

Reviewer #2

Authors present paper about hypothermic cardiac arrest survivors, but as a Reviewer I have some comments and suggestions.

Authors have to check one more time the Instruction for Authors of Journal of Clinical Medicine.

Authors' response: Thank you. The Journal's *Instructions for Authors* have been re-checked and the manuscript has now been prepared accordingly.

Authors have to verify the space between words in the whole manuscript (for example – line 30 in the bracket)

Authors' response: Thank you. This has been done.

The abstract should be without headings (Background etc.).

Authors' response: This has been corrected.

Introduction is very short – provide more information.

Authors' response: The Introduction section has been improved.

Second section should be Materials and Methods not Experimental Section.

Authors' response: Thank you. This has been corrected.

Authors should provide also exclusion criteria, information about when and where was the study provide. Supplementary Materials should be presented in main paper.

Authors' response: The reviewer is right. The study was conducted at the Emergency Department at the General Hospital of Vienna, one of Europe's largest tertiary care facilities. The Emergency Department comprises an outpatient care section and an affiliated critical care unit covering more than 90,000 patients overall and treats about 250 cardiac arrest patients per year.

Between December 2017 and October 2019 we included adult out-of-hospital cardiac arrest survivors with STEMI, who were treated with hypothermia ($33\pm 1^{\circ}\text{C}$), underwent acute PCI and received an intravenous P2Y₁₂ inhibition with cangrelor, followed by a loading dose of crushed ticagrelor.

Patients with a history of oral P2Y12 inhibitor therapy and patients who received intravenous thrombolysis or were treated using an extracorporeal life support device were excluded.

This is now stated more clearly in the manuscript:

Methods (P2/L65-72): *“This prospective observational cohort pilot study was conducted at the critical care unit of the Emergency Department at the general hospital of Vienna, a 2500-bed tertiary care facility in Austria, Europe. We included adult out-of-hospital cardiac arrest survivors with STEMI, who were treated with targeted temperature management (TTM, 33±1°C), underwent acute PCI and received an intravenous P2Y12 inhibition with cangrelor (30µg/kg intravenous bolus, 4µg/kg/min continuous infusion), followed by a 180mg oral loading dose of crushed ticagrelor via a nasogastric tube before cangrelor cessation. Exclusion criteria comprised a history of oral P2Y12 inhibitor therapy, administration of intravenous thrombolysis or use of an extracorporeal life support device.”*

Following your suggestion, we added supplemental figure 1 (showing the study flow chart) to the main paper (Figure 1).

line 112 – this information should be smaller size of letter

Authors’ response: This has been corrected.

Figure 1 –this figure need legend

Authors’ response: Thank you.

Following legend is provided:

“Platelet function from coronary stent placement (stent) to 24 hours after end of cangrelor infusion (x-axis) was measured using whole blood aggregometry and is given in U (y-axis). Minutes 30 to 1440 refer to the time after cangrelor cessation. Cangrelor sufficiently inhibited P2Y12 at the time of coronary stent placement. Transitioning to ticagrelor within 39 minutes (IQR 5-50) before cangrelor cessation resulted in high platelet reactivity (HPR) in 44% (7/16) of patients within the first 90 minutes after end of cangrelor infusion. Red dashed line, HPR threshold of >46U.”

(NB: Following your suggestion, supplemental figure 1 was added to the main text. Consequently, formerly Figure 1 has been changed into Figure 2.)

Discussion as the Introduction is very short – provide more information – compare your results with other Authors' research.

Authors' response: Thank you very much for your suggestions. We agree with the reviewer. The Discussion section has been improved.

Data on platelet function in cardiac arrest patients receiving cangrelor during PCI are scarce. So far, two observational studies have investigated the antiplatelet effect of intravenous cangrelor in resuscitated patients treated with therapeutic hypothermia [1,2]. As of yet no study has investigated the dynamics of platelet reactivity during and shortly after the transition phase from iv to oral P2Y₁₂ inhibition in cardiac arrest survivors. The limited availability of data makes it difficult to compare our results with those of previous studies.

Given the negative pharmacodynamic interactions between cangrelor and thienopyridines [3,4] on the one hand, and the safe and effective use of ticagrelor in non-cardiac arrest patients receiving cangrelor [5] on the other hand, a *cangrelor-to-ticagrelor transition regimen* seems reasonable in hypothermic cardiac arrest patients. The optimal timing of P2Y₁₂ inhibitor transition, however, remains unclear. The results of our study may highlight this knowledge gap and underline the need for further research aimed at optimal timing of P2Y₁₂ inhibitor transition. Our findings and conclusions are in line with the most recent conference expert statement on switching platelet P2Y₁₂ receptor-inhibiting therapies. Angiolillo and colleagues state that “*early administration of ticagrelor should be considered over administration at the end of cangrelor infusion because it would minimize the potential gap in platelet inhibition during the transition phase*” [4].

There is solid evidence that opiate treatment, hypothermia, hemodynamic compromise and primary PCI impair the pharmacodynamic onset of oral antiplatelet agents [6-8], all of which are accentuated in cardiac arrest patients. Previous prospective cohort studies on hypothermic cardiac arrest patients with acute coronary syndrome receiving ticagrelor or prasugrel found a significant delay of sufficient P2Y₁₂ inhibition with HPR rates of up to 40-50% four to six hours after loading [6], which compares well to the 44% HPR rate found in our study. Even in non-resuscitated patients with acute coronary syndrome treated with morphine and ticagrelor,

the prevalence of high on-treatment platelet reactivity was still 50% 2 hours after ticagrelor administration in a recent multicenter randomized clinical trial [9]. These data (along with results from our study) suggest that early concomitant administration of cangrelor and ticagrelor at the time of PCI scheduling or the extension of the cangrelor infusion beyond ticagrelor loading could possibly be appropriate transition regimens to avoid absence of P2Y₁₂ inhibition or platelet function recovery and thus reduce the risk of stent thrombosis in cardiac arrest survivors. However, further larger-scaled research is needed before any conclusions can be drawn for clinical practice.

Discussion section (P8/L199-203): ... *"This in line with a recent expert statement on switching platelet P2Y₁₂ receptor-inhibiting therapies. Angiolillo and colleagues state that "early administration of ticagrelor should be considered over administration at the end of cangrelor infusion because it would minimize the potential gap in platelet inhibition during the transition phase" [3].*

As the results of the recently published ISAR-REACT trial [10] may have substantial impact on the antithrombotic treatment of patients with acute coronary syndrome undergoing PCI, including those with cardiac arrest, a more detailed description of its findings have been added to the manuscript.

Discussion section (P7,8/L180-184): ... *"This behavior, however, might change following the results of the recently published ISAR-REACT trial, which compared prasugrel with ticagrelor in patients with acute coronary syndrome with or without ST-segment elevation myocardial infarction. This trial found a significantly lower incidence of death, myocardial infarction, or stroke at one year among patients who received prasugrel than among those who received ticagrelor."*

Limitations section (P8/L213-216): *"Furthermore, the study only included patients who were transitioned from cangrelor to the oral P2Y₁₂ inhibitor ticagrelor. From our results no inferences must be made as to platelet reactivity or potential drug-drug interactions after transitioning from cangrelor to clopidogrel or prasugrel."*

References:

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