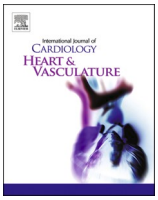
IJC Heart & Vasculature 50 (2024) 101344

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature



Cangrelor in contemporary patients with ST-segment elevation myocardial infarction pretreated with Ticagrelor: Pharmacodynamic data from the POMPEII study

Giuseppe Gargiulo [a,*], Plinio Cirillo [a], Luca Sperandeo [a], Imma Forzano [a], Domenico Simone Castiello [a], Domenico Florimonte [a], Fiorenzo Simonetti [a], Roberta Paolillo [a], Lina Manzi [a], Alessandra Spinelli [a], Carmen Anna Maria Spaccarotella [a], Raffaele Piccolo [a], Luigi Di Serafino [a], Anna Franzone [a], Piera Capranzano [b], Marco Valgimigli [c], Giovanni Esposito [a]

[a] Department of Advanced Biomedical Sciences, Federico II University of Naples, Italy
[b] Azienda Ospedaliero-Universitaria Policlinico "G. Rodolico-San Marco", University of Catania, Italy
[c] Cardiocentro Institute, Ente Ospedaliero Cantonale, Università della Svizzera Italiana (USI), Lugano, Switzerland

ARTICLE INFO

Keywords:
STEMI
Primary PCI
Cangrelor
Pharmacodynamic assessment
Platelet inhibition
Ticagrelor pretreatment

ABSTRACT

Background: There are limited data to assess pharmacodynamic (PD) profiles of patients with STEMI undergoing primary percutaneous coronary intervention (PCI) and receiving cangrelor after pretreatment with ticagrelor.
Methods: The PharmacOdynaMic effects of cangrelor in PatiEnts wIth acute or chronIc coronary syndrome undergoing percutaneous coronary intervention (POMPEII) registry (NCT04790032) is a prospective study conducted at Federico II University of Naples enrolling all patients undergoing PCI receiving cangrelor at operator's discretion. PD assessments were performed with 3 assays: (1) the gold standard light transmittance aggregometry (LTA) (20- and 5-μM adenosine diphosphate [ADP] stimuli); (2) VerifyNow $P2Y_{12}$-test; (3) Multiplate electrode aggregometry (MEA), ADP-test.
Results: We analyzed 13 STEMI patients pretreated with ticagrelor within 1 h at the time they underwent primary PCI receiving cangrelor. All patients showed low maximal platelet aggregation at 30-minute during cangrelor infusion, as well as at 3 h and 4–6 h (corresponding to 1 h and 2–4 h after stopping cangrelor infusion) with no cases of high residual platelet reactivity. These results were consistent with all assays.
Conclusions: PD data show that in contemporary real-world STEMI patients pretreated within 1 h with ticagrelor undergoing primary PCI, adding cangrelor resulted in fast and potent platelet inhibition, thus suggesting that cangrelor may bridge the gap until ticagrelor reaches its effect.

1. Introduction

Cangrelor is currently approved to reduce thrombotic complications in $P2Y_{12}$-inhibitor naïve patients with acute and chronic coronary syndrome (ACS and CCS) undergoing percutaneous coronary intervention (PCI)[1].

The optimal antithrombotic management of patients with ST-segment elevation myocardial infarction (STEMI) undergoing PCI remains of debate[2,3]. Indeed, in ACS patients the full antiplatelet effect of oral $P2Y_{12}$-inhibitor may be delayed of some hours and cangrelor could be a useful option. However, the different pharmacological properties of cangrelor and oral $P2Y_{12}$-inhibitor may expose to drug-drug interactions (DDI) potentially mitigating or abolishing the prevention of thrombotic events. Pharmacokinetic (PK) and pharmacodynamic (PD) investigations suggest that in contrast with clopidogrel and prasugrel, ticagrelor may not have DDI in cangrelor-treated patients [3–5], however most data derive from studies in which ticagrelor was not administered before cangrelor.

A recent randomized study demonstrated that cangrelor in patients pretreated with ticagrelor enhanced platelet inhibition with no differences in PK/PD profiles after discontinuation of drug infusion indicating the absence of a DDI[6]. However, this study included patients with

* Corresponding author at: Division of Cardiology, Department of Advanced Biomedical Sciences, Federico II University of Naples, Via S. Pansini 5, 80131 Naples, Italy.
E-mail address: peppegar83@libero.it (G. Gargiulo).

https://doi.org/10.1016/j.ijcha.2024.101344
Received 19 December 2023; Received in revised form 12 January 2024; Accepted 14 January 2024
Available online 23 January 2024

stable coronary artery disease and contemporary data in STEMI patients pretreated with ticagrelor are warranted.

2. Methods

The PharmacOdynaMic effects of cangrelor in PatiEnts wIth acute or chronIc coronary syndrome undergoing percutaneous coronary intervention (POMPEII) registry (NCT04790032) is a prospective study conducted at Federico II University of Naples enrolling all patients undergoing PCI receiving cangrelor at operator's discretion[4].

PD assessments were performed with 3 assays: 1) the gold standard light transmittance aggregometry (LTA) (20- and 5-μM adenosine diphosphate [ADP] stimuli); 2) VerifyNow $P2Y_{12}$-test; 3) Multiplate electrode aggregometry (MEA), ADP-test.

Among 123 patients enrolled from March 2021 to August 2023, 13 patients presented with STEMI and were pretreated with ticagrelor within 1 h at the time they underwent primary PCI receiving cangrelor. All patients received aspirin, unfractionated heparin, and cangrelor (30-μg/kg bolus followed by 4-μg/kg/min infusion for 2 h) prior to the start of PCI per standard of care. Blood samples for PD assessments were collected at baseline (ticagrelor pretreatment within 1 h and before cangrelor bolus administration), at 30 min, 3 h (thus, 1 h after cangrelor infusion stop) and 4–6 h (thus, 2–4 h after cangrelor infusion stop) after cangrelor initiation. All PD tests were performed within 30 min from blood collection by experienced laboratory personnel and high residual platelet reactivity (HRPR) standard definitions were used as previously described[2–5].

Clinical events were adjudicated by an independent clinical event committee composed of two cardiologists not involved in patients' recruitment or management.

The study complied with the Declaration of Helsinki, was approved by the internal ethics committee, and all patients gave their written informed consent.

3. Results

The mean age of the study population was 56.5 ± 14.8 years, and 15 % were female. Primary PCI was performed by transradial access in all cases, and mean duration of PCI was 57.3 ± 27.0 min. All PCIs were successful and no bailout with glycoprotein IIb/IIIa inhibitor (GPI) was

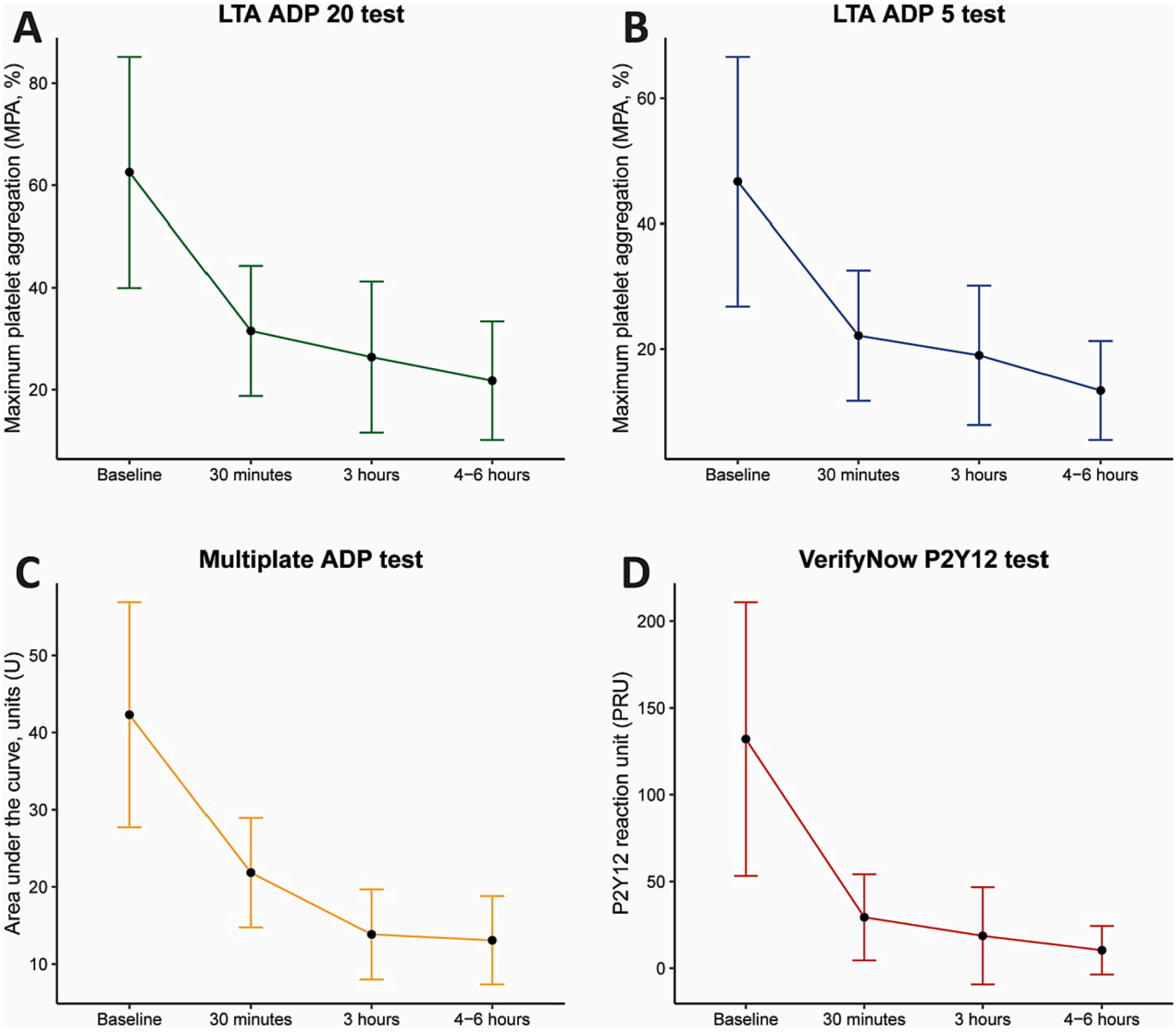


Fig. 1. Pharmacodynamic data in Ticagrelor-pretreated STEMI patients at baseline, 30 min (thus, during cangrelor infusion), 3 h (thus, 1 h after cangrelor infusion stop) and 4–6 h (thus, 2–4 h after cangrelor infusion stop) from cangrelor administration. A and B: Maximum platelet aggregation (MPA, %) at LTA with ADP 20-μM and 5-μM stimulation, respectively. C: Units of area under the curve (AUC) at MEA with ADP test. D: $P2Y_{12}$ reaction unit (PRU) at VerifyNow with ADP test.

needed. Ticagrelor pretreatment with 180 mg oral loading-dose was performed 45.4 ± 14.5 min (min. 23, max. 60) before cangrelor bolus administration.

At baseline, after ticagrelor pretreatment, maximum platelet aggregation (MPA, %) was 62.5 ± 22.6 % at LTA 20-μM-ADP and 46.7 ± 19.9 % at LTA 5-μM-ADP with 9 (69 %) and 7 (54 %) being defined as HRPR respectively. All patients showed low MPA at 30-minute during cangrelor infusion with a mean MPA of 31.5 ± 12.8 % at LTA 20-μM-ADP and 22.2 ± 10.4 % at LTA 5-μM-ADP (**Fig. 1**, **panels A-B**) with no cases of HRPR. Similarly, MPA progressively reduced at 3 h (26.4 ± 14.8 % at LTA 20-μM-ADP and 19.0 ± 11.2 % at LTA 5-μM-ADP) and 4–6 h (21.8 ± 11.6 % at LTA 20-μM-ADP and 13.4 ± 7.9 % at LTA 5-μM-ADP) corresponding to 1 h and 2–4 h after stopping cangrelor infusion with no cases of HRPR.

These results were consistent with alternative methods of VerifyNow and MEA (**Fig. 1**, **panels C-D**).

No deaths, no ischemic events and 1 (7.7 %) minor bleeding occurred within 48 h.

4. Discussion

This study provides PD data in contemporary STEMI patients pretreated within 1 h with ticagrelor and undergoing primary PCI. Adding cangrelor was effective and safe with all patients having appropriate platelet inhibition during and after primary PCI without cases of HRPR up to 6 h.

Prior data exploring DDI among cangrelor and oral $P2Y_{12}$-inhibitors seem to suggest that the ideal association of cangrelor is with ticagrelor. While active metabolites of clopidogrel and prasugrel have a half-life shorter than duration of cangrelor infusion requiring they need to be administered at the end of cangrelor infusion, ticagrelor has a longer half-life making it available to bind the $P2Y_{12}$ receptor when cangrelor infusion is stopped. Yet, prior PD data showed that cangrelor interruption at 2 h might expose some patients to a rebound effect[1–5]. Our study adds to a previous smaller study in which only PRU values were assessed up to 30 min[5], and expands to STEMI patients what recently described in elective patients in the SWAP-5[4], that in the case of ticagrelor-pretreated patients no HRPR is present during and after cangrelor administration, thus limiting the risk of mitigating the periprocedural thrombotic protection.

These findings can be clinically relevant considering that in the daily practice STEMI patients are often pretreated with ticagrelor at first medical contact but most patients have not yet reached adequate platelet inhibition at the time of or immediately after PCI. Yet, the recent CAMEO registry[7] shows that many patients with acute MI in the daily practice might receive off-label use of cangrelor despite being not naïve from oral P2Y12 inhibitors, therefore, our data suggesting safety and efficacy of such strategy are novel and of clinical relevance.

5. Limitations

This is a small observational single-arm pharmacodynamic study with no pharmacokinetic analysis and underpowered for clinical events. The clinical implications of these findings need further investigation in an adequately powered clinical trial.

6. Conclusions

Pharmacodynamic data show that in contemporary real-world STEMI patients pretreated within 1 h with ticagrelor undergoing primary PCI, adding cangrelor resulted in fast and potent platelet inhibition, thus suggesting that cangrelor may bridge the gap until ticagrelor reaches its effect.

7. Statement

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Funding

This study was internally supported by University Federico II and Azienda Ospedaliera Universitaria Federico II. No direct or indirect external funding was received.

Disclosures

Dr Valgimigli has received personal fees from AstraZeneca; has received grants and personal fees from Terumo; and has received personal fees from Alvimedica/CID, Abbott Vascular, Daiichi-Sankyo, Bayer, CoreFLOW, Idorsia Pharmaceuticals Ltd, Departement Klinische Forschung of Universität Basel, Bristol Myers Squibb SA, Medscape, Biotronik, and Novartis, outside the submitted work.

The other authors have nothing to disclose.

CRediT authorship contribution statement

Giuseppe Gargiulo: Writing – review & editing, Methodology, Investigation, Data curation, Visualization, Validation, Supervision, Conceptualization. **Plinio Cirillo:** Writing – review & editing, Methodology, Investigation. **Luca Sperandeo:** Investigation, Data curation. **Imma Forzano:** Writing – review & editing, Investigation. **Domenico Simone Castiello:** Writing – review & editing, Investigation, Data curation. **Domenico Florimonte:** Writing – review & editing, Investigation, Data curation. **Fiorenzo Simonetti:** Writing – review & editing, Visualization, Investigation, Data curation. **Roberta Paolillo:** Writing – review & editing, Investigation, Data curation. **Lina Manzi:** Writing – review & editing, Investigation, Data curation. **Alessandra Spinelli:** Writing – review & editing, Data curation. **Carmen Anna Maria Spaccarotella:** . **Raffaele Piccolo:** Writing – review & editing, Investigation. **Luigi Di Serafino:** Writing – review & editing, Investigation. **Anna Franzone:** Writing – review & editing, Investigation. **Piera Capranzano:** Writing – review & editing, Conceptualization. **Marco Valgimigli:** Writing – review & editing, Validation, Methodology. **Giovanni Esposito:** Writing – review & editing, Validation, Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] R.A. Byrne, X. Rossello, J.J. Coughlan, E. Barbato, C. Berry, A. Chieffo, M.J. Claeys, G.A. Dan, M.R. Dweck, M. Galbraith, M. Gilard, L. Hinterbuchner, E.A. Jankowska, P. Jüni, T. Kimura, V. Kunadian, M. Leosdottir, R. Lorusso, R.F.E. Pedretti, A. G. Rigopoulos, M. Rubini Gimenez, H. Thiele, P. Vranckx, S. Wassmann, N. K. Wenger, B. Ibanez, ESC Scientific Document Group, 2023 ESC Guidelines for the management of acute coronary syndromes, Eur Heart J. 25 (2023 Aug) ehad191, https://doi.org/10.1093/eurheartj/ehad191.

[2] G. Gargiulo, G. Esposito, M. Avvedimento, M. Nagler, P. Minuz, G. Campo, F. Gragnano, N. Manavifar, R. Piccolo, M. Tebaldi, P. Cirillo, L. Hunziker, P. Vranckx, S. Leonardi, D. Heg, S. Windecker, M. Valgimigli, Cangrelor, tirofiban, and chewed or standard prasugrel regimens in patients with ST-segment-elevation myocardial infarction: primary results of the FABOLUS-FASTER trial, Circulation. 142 (5) (2020) 441–454, https://doi.org/10.1161/circulationaha.120.046928.

[3] F. Franchi, F. Rollini, A. Rivas, M. Wali, M. Briceno, M. Agarwal, Z. Shaikh, A. Nawaz, G. Silva, L. Been, R. Smairat, M. Kaufman, A.M. Pineda, S. Suryadevara, D. Soffer, M.M. Zenni, T.A. Bass, D.J. Angiolillo, Platelet inhibition with cangrelor and crushed ticagrelor in patients with ST-segment-elevation myocardial infarction

undergoing primary percutaneous coronary intervention, Circulation. 139 (14) (2019) 1661–1670, https://doi.org/10.1161/circulationaha.118.038317.

[4] G. Gargiulo, A. Marenna, L. Sperandeo, L. Manzi, M. Avvedimento, F. Simonetti, M. E. Canonico, R. Paolillo, A. Spinelli, F. Borgia, L. Diserafino, A. Franzone, E. Stabile, R. Piccolo, P. Cirillo, M. Valgimigli, G. Esposito, Pharmacodynamic effects of cangrelor in elective complex PCI: insights from the POMPEII Registry, EuroIntervention. 18 (15) (2023) 1266–1268, https://doi.org/10.4244/EIJ-D-22-00594.

[5] F. Franchi, L. Ortega-Paz, F. Rollini, M. Galli, L. Been, G. Ghanem, A. Shalhoub, T. Ossi, A. Rivas, X. Zhou, A.M. Pineda, S. Suryadevara, D. Soffer, M.M. Zenni, B. Reiter, B. Jilma, D.J. Angiolillo, Cangrelor in patients with coronary artery disease pretreated with ticagrelor: the switching antiplatelet (SWAP)-5 study, JACC Cardiovasc. Interv. 16 (1) (2023) 36–46, https://doi.org/10.1016/j.jcin.2022.10.034. Epub 2022 Oct 31.

[6] M.A. Mohammad, P. Andell, S. Koul, S. James, F. Scherstén, M. Götberg, D. Erlinge, Cangrelor in combination with ticagrelor provides consistent and potent P2Y12-inhibition during and after primary percutaneous coronary intervention in real-world patients with ST-segment-elevation myocardial infarction, Platelets. 28 (4) (2017 Jun) 414–416, https://doi.org/10.1080/09537104.2016.1246714.

[7] J.A. Rymer, D.L. Bhatt, D.J. Angiolillo, M. Diaz, K.N. Garratt, R. Waksman, L. Edwards, G. Tasissa, K. Salahuddin, H. El-Sabae, C. Dell'Anna, L. Davidson-Ray, J. B. Washam, E.M. Ohman, T.Y. Wang, Cangrelor use patterns and transition to oral P2Y12 inhibitors among patients with myocardial infarction: initial results from the CAMEO registry, J. Am. Heart Assoc. 11 (11) (2022 Jun 7) e024513, https://doi.org/10.1161/JAHA.121.024513.