes. Oral dual antiplatelet therapy is the current treatment of choice in STEMI patients undergoing PCI for the prevention of thrombotic events. However, the platelet inhibition achieved by this regimen during the first hours after STEMI onset is suboptimal, owing to hemodynamic changes and/or delayed intestinal absorption as a result of vomiting or opioids. Insufficient inhibition of platelets is a significant predictor of periprocedural and late thrombotic complications, including stent

thrombosis and death, respectively.^{4,12,15} Also, there is no evidence that oral P2Y₁₂ inhibitors can expedite myocardial reperfusion before pPCI. Thus, it is fundamental to focus on new strategies in the early period after STEMI onset to improve platelet inhibition and clinical outcomes.

One emerging strategy to mitigate the impact of suboptimal early platelet inhibition involves the administration of parenteral antiplatelet agents. Unlike oral antiplatelet drugs, these agents provide immediate platelet inhibition by circumventing gastrointestinal absorption. Therefore, parenteral antiplatelet therapy is more effective to achieve rapid platelet inhibition. Despite demonstrated superior and faster platelet inhibition of the approved intravenous GPIs over oral P2Y₁₂ inhibitors, their role has diminished over the past years due to an unfavorable safety profile.²⁴ However, it is arguable that this recommendation is based on inconclusive evidence, because the data for GPIs when administered early and as high-dose bolus in the prehospital setting are favorable.^{25,27,36,37,60} Notwithstanding the concerns on bleeding risk, various new parenteral antiplatelet agents, like cangrelor, zalunfiban, and selatogrel, have been developed to overcome the disadvantages of intravenous GPIs.

Selatogrel and cangrelor are both P2Y₁₂ inhibitors that inhibit platelet activation, while zalunfiban inhibits platelet aggregation by locking the glycoprotein IIb/IIIa receptor in its inactive state. All three agents are characterized by fast onset—and short duration—of high-grade platelet inhibition, with the GPI having broader inhibitory effects on platelet function than P2Y₁₂ inhibitors.^{43,52,58} The pharmacodynamic profiles of cangrelor and zalunfiban make these drugs particularly promising with regards to safety as the antiplatelet effects of these drugs wear off roughly at the time when oral P2Y₁₂ inhibitors become effective, thereby decreasing hemorrhagic risk and allowing for emergency cardiac surgery when indicated.^{52,57} Also, the risk of GPI-induced thrombocytopenia by zalunfiban is expected to be lower or absent when compared with currently available GPIs, given the molecular mechanism responsible for locking the GPIIb/IIIa receptor. However, large randomized clinical trials will need to establish the true safety and efficacy profile of this agent.

Zalunfiban and selatogrel are designed to be administered subcutaneously to facilitate use in the prehospital setting, while cangrelor requires continuous infusion with an electronic pump which effectively constrains it to in-hospital use. Importantly, cangrelor is only permitted in P2Y₁₂ inhibitor-naïve patients, while selatogrel and zalunfiban are intended as adjunct to P2Y₁₂ inhibitors.⁴⁶ Prehospital administration of cangrelor has not yet been investigated. Zalunfiban and selatogrel are intended for prehospital administration, yet both drugs were administered in an in-hospital setting in their respective phase II trials.^{52,58} Despite rapid platelet inhibition within 15 to 30 minutes achieved by both agents, selatogrel and zalunfiban have different prehospital timing of administration. Zalunfiban is to be given in the ambulance after STEMI diagnosis has been confirmed while selatogrel is intended for self-administration after onset of symptoms suggestive of acute myocardial infarction. The ongoing randomized,

placebo-controlled, blinded SOS-AMI (Selatogrel Outcome Study in Suspected Acute Myocardial Infarction) trial will assess the clinical efficacy and safety of subcutaneous self-administered selatogrel 16 mg in 14,000 patients with occurrence of symptoms suggestive of an acute myocardial infarction. Eligible patients are those with a history of recent ST or non-ST elevation acute myocardial infarction (within 4 weeks) and presence of high-ischemic risk factors (NCT04957719). Participating subjects will be trained on how to recognize acute myocardial infarction symptoms. Self-administration could potentially achieve very early platelet inhibition, but such a strategy has never been investigated, which makes this trial design unique. The safety endpoint will be crucial, as patient-initiated self-medication carries the inherent risks of overtreatment and may increase bleeding complications. The primary efficacy outcome (death within 7 days or myocardial infarction of different severities within 2 days of administration) will be quantified on an ordinal scale. The primary safety outcome will be BARC (Bleeding Academic Research Consortium) 3 and 5 bleeds within 2 days of administration. Secondary outcome measures will involve follow-up up to 1 month.

Unlike selatogrel, zalunfiban is intended to be administered in the ambulance by ambulance staff. The ongoing international, double-blinded, randomized, placebo-controlled CELEBRATE trial is enrolling 2,499 STEMI patients to assess the effects of zalunfiban on safety and efficacy clinical endpoints as well as the restoration of coronary artery blood flow before pPCI and resolution of ST segment deviation 1 hour post-pPCI (NCT04825743). After diagnosis of STEMI and informed consent, eligible subjects are randomized in the ambulance in 1:1:1 ratio to receive either a single subcutaneous injection of weight-adjusted zalunfiban 0.110 mg/kg, 0.130 mg/kg, or placebo. Safety outcomes include injection-site reactions, platelet count up to 72 hours, and GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) severe bleeds up to 1 month after randomization.

Other Approaches to Improve Suboptimal Early Platelet Inhibition

Delayed gastric emptying related to opioid administration has prompted other interesting approaches to mitigate the unfavorable opioid–oral P2Y₁₂ interaction.⁶¹ The prokinetic agent metoclopramide was investigated in the METAMORPHOSIS (METoclopramide Administration as a Strategy to Overcome MORPHine–ticagrelOr Interaction in PatientS with Unstable Angina PectorIS) trial to counteract the effects of opioids and showed a beneficial effect on both plasma levels and platelet reactivity at 30 minutes after administration in patients with unstable angina.⁶² However, HPR due to delayed absorption remains a risk despite metoclopramide use in STEMI patients.⁶³ Another approach aimed to antagonize the delayed gastric emptying with the use of methylnaltrexone, a peripheral opioid-receptor antagonist, but showed no differences in platelet

reactivity determined by the VerifyNow assay nor by LTA or vasodilator-stimulated phosphoprotein assay.⁶⁴ Also, nonopioid analgesics have been investigated to increase bioavailability of oral P2Y₁₂ inhibitors and reduce HPR. The impact of intravenous acetaminophen on the level of platelet inhibition was assessed in the ON-TIME 3 (The Opioids and Crushed Ticagrelor In Myocardial infarction Evaluation) trial.⁶⁵ This study did not report lower levels of platelet reactivity compared with intravenous fentanyl in STEMI patients, although plasma levels were significantly increased. Another trial, the LOCAL trial, investigated the use of intravenous lignocaine as an alternative to intravenous fentanyl and showed a significantly lower rate of HPR at 60 minutes after administration in non-STEMI patients (lignocaine 6 vs. fentanyl 59%, $p < 0.001$ measured with the VerifyNow assay).⁶⁶ Although the results of the LOCAL study are promising, the results should be interpreted with some caution as STEMI patients were excluded, pain levels were very low at baseline, and the study had a small sample size.

Conclusion

The present review has described the limitations of current antiplatelet regimens for the early management of patients with STEMI and the evolving landscape of parenteral antiplatelet drugs. New agents like cangrelor, zalunifiban, and selatogrel show promising results and might overcome the drawbacks of currently available antiplatelet drugs. How these new parenteral antiplatelet drugs will fit in the antithrombotic arena and whether they will improve clinical efficacy while preserving hemostasis, remains to be determined.

Conflict of Interest

S.A.O.F.R. has nothing to declare. R.F.S. reports research grants and personal fees from AstraZeneca, Cytosorbents, GlyCardial Diagnostics and Thromboserin, and personal fees from Alnylam, Bayer, Bristol Myers Squibb/Pfizer, Chiesi, CSL Behring, HengRui, Idorsia, Intas Pharmaceuticals, Medscape, Novartis, PhaseBio, Portola, and Sanofi Aventis. F.A. reports lecture or consultancy fees from Amgen, AstraZeneca, Bayer, BMS/Pfizer, and Daiichi Sankyo. P.C. has previously or currently been involved in research contracts, consulting, and speaker bureau or received research and educational grants from: Abbott, AstraZeneca, Aventis, Abiomed, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli-Lilly, Evolva, Fiberx, Idorsia, Janssen, Merck, Myogen, Medtronic, Mitsubishi Pharma, The Medicines Company, Nycomed, Organon, Pfizer, Pharmacia, Regado, Sanofi, Searle, Servier. J.M.T.B. reports grants from the Netherlands Organization for Health Research and Development, a Dutch government institution called ZonMw. J. M. ten Berg reports speaker fees from AstraZeneca, Daiichi Sankyo, Eli Lilly, the Medicines Company, Accumetrics, Boehringer-Ingelheim, Bayer, BMS, Pfizer, and Ferrer.

References

- Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2095–2128
- Greulich S, Mayr A, Gloekler S, et al. Time-dependent myocardial necrosis in patients with ST-segment-elevation myocardial infarction without angiographic collateral flow visualized by cardiac magnetic resonance imaging: results from the multicenter STEMI-SCAR project. *J Am Heart Assoc* 2019;8(12):e012429
- García-García C, Oliveras T, Serra J, et al; Ruti-STEMI Investigators †Trends in short-and long-term st-segment-elevation myocardial infarction prognosis over 3 decades: a mediterranean population-based st-segment-elevation myocardial infarction registry. *J Am Heart Assoc* 2020;9(20):e017159
- Ibanez B, James S, Agewall S, et al; ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39(02):119–177
- Neumann FJ, Sousa-Uva M, Ahlsson A, et al; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;40(02):87–165
- Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357(20):2001–2015
- Wallentin L, Becker RC, Budaj A, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361(11):1045–1057
- Vogel RF, Delewi R, Angiolillo DJ, et al. Pharmacodynamic effects of pre-hospital administered crushed prasugrel in patients with ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 2021;14(12):1323–1333
- Khan N, Cox AR, Cotton JM. Pharmacokinetics and pharmacodynamics of oral P2Y₁₂ inhibitors during the acute phase of a myocardial infarction: a systematic review. *Thromb Res* 2016;143(143):141–148
- Silvain J, Storey RF, Cayla G, et al. P2Y₁₂ receptor inhibition and effect of morphine in patients undergoing primary PCI for ST-segment elevation myocardial infarction. The PRIVATE-ATLANTIC study. *Thromb Haemost* 2016;116(02):369–378
- Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. *J Am Coll Cardiol* 2013;61(15):1601–1606
- Alexopoulos D, Xanthopoulou I, Gkizas V, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv* 2012;5(06):797–804
- Valgimigli M, Tebaldi M, Campo G, et al; FABOLUS PRO Investigators. Prasugrel versus tirofiban bolus with or without short post-bolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: the FABOLUS PRO (Facilitation through Aggrastat By drOPping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) trial. *JACC Cardiovasc Interv* 2012;5(03):268–277
- Capranzano P, Capodanno D, Bucciarelli-Ducci C, et al. Impact of residual platelet reactivity on reperfusion in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Eur Heart J Acute Cardiovasc Care* 2016;5(05):475–486

- 15 Nishikawa M, Takeda Y, Isomura N, et al; j-CHIPS group. Association between high platelet reactivity following dual antiplatelet therapy and ischemic events in Japanese patients with coronary artery disease undergoing stent implantation. *J Atheroscler Thromb* 2020;27(01):13–24
- 16 Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Hackeng CM, ten Berg JM. The relationship between platelet reactivity and infarct-related artery patency in patients presenting with a ST-elevation myocardial infarction. *Thromb Haemost* 2011;106(02):331–336
- 17 McEvoy JW, Ibrahim K, Kickler TS, et al. Effect of intravenous fentanyl on ticagrelor absorption and platelet inhibition among patients undergoing percutaneous coronary intervention: the PACIFY randomized clinical trial (Platelet Aggregation With Ticagrelor Inhibition and Fentanyl). *Circulation* 2018;137(03):307–309
- 18 Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J* 2017;38(11):804–810
- 19 Teng R, Oliver S, Hayes MA, Butler K. Absorption, distribution, metabolism, and excretion of ticagrelor in healthy subjects. *Drug Metab Dispos* 2010;38(09):1514–1521
- 20 Sullivan AE, Nanna MG, Wang TY, et al. Bridging antiplatelet therapy after percutaneous coronary intervention: JACC review topic of the week. *J Am Coll Cardiol* 2021;78(15):1550–1563
- 21 Montalescot G, van 't Hof AW, Lapostolle F, et al; ATLANTIC Investigators. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med* 2014;371(11):1016–1027
- 22 Parodi G, Bellandi B, Xanthopoulos I, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. *Circ Cardiovasc Interv* 2014;8(01):e001593
- 23 Vlachojannis GJ, Wilschut JM, Vogel RF, et al. Effect of prehospital crushed prasugrel tablets in patients with ST-segment-elevation myocardial infarction planned for primary percutaneous coronary intervention: the randomized COMPARE CRUSH trial. *Circulation* 2020;142(24):2316–2328
- 24 Gargiulo G, Esposito G, Avvedimento M, et al. Cangrelor, tirofiban, and chewed or standard prasugrel regimens in patients with ST-segment-elevation myocardial infarction: primary results of the FABOLUS-FASTER trial. *Circulation* 2020;142(05):441–454
- 25 Van't Hof AWJ, Ten Berg J, Heestermaans T, et al; Ongoing Tirofiban In Myocardial Infarction Evaluation (On-TIME) 2 study group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet* 2008;372(9638):537–546
- 26 Topol EJ, Byzova TV, Plow EF. Platelet GPIIb-IIIa blockers. *Lancet* 1999;353(9148):227–231
- 27 De Luca G, Gibson CM, Bellandi F, et al. Early glycoprotein IIb/IIIa inhibitors in primary angioplasty (EGYPT) cooperation: an individual patient data meta-analysis. *Heart* 2008;94(12):1548–1558
- 28 Gibson CM, Kirtane AJ, Murphy SA, et al; TIMI Study Group. Early initiation of eptifibatid in the emergency department before primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: results of the Time to Integrilin Therapy in Acute Myocardial Infarction (TITAN)-TIMI 34 trial. *Am Heart J* 2006;152(04):668–675
- 29 Zeymer U, Zahn R, Schiele R, et al. Early eptifibatid improves TIMI 3 patency before primary percutaneous coronary intervention for acute ST elevation myocardial infarction: results of the randomized integrilin in acute myocardial infarction (INTAMI) pilot trial. *Eur Heart J* 2005;26(19):1971–1977
- 30 Huber K, Holmes DR Jr, van 't Hof AW, et al. Use of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention: insights from the APEX-AMI trial. *Eur Heart J* 2010;31(14):1708–1716
- 31 Silvain J, Collet J-P, Nagaswami C, et al. Composition of coronary thrombus in acute myocardial infarction. *J Am Coll Cardiol* 2011;57(12):1359–1367
- 32 De Luca G, Van't Hof AWJ, Gibson CM, et al; EGYPT cooperation. Impact of time from symptom onset to drug administration on outcome in patients undergoing glycoprotein IIb-IIIa facilitated primary angioplasty (from the EGYPT cooperation). *Am J Cardiol* 2015;115(06):711–715
- 33 Heestermaans T, van 't Hof AWJ, ten Berg JM, et al. The golden hour of prehospital reperfusion with triple antiplatelet therapy: a sub-analysis from the Ongoing Tirofiban in Myocardial Evaluation 2 (On-TIME 2) trial early initiation of triple antiplatelet therapy. *Am Heart J* 2010;160(06):1079–1084
- 34 ten Berg JM, van 't Hof AWJ, Dill T, et al; On-TIME 2 Study Group. Effect of early, pre-hospital initiation of high bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short- and long-term clinical outcome. *J Am Coll Cardiol* 2010;55(22):2446–2455
- 35 Pels K, Schröder J, Witzensbichler B, et al. Prehospital versus periprocedural abciximab in ST-elevation myocardial infarction treated by percutaneous coronary intervention. *Eur J Emerg Med* 2008;15(06):324–329
- 36 Ellis SG, Tendera M, de Belder MA, et al; FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 2008;358(21):2205–2217
- 37 Mehilli J, Kastrati A, Schulz S, et al; Bavarian Reperfusion Alternatives Evaluation-3 (BRAVE-3) Study Investigators. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation* 2009;119(14):1933–1940
- 38 Franchi F, Rollini F, Rivas A, et al. Platelet inhibition with cangrelor and crushed ticagrelor in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Circulation* 2019;139(14):1661–1670
- 39 Zwart B, Yazdani M, Ow KW, et al. Use of glycoprotein IIb/IIIa antagonists to prevent stent thrombosis in morphine-treated patients with ST-elevation myocardial infarction. *Platelets* 2020;31(02):174–178
- 40 Storey RF, Oldroyd KG, Wilcox RG. Open multicentre study of the P2T receptor antagonist AR-C69931MX assessing safety, tolerability and activity in patients with acute coronary syndromes. *Thromb Haemost* 2001;85(03):401–407
- 41 Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med* 2009;361(24):2318–2329
- 42 Bhatt DL, Lincoff AM, Gibson CM, et al; CHAMPION PLATFORM Investigators. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med* 2009;361(24):2330–2341
- 43 Bhatt DL, Stone GW, Mahaffey KW, et al; CHAMPION PHOENIX Investigators. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med* 2013;368(14):1303–1313
- 44 Steg PG, Bhatt DL, Hamm CW, et al; CHAMPION Investigators. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. *Lancet* 2013;382(9909):1981–1992
- 45 Ubaid S, Ford TJ, Berry C, et al. Cangrelor versus ticagrelor in patients treated with primary percutaneous coronary intervention: impact on platelet activity, myocardial microvascular function and infarct size: a randomized controlled trial. *Thromb Haemost* 2019;119(07):1171–1181
- 46 Collet J-P, Thiele H, Barbato E, et al; ESC Scientific Document Group. 2020 ESC guidelines for the management of acute

- coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;42(14):1289–1367
- 47 Judge HM, Buckland RJ, Jakubowski JA, Storey RF. Cangrelor inhibits the binding of the active metabolites of clopidogrel and prasugrel to P2Y₁₂ receptors in vitro. *Platelets* 2016;27(03):191–195
 - 48 Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus on switching platelet P2Y₁₂ receptor-inhibiting therapies. *Circulation* 2017;136(20):1955–1975
 - 49 Li J, Vootukuri S, Shang Y, et al. RUC-4: a novel α IIb β 3 antagonist for prehospital therapy of myocardial infarction. *Arterioscler Thromb Vasc Biol* 2014;34(10):2321–2329
 - 50 Kereiakes DJ, Henry TD, DeMaria AN, et al. First human use of ruc-4: a nonactivating second-generation small-molecule platelet glycoprotein IIb/IIIa (integrin α IIb β 3) inhibitor designed for subcutaneous point-of-care treatment of st-segment-elevation myocardial infarction. *J Am Heart Assoc* 2020;9(17):e016552
 - 51 Vootukuri S, Li J, Nedelman M, et al. Preclinical studies of RUC-4, a novel platelet α IIb β 3 antagonist, in non-human primates and with human platelets. *J Clin Transl Sci* 2019;3(2–3):65–74
 - 52 Bor WL, Zheng KL, Tavenier AH, et al. Pharmacokinetics, pharmacodynamics, and tolerability of subcutaneous administration of a novel glycoprotein IIb/IIIa inhibitor, RUC-4, in patients with ST-segment elevation myocardial infarction. *EuroIntervention* 2021;17(05):e401–e410
 - 53 Jennings LK, Jacoski MV, White MM. The pharmacodynamics of parenteral glycoprotein IIb/IIIa inhibitors. *J Interv Cardiol* 2002;15(01):45–60
 - 54 Parker WAE, Storey RF. Pharmacology and potential role of selatogrel, a subcutaneous platelet P2Y₁₂ receptor antagonist. *Expert Opin Emerg Drugs* 2020;25(01):1–6
 - 55 Rey M, Kramberg M, Hess P, et al. The reversible P2Y₁₂ antagonist ACT-246475 causes significantly less blood loss than ticagrelor at equivalent antithrombotic efficacy in rat. *Pharmacol Res Perspect* 2017;5(05):1–11
 - 56 Juif P-EE, Boehler M, Dobrow M, Ufer M, Dingemans J. Clinical pharmacology of the reversible and potent P2Y₁₂ receptor antagonist ACT-246475 after single subcutaneous administration in healthy male subjects. *J Clin Pharmacol* 2019;59(01):123–130
 - 57 Storey RF, Gurbel PA, Ten Berg J, et al. Pharmacodynamics, pharmacokinetics, and safety of single-dose subcutaneous administration of selatogrel, a novel P2Y₁₂ receptor antagonist, in patients with chronic coronary syndromes. *Eur Heart J* 2020;41(33):3132–3140
 - 58 Sinnaeve P, Fahrni G, Schelfaut D, et al. Subcutaneous selatogrel inhibits platelet aggregation in patients with acute myocardial infarction. *J Am Coll Cardiol* 2020;75(20):2588–2597
 - 59 Henrich A, Claussen CH, Dingemans J, Krause A. Pharmacokinetic/pharmacodynamic modeling of drug interactions at the P2Y₁₂ receptor between selatogrel and oral P2Y₁₂ antagonists. *CPT Pharmacometrics Syst Pharmacol* 2021;10(07):735–747
 - 60 De Luca G, Savonitto S, van't Hof AW, Suryapranata H. Platelet GP IIb-IIIa receptor antagonists in primary angioplasty: back to the future. *Drugs* 2015;75(11):1229–1253
 - 61 Fernando H, Shaw JA, Myles PS, Peter K, Stub D. The opioid-P2Y₁₂ inhibitor interaction: potential strategies to mitigate the interaction and consideration of alternative analgesic agents in myocardial infarction. *Pharmacol Ther* 2021;217:107665
 - 62 Sikora J, Niezgodá P, Baránska M, et al. METoclopramide Administration as a Strategy to Overcome MORPHine-ticagrelOr Interaction in Patients with Unstable Angina Pectoris-The METAMORPHOSIS Trial. *Thromb Haemost* 2018;118(12):2126–2133
 - 63 Sumaya W, Parker WAE, Fretwell R, et al. Pharmacodynamic Effects of a 6-Hour Regimen of Enoxaparin in Patients Undergoing Primary Percutaneous Coronary Intervention (PENNY PCI Study). *Thromb Haemost* 2018;118(07):1250–1256
 - 64 Franchi F, Rollini F, Park Y, et al. Effects of methylnaltrexone on ticagrelor-induced antiplatelet effects in coronary artery disease patients treated with morphine. *JACC Cardiovasc Interv* 2019;12(16):1538–1549
 - 65 Tavenier AH, Hermanides RS, Ottervanger JP, et al. Impact of opioids on P2Y₁₂ receptor inhibition in patients with ST-elevation myocardial infarction who are pre-treated with crushed ticagrelor: Opioids and crushed Ticagrelor In Myocardial infarction Evaluation (ON-TIME 3) trial. *Eur Heart J Cardiovasc Pharmacother* 2022;8(01):4–12
 - 66 Fernando H, Duong T, Huynh K, et al. Effects of lignocaine vs. opioids on antiplatelet activity of ticagrelor: the LOCAL trial. *Eur Heart J* 2021;42(39):4025–4036