Journal of Thrombosis and Thrombolysis (2024) 57:754–756
https://doi.org/10.1007/s11239-024-02999-8

EDITORIAL

Optimal intravenous antiplatelet therapy in patients with ST-elevation myocardial infarction: is the picture becoming clearer?

Mohamed Farag[1,2]

Accepted: 30 April 2024 / Published online: 8 May 2024

In patients with ST-elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI), immediate and effective platelet inhibition is crucial to prevent thrombotic complications and reduce ischemic events. The current standard of care is to administer oral loading doses of potent third-generation $P2Y_{12}$ receptor inhibitors (ticagrelor or prasugrel) upon diagnosis. However, oral $P2Y_{12}$ receptor inhibitor treatment in STEMI is frequently limited by the delayed onset of action, requiring up to 4–6 h to achieve full antiplatelet effects, and exposing patients to unnecessary early risk of thrombotic complications during and shortly after PCI [1]. This is also aggravated by the impaired gastrointestinal absorption driven by a combination of hemodynamic instability and the effect of frequently coadministered opioid sedatives [2]. To bridge the gap in platelet inhibition, two classes of intravenous antiplatelet agents have been used in the early stage of STEMI management, namely intravenous $P2Y_{12}$ receptor inhibitors and glycoprotein IIb/IIIa receptor inhibitors (GPI). Nonetheless, the beneficial effect of intravenous agents on thrombosis has been partially counterbalanced by an increased risk of bleeding.

Cangrelor, a potent intravenous $P2Y_{12}$ receptor inhibitor, provides a rapid, effective and predictable onset and offset of platelet inhibition. Its reversible binding properties allow for quick reversal of its effects and facilitate timely interventions with reduced bleeding risks. Similarly, tirofiban, a GPI also exerts potent antiplatelet effects, but through a different mechanism. Its use in current clinical practice is predominantly limited to bailout administration where there is evidence of significant thrombus burden or suboptimal response to PCI with or without stent placement [3]. Due to a lack of randomized data, there is no consensus on the optimal intravenous antithrombotic agent during PCI for STEMI, with decisions left at the physician's discretion considering individual patient circumstances.

In this issue of the Journal of Thrombosis and Thrombolysis, Silverio and colleagues from the INVEST-STEMI (Intravenous antiplatelet therapy in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention) group conducted a prospective multicentre registry of 627 STEMI patients from seven Italian centres who received either cangrelor or tirofiban during PCI and reported procedural characteristics and in-hospital ischemic and bleeding outcomes [4]. Intravenous antiplatelet therapy was administered after identifying the coronary anatomy on emergency angiography. Patients with prior myocardial infarction, prior PCI or multivessel disease with high SYNTAX (SYNergy between percutaneous intervention with TAXus DES and cardiac surgery) score on presentation were frequently given tirofiban by the treated physician, and those with early presentation and short ischemic time (within 3 h from symptom onset) were frequently given cangrelor. Importantly, preloading with oral $P2Y_{12}$ receptor inhibitors constituted one-fifth of the study patients and did not differ between the two groups. Moreover, procedural characteristics with angiographic thrombus burden, as assessed by the Thrombolysis In Myocardial Infarction (TIMI) thrombus grade, and the type and flow of culprit vessel before PCI did not differ between the groups.

The primary efficacy outcome of angiographic evidence of TIMI flow < 3 after PCI occurred in approximately 22% of patients and was half as commonly seen with cangrelor compared to tirofiban (14.1% vs. 30.5%, adjusted odds ratio [OR] 0.40; 95% CI: 0.30–0.53). In-hospital clinically relevant bleeding, BARC (Bleeding Academic Research Consortium) types 2–5, occurred in approximately 9% of patients, BARC types 3–5 occurred in approximately 4% of patients, death occurred in approximately 5% of patients and

✉ Mohamed Farag
mohamedfarag@nhs.net

[1] Cardiothoracic Department, Freeman Hospital, Newcastle upon Tyne, Tyne and Wear NE7 7DN, UK

[2] School of Life and Medical Sciences, University of Hertfordshire, Hertfordshire, UK

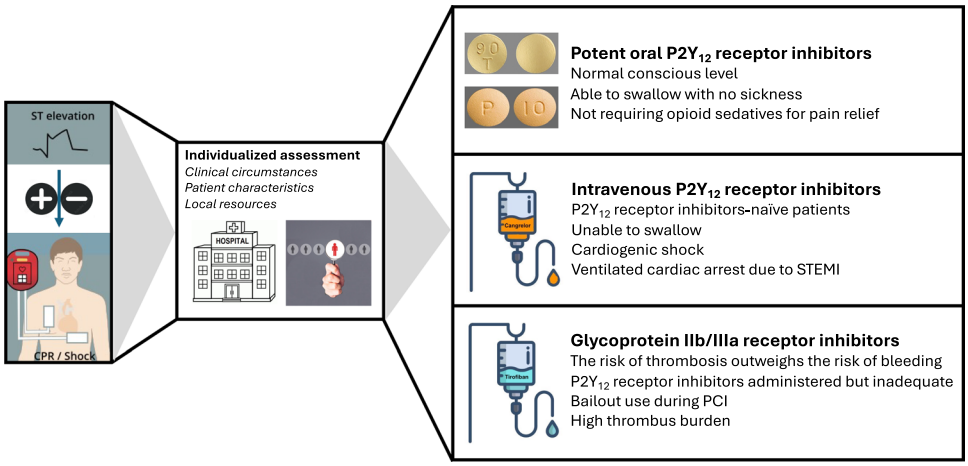

Fig. 1 Optimal antiplatelet therapy in patients with ST-elevation myocardial infarction undergoing emergency percutaneous coronary intervention. In selected patients, the choice between cangrelor and tirofiban should be individualized based on clinical circumstances, patient characteristics and local resources

periprocedural myocardial infarction occurred in approximately 5% of patients, and these outcomes were not different between the two treatments. In sensitivity analyses, gender, age, diabetes and kidney disease status, cardiogenic shock presentation, PCI access site and total ischemic time exerted no different effect on the observed study results. As compared to tirofiban, patients treated with cangrelor had better left ventricular systolic function, as assessed by transthoracic echocardiography before hospital discharge.

The INVEST-STEMI is the largest study to evaluate the efficacy and safety of cangrelor versus tirofiban in a real-world STEMI cohort. The main study limitation remains the observational design with a high risk for selection bias, however, the authors attempted to mitigate this risk by applying the propensity score weighting method to account for potential selection bias in treatment assignments. Also, the lack of long-term follow-up data represents another important limitation. Nonetheless, the implications of the study findings are several. First, intravenous cangrelor or tirofiban administration during PCI for STEMI appears safe with no differential effect on in-hospital death or bleeding outcomes. Second, cangrelor may be associated with improved myocardial reperfusion following PCI for STEMI as compared to tirofiban and this result was consistent across prespecified subgroups, including patients presenting early or late, or those with or without kidney disease, diabetes or cardiogenic shock on presentation. Third, the observed benefit of cangrelor on myocardial reperfusion may potentially translate into an improvement in left ventricular systolic function. Finally, the angiographic thrombus burden, type and flow of the culprit vessel before PCI did not influence the physician's preference for either drug given during the procedure.

Most of the trials evaluating GPI in STEMI predate the era of routine upfront dual therapy with potent oral $P2Y_{12}$ receptor inhibitors [5]. It is important to note that there is no strong evidence for any additional benefit with the routine use of GPI in STEMI, with current opinion to reserve their use in patients with peri-PCI ischemic complications. It is also important to note that available data demonstrating the benefit of cangrelor in STEMI is scarce. Consequently, there has been limited penetration of cangrelor in routine practice. However, due to its proven efficacy in mitigating early thrombotic complications [6], practice guidelines recommend considering cangrelor on a case-by-case basis in $P2Y_{12}$ receptor inhibitor-naïve patients undergoing PCI, including those presenting with cardiogenic shock or requiring mechanical ventilation [3, 7, 8]. Notably, those high-risk patients were not included in the CHAMPION (Cangrelor versus standard therapy to achieve optimal management of platelet inhibition) trials [9–11].

Several prognostic models have been developed to evaluate the trade-off between thrombotic and bleeding risks in individuals presenting with acute coronary syndromes [12, 13]. This has the potential to help physicians choose the most appropriate antithrombotic regime for those patients long-term. However, the relationship and balance between thrombotic and bleeding risks in the acute phase is often complex with bleeding complications remaining to be the Achilles' heel of antiplatelet therapy. Identifying a therapeutic window 'sweet spot' of optimal protection and safety, where the combined risk of thrombosis and bleeding is low, can be challenging in the STEMI population undergoing emergency PCI. Of note, the individual responsiveness to $P2Y_{12}$ receptor inhibitors in STEMI presentation may be assessed through point-of-care platelet function tests with timely results to potentially guide treatments [14]. However, the uptake of platelet function testing in clinical practice is still limited due to the variability in results and the lack of clarity on its usefulness [15].

Ultimately, and until random data emerge, the choice between cangrelor and tirofiban in selected patients should be individualized based on clinical circumstances, patient characteristics and local resources (Fig. 1). Furthermore, future studies need to provide a better understanding of

the individual ischemic and bleeding risk profiles as well as the predicted personalized responsiveness to antithrombotic agents to effectively define the optimal regimen for the individual patient [16].

The present study is the first multicentre study to evaluate the use of cangrelor and tirofiban in a real-world STEMI population. Both agents appear safe and effective in selected STEMI patients undergoing PCI. The valuable qualities of cangrelor certainly warrant further study aimed at identifying more appropriate approaches to its use.

Declarations

Conflict of interests MF received honoraria from Medtronic, Abbott, AstraZeneca and Chiesi.

References

1. Angiolillo DJ, Galli M, Collet JP, Kastrati A, O'Donoghue ML (2022) Antiplatelet therapy after percutaneous coronary intervention. EuroIntervention 17(17):e1371–e1396
2. Farag M, Spinthakis N, Srinivasan M, Gorog DA (2018) Should STEMI patients receive opiate analgesia? The morphine paradox. Curr Vasc Pharmacol 16(5):477–483
3. Byrne RA, Rossello X, Coughlan JJ et al (2023) 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J 44(38):3720–3826
4. Silverio A, Bellino M, Scudiero F et al (2024) Intravenous antiplatelet therapy in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention : A report from the INVEST-STEMI group. J Thromb Thrombolysis. https://doi.org/10.1007/s11239-024-02970-7
5. Boersma E, Harrington RA, Moliterno DJ et al (2002) Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 359(9302):189–198
6. Steg PG, Bhatt DL, Hamm CW, CHAMPION Investigators (2013) Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. Lancet 382(9909):1981–1992
7. Lawton JS, Tamis-Holland JE, Bangalore S et al (2022) 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. Circulation 145(3):e18–e114
8. Gorog DA, Price S, Sibbing D et al (2021) Antithrombotic therapy in patients with acute coronary syndrome complicated by cardiogenic shock or out-of-hospital cardiac arrest: a joint position paper from the European Society of Cardiology (ESC) Working Group on Thrombosis, in association with the Acute Cardiovascular Care Association (ACCA) and European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J Cardiovasc Pharmacother 7(2):125–140
9. Bhatt DL, Lincoff AM, Gibson CM, CHAMPIONPLATFORM Investigators (2009) Intravenous platelet blockade with cangrelor during PCI. N Engl J Med 361(24):2330–2341
10. Harrington RA, Stone GW, McNulty S et al (2009) Platelet inhibition with cangrelor in patients undergoing PCI. N Engl J Med 361(24):2318–2329
11. Bhatt DL, Stone GW, Mahaffey KW, CHAMPIONPHOENIX Investigators (2013) Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med 368(14):1303–1313
12. Baber U, Mehran R, Giustino G et al (2016) Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. J Am Coll Cardiol 67(19):2224–2234
13. Urban P, Gregson J, Owen R et al (2021) Assessing the risks of bleeding vs thrombotic events in patients at high bleeding risk after coronary stent implantation: the ARC-high bleeding risk trade-off model. JAMA Cardiol 6(4):410–419
14. Farag M, Spinthakis N, Gue YX et al (2019) Impaired endogenous fibrinolysis in ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention is a predictor of recurrent cardiovascular events: the RISK PPCI study. Eur Heart J 40(3):295–305
15. Farag M, Gorog DA (2017) Platelet function testing: a role for personalised therapy in coronary disease. Curr Pharm Des 23(9):1315–1327
16. Gorog DA, Ferreiro JL, Ahrens I et al (2023) De-escalation or abbreviation of dual antiplatelet therapy in acute coronary syndromes and percutaneous coronary intervention: a consensus statement from an international expert panel on coronary thrombosis. Nat Rev Cardiol 20(12):830–844