American Heart Journal Plus: Cardiology Research and Practice 23 (2022) 100222

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Short communication

Post-PCI corrected TIMI Frame Count predicts left ventricular global longitudinal strain at 90 days post-STEMI in thrombolysis-treated patients: A pre-specified analysis of the MIRTOS study

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ARTICLE INFO

Keywords:
STEMI
Clopidogrel
Ticagrelor
LVEF
LV-GLS
Thrombolysis

ABSTRACT

Introduction: Ticagrelor has been established as the $P2Y_{12}$-inhibitor of choice in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI); however, its use has not been adequately studied in the context of thrombolysis. In the present study, we sought to investigate whether the administration of ticagrelor together with thrombolysis could result in a greater degree of left ventricular systolic function recovery compared to clopidogrel, at 90 days post-STEMI, as well as to evaluate post-PCI corrected TIMI Frame Count (CTFC) as a predictive marker of myocardial recovery in thrombolysis-treated patients.

Material and methods: In this pre-specified analysis of the MIRTOS trial, the degree of change in left ventricular ejection fraction (ΔLVEF) and left ventricular longitudinal strain (ΔLV-GLS) from baseline to 90 days post-randomization in all patients who underwent conventional and speckle-tracking echocardiography at both timepoints was compared between the ticagrelor and clopidogrel groups. In addition, speckle-tracking echocardiographic measurements were evaluated for any correlations to post-PCI CTFC.

Results: No statistically significant differences were detected between the ticagrelor and clopidogrel groups for ΔLVEF (+3.61 ± 5.08 % versus +2.21 ± 4.78 %; P = 0.18) and ΔLV-GLS (−1.53 ± 2.7 % versus −1.21 ± 3.05 %; P = 0.73). A strong negative correlation was found between post-PCI CTFC and the absolute value of LV-GLS at 90 days post-randomization (r = −0.33, P = 0.014).

Conclusions: Our work suggests that both P2Y12-inhibitors are accompanied with a similar degree of myocardial recovery in the context of lytic therapy. Importantly, post-PCI microvascular integrity is a predictor of 3-month left ventricular systolic function in STEMI patients initially treated with thrombolysis.

1. Introduction

Primary percutaneous coronary intervention (PCI) constitutes the reperfusion modality of choice in the setting of ST-segment elevation myocardial infarction (STEMI); however, in cases where the procedure cannot be performed within the recommended time limit after first medical contact, intravenous (IV) thrombolysis is indicated as the preferred management strategy [1].

Dual antiplatelet therapy with the combination of low-dose aspirin and a $P2Y_{12}$-inhibitor, on the other hand, is a sine qua non in the management of STEMI patients, irrespective of the reperfusion modality utilized [1]. Ticagrelor, has been established as the $P2Y_{12}$-inhibitor of choice in STEMI patients undergoing primary PCI, as its administration has been associated with improved outcome–compared to clopidogrel

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ahjo.2022.100222
Received 16 August 2021; Received in revised form 8 June 2022; Accepted 1 November 2022
Available online 3 November 2022

[1]. Contrary to this, its use has not been sufficiently studied in patients treated with thrombolysis, in which clopidogrel remains the only recommended $P2Y_{12}$-inhibitor [1]. The faster and more potent and predictable inhibition of the ADP-mediated platelet aggregation associated with ticagrelor - compared to clopidogrel - could theoretically be beneficial in the context of thrombolysis, as the administration of fibrinolytic agents is associated with platelet over-reactivity [2]. In the present study, we sought to investigate whether these properties of ticagrelor could result in a greater degree of left ventricular systolic function recovery than clopidogrel at 90 days post-STEMI in patients receiving thrombolysis. Additionally, we aimed to evaluate post-PCI corrected Thrombolysis In Myocardial Infarction Frame Count (CTFC) as a predictive marker of myocardial recovery in this patient population.

2. Material and methods

The present study is a prespecified sub-analysis of the MIRTOS study [3]. MIRTOS was a multicenter prospective, randomized, open-label blinded endpoint (PROBE) trial that investigated for the first time the efficacy and safety of the administration of ticagrelor, compared to clopidogrel, in STEMI patients <75 years old at the same time with thrombolysis. STEMI patients presenting to non-PCI-capable hospitals, for whom thrombolysis was the reperfusion modality of choice, were randomized in a 1:1 ratio to receive either ticagrelor or clopidogrel together with low-dose aspirin and a fibrin-specific thrombolytic agent. Further details concerning the study design and methodology are mentioned elsewhere [4]. All participating subjects were followed up by clinical, electrocardiographic, laboratory and echocardiographic assessment before discharge from index hospitalization, and again at 30 days and at 90 days post-randomization. Importantly, the $P2Y_{12}$-inhibitor remained unchanged in each randomization group during the 3-month follow-up.

The objectives of this pre-specified analysis of the MIRTOS study were:

a) To compare the degree of recovery of left ventricular systolic function between the two randomization groups, as expressed by the change from baseline to end of study (90 days post-STEMI) in left ventricular ejection fraction (LVEF), as well as left ventricular global longitudinal strain (LV-GLS).
b) To investigate if post-PCI CTFC is a predictive marker of 3-month left ventricular recovery in STEMI patients reperfused with thrombolysis.

Data were analyzed in all patients who completed the study and underwent echocardiographic evaluation with myocardial deformation imaging both at baseline and at 90 days post-STEMI and compared between the two randomization groups. In addition, LV-GLS values at baseline and at 90-days post-STEMI, as well as ΔLV-GLS values, were evaluated for any correlations to post-PCI CTFC, which was the primary endpoint of the main trial.

CTFC was assessed on angiographic images acquired during catheterization for the index STEMI. Interventional cardiologists were advised to perform contrast media injections with adequate manual force into the vessel to ensure rapid filling and the presence of backflow. All images should be acquired after intracoronary nitroglycerin administration, and during breath hold, avoiding diaphragm and large blood vessels in field of view of distal infarct-related area. For the assessment of the left anterior descending artery (LAD), the most distal branch should be clearly filmed. Mandatory imaging projections included left anterior oblique −60 to 90° for the LAD and right anterior oblique −30° for the left circumflex and right coronary arteries. All films were analyzed at an independent Corelab (Cardialysis, the Netherlands).

For the calculation of LV-GLS, at least three cardiac circles were recorded from the apical 2-, 3- and 4-chamber views, while image analysis was performed in accordance with the most recent recommendations valid at the time of conduct of the MIRTOS study [4].

Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of each site prior to initiation of subjects' recruitment.

3. Results

From the 335 subjects that were initially randomized, 123 were early terminated for various reasons and the remainder (n = 206) completed the 90-day follow-up period. Of the latter, echocardiographic images of sufficient quality for the performance of speckle-tracking echocardiography with estimation of peak LV-GLS both at hospitalization for the index event and at end-of-study were obtained in 94 subjects (ticagrelor: 42, clopidogrel: 52).

Table 1 summarizes key clinical characteristics, baseline LVEF, baseline LV-GLS and the degree of change in LVEF and LV-GLS (ΔLVEF and ΔLV-GLS, respectively) during the 3-month participation in the study of the 94 subjects that underwent a myocardial deformation imaging study both at index hospitalization and at termination of their participation.

Baseline clinical characteristics, including success rate of thrombolytic therapy, did not differ significantly between randomization groups. Mean LVEF and peak LV-GLS at index hospitalization were estimated at 48.2 ± 7.88 % and −15.67 ± 4.14 %, respectively, in the ticagrelor group, and at 47.82 ± 7.99 % and −16.07 ± 3.77, respectively, in the clopidogrel group (P = 0.69/0.52).

No statistically significant differences were detected between the ticagrelor and clopidogrel groups for ΔLVEF (+3.61 ± 5.08 % versus +2.21 ± 4.78 %; P = 0.18) and ΔLV-GLS (−1.53 ± 2.7 % versus −1.21 ± 3.05 %; P = 0.73). A strong negative correlation was found between post-PCI CTFC and the absolute value of LV-GLS at 90 days post-randomization (r = −0.33, P = 0.014). Spearman correlation analyses between post-PCI CTFC and baseline LV-GLS, ΔLV-GLS and LV-GLS at end-of-study are illustrated in Fig. 1.

4. Discussion

Based on our results, both $P2Y_{12}$-inhibitors were associated with a similar degree of improvement in left ventricular systolic performance at

Table 1
Subjects' baseline clinical characteristics, baseline echocardiographic parameters and degree of change in left ventricular ejection fraction and left ventricular global longitudinal strain in each randomization group.

	Ticagrelor	Clopidogrel	P value
N	42 (44.7 %)	52 (55.3 %)	N/A
Males	33 (78.6 %)	47 (90.4 %)	0.14
Smokers	32 (76.2 %)	36 (69.2 %)	0.49
Arterial hypertension	15 (35.7 %)	23 (44.2 %)	0.53
Diabetes mellitus	8 (19.0 %)	13 (25.0 %)	0.62
Successful thrombolysis	32 (76.2 %)	45 (86.5 %)	0.28
RCA stenosis	15	28	0.10
LAD/DG stenosis	20	16	0.13
LCx/OM stenosis	8	6	0.39
LM stenosis	1	0	0.45
RI stenosis	0	2	0.50
2VD	2	0	0.20
Baseline LVEF (%)	48.2 ± 7.88	47.82 ± 7.99	0.69
ΔLVEF (%)	+3.61 ± 5.08	+2.21 ± 4.78	0.18
Baseline LV-GLS (%)	−15.67 ± 4.14	−16.07 ± 3.77	0.52
ΔLV-GLS (%)	−1.53 ± 2.7	−1.21 ± 3.05	0.73

RCA: right coronary artery; LAD: left anterior descending artery; DG: diagonal branch; LCx: left circumflex artery; OM: obtuse marginal branch; LM: left main coronary artery; RI: ramus intermedius; LVEF: left ventricular ejection fraction; LV-GLS: left ventricular global longitudinal strain; ΔLVEF and ΔLV-GLS: degree of change in left ventricular ejection fraction and left ventricular global longitudinal strain from baseline to 90-days post-randomization, respectively.

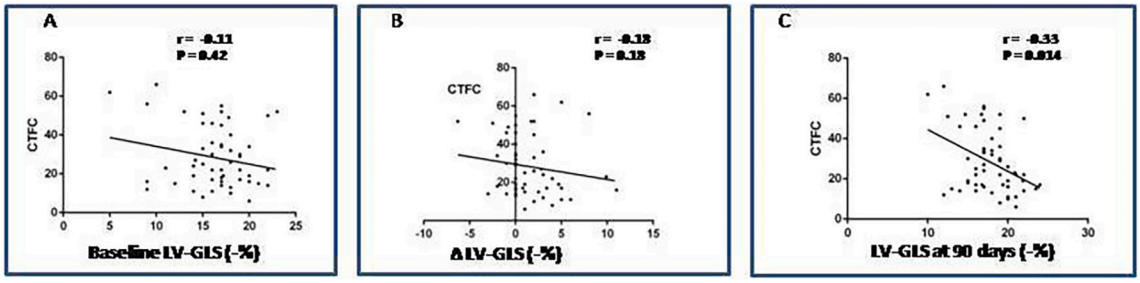

Fig. 1. Spearman correlation analysis between post-percutaneous-coronary-intervention corrected TIMI frame count and speckle tracking echocardiographic measurements.
Panel A: Correlation between post-percutaneous-coronary-intervention corrected TIMI frame count and baseline left ventricular global longitudinal strain.
Panel B: Correlation between post-percutaneous-coronary-intervention corrected TIMI frame count and the degree of change in left ventricular global longitudinal strain from baseline to 90 days post-randomization.
Panel C: Correlation between post-percutaneous-coronary-intervention corrected TIMI frame count and left ventricular global longitudinal strain at 90 days post-randomization.
CTFC: corrected Thrombolysis In Myocardial Infarction Frame Count post percutanecous coronary intervention; LV-GLS: left ventricular global longitudinal strain; ΔLV-GLS: degree of change in left ventricular global longitudinal strain from baseline to 90 days post-randomization (absolute value).

90 days post-STEMI in patients reperfused with IV thrombolysis. In addition, a strong correlation between post PCI CTFC and 90-days LV-GLS was found.

The similar improvement in LV function between the 2 antiplatelet agents is in agreement with the primary finding of the MIRTOS study, in which no significant difference in post-PCI CTFC was detected between the ticagrelor and clopidogrel groups. This indicates that the well-known pharmacodynamic advantages of ticagrelor over clopidogrel in terms of platelet inhibition and the potential to preserve coronary microcirculation and endothelial function might not be applicable in patients treated with lytic therapy.

Doubtlessly, our study's most notable finding is the strong negative association observed between post-PCI CTFC and the absolute value of LV-GLS at 90 days post-STEMI. To our knowledge, this association has not been previously reported in the literature and indicates that lower CTFC values predicts a greater degree of myocardial recovery in STEMI patients initially treated with thrombolysis, as has been demonstrated in patients undergoing primary PCI [5].

There are two key facts that, to our perception, render this latter finding clinical significant: First, CTFC is a well-established marker of microvascular function, which has been consistently shown to positively correlate with myocardial recovery after acute myocardial infarction, and, ultimately with prognosis [6,7]. Second, the strong negative correlation between post-PCI CTFC and LV-GLS absolute value was observed at 90 days post-STEMI, a time point where myocardial stunning has largely resolved and little further improvement in the systolic function of the myocardial segments affected by the acute ischemic event is expected. It should be emphasized that LV-GLS – an index characterized by superior reproducibility in the precise estimation of ventricular systolic function compared to conventional echocardiographic indices [8] – has been shown to correlate well with cardiac magnetic resonance imaging (CMR)-derived infarct size and carries a well-established prognostic value in STEMI patients [9,10].

Taken together, the data outlined above confirm the key role of post-PCI coronary microcirculatory function in the determination of left ventricular recovery - and thus potentially also prognosis - in STEMI patients initially reperfused with thrombolysis. In addition, the clinical significance of the findings of the primary MIRTOS study - in which CTFC served as the primary efficacy endpoint - is reinforced.

Our analysis has some limitations: First, sample size was lower than initially planned. This is explained by the fact that a significant proportion of subjects had not adequate acoustic windows for the performance of a reliable speckle-tracking echocardiographic study. In addition, routine echocardiographic examination was not feasible at 90 days follow-up visit in some of the enrolled patients, for logistical reasons. Second, the distribution of patients that underwent comprehensive echocardiographic assessment in each randomization group was uneven. Nevertheless, this is – to our knowledge – the first prospective randomized study to evaluate the effect of ticagrelor versus clopidogrel on the mid-term recovery of left ventricular systolic function post-STEMI in patients reperfused with thrombolysis.

Adequately powered prospective randomized trials are required to elucidate whether ticagrelor is associated with improved echocardiographic parameters compared to clopidogrel, in thrombolysed STEMI patients.

5. Conclusions

Our work suggests that both ticagrelor and clopidogrel are accompanied with a similar degree of microvascular function and myocardial recovery in the context of lytic therapy. Moreover, the strong correlation of post-PCI CFTC with LV-GLS at 90 days post-STEMI indicates that myocardial injury assessed immediately post PCI is a strong predictive index of 3-month left ventricular systolic function in patients initially reperfused with thrombolysis.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

- Ioannis Anastasiou reports non-financial support from the Hellenic Cardiovascular Research Society.
- Alexandros Patrianakos reports non-financial support from the Hellenic Cardiovascular Research Society.
- Michail Vernardos reports non-financial support from the Hellenic Cardiovascular Research Society.
- Emmanouil Foukarakis reports non-financial support from the Hellenic Cardiovascular Research Society.
- Michail Pitarokoilis has nothing to disclose.
- Stylianos Petousis reports grants from the Hellenic Cardiovascular Research Society.
- Evangelos Zacharis reports non-financial support from the Hellenic Cardiovascular Research Society, and personal fees from Sanofi and Amgen.
- Maria Marketou has nothing to disclose.
- Emmanouil Skalidis reports grants from the Hellenic Cardiovascular Research Society, and personal fees from AstraZeneca, Medtronic, Boehringer-Ingelheim and Pfizer.

- George Kochiadakis reports non-financial support from the Hellenic Cardiovascular Research Society, personal fees from AstraZeneca and Sanofi, and grants from Innovis, Servier and Abbott.
- Fragkiskos Parthenakis reports grants from the Hellenic Cardiovascular Research Society.
- Panos Vardas reports personal fees from Menarini International, Dean Medicus, Servier, the European Society of Cardiology and Hygeia Hospitals Group.
- Michalis Hamilos reports grants and personal fees from the Hellenic Cardiovascular Research Society, and personal fees from AstraZeneca and Sanofi.

References

[1] B. Ibanez, S. James, S. Agewall, M.J. Antunes, C. Bucciarelli-Ducci, H. Bueno, A.L. P. Caforio, F. Crea, J.A. Goudevenos, S. Halvorsen, 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. 39 (2018) 119–177, https://doi.org/10.1093/eurheartj/ehx393.

[2] A. Diego, A.P. de Prado, C. Cuellas, A. de Miguel, B. Samaniego, D. Alonso-Rodríguez, R. Bangueses, B. Vega, J. Martín, F. Fernandez-Vazquez, P2Y12 platelet reactivity after thrombolytic therapy for ST-segment elevation myocardial infarction, Thromb. Res. 130 (3) (2012) e31–e36, https://doi.org/10.1016/j.thromres.2012.05.031.

[3] M. Hamilos, J. Kanakakis, I. Anastasiou, et al., Ticagrelor versus clopidogrel in patients with STEMI treated with thrombolysis: the MIRTOS trial, EuroIntervention 16 (14) (2021) 1163–1169, https://doi.org/10.4244/EIJ-D-20-00268.

[4] J.U. Voigt, G. Pedrizzetti, P. Lysyansky, et al., Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry task force to standardize deformation imaging, J. Am. Soc. Echocardiogr. 28 (2) (2015) 183–193, https://doi.org/10.1016/j.echo.2014.11.003.

[5] S. Hamada, T. Nishiue, S. Nakamura, et al., TIMI frame count immediately after primary coronary angioplasty as a predictor of functional recovery in patients with TIMI 3 reperfused acute myocardial infarction, J. Am. Coll. Cardiol. 38 (3) (2001) 666–671, https://doi.org/10.1016/s0735-1097(01)01424-3.

[6] C.M. Gibson, C.P. Cannon, W.L. Daley, et al., TIMI frame count: a quantitative method of assessing coronary artery flow, Circulation 93 (5) (1996) 879–888, https://doi.org/10.1161/01.cir.93.5.879.

[7] M. Canu, C. Khouri, S. Marliere, Prognostic significance of severe coronary microvascular dysfunction post-PCI in patients with STEMI: a systematic review and meta-analysis, PLoS One 17 (5) (2022), e0268330, https://doi.org/10.1371/journal.pone.0268330. Published 2022 May 16.

[8] S. Karlsen, T. Dahlslett, B. Grenne, B. Sjøli, O. Smiseth, T. Edvardsen, H. Brunvand, Global longitudinal strain is a more reproducible measure of left ventricular function than ejection fraction regardless of echocardiographic training, Cardiovasc. Ultrasound 17 (1) (2019) 18, https://doi.org/10.1186/s12947-019-0168-9.

[9] G. Joseph, T. Zaremba, M.B. Johansen, et al., Echocardiographic global longitudinal strain is associated with infarct size assessed by cardiac magnetic resonance in acute myocardial infarction, Echo Res. Pract. 6 (4) (2019) 81–89, https://doi.org/10.1530/ERP-19-0026. Published 2019 Aug 7.

[10] M. Holzknecht, M. Reindl, C. Tiller, et al., Global longitudinal strain improves risk assessment after ST-segment elevation myocardial infarction: a comparative prognostic evaluation of left ventricular functional parameters [published online ahead of print, 2021 apr 21], Clin. Res. Cardiol. (2021), https://doi.org/10.1007/s00392-021-01855-6, 10.1007/s00392-021-01855-6.