Author's response to reviews

Title: Influence of Morphine on Pharmacokinetics and pharmacodynamics of ticagrelor in patients with acute myocardial InfarctiON (IMPRESSION): study protocol for a randomized controlled trial

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Author's response to reviews: see over
We appreciate very much the careful review of our manuscript.

We have done our best to resolve the issues raised by the editor and the reviewer, and have made appropriate changes accordingly.

Please find attached the detailed reply to all editor’s and reviewer's comments/suggestions.

We trust that you will find these changes satisfactory and we look forward to hearing from you at your earliest convenience.

Yours sincerely,

on behalf of all authors

Piotr Adamski, MD

Editorial request:

Please upload figure 2 in a different format, as unfortunately this is not appearing correctly in the current format.

Figure 2 has been uploaded in a different format to ensure it displays properly.

Referee 1:

The exact type and route of aspirin administration is of importance, and should be described.

The requested information has been added to the manuscript:

After admission to the study center (Cardiology Clinic, Dr. A. Jurasz University Hospital, Bydgoszcz, Poland) and confirmation of the initial STEMI or NSTEMI diagnosis, patients will receive orally 300 mg loading dose of plain aspirin and will be screened for eligibility for the study.
Data from the pilot study should be briefly described in relation for the sample size calculation.

The requested information has been added to the manuscript:

Since there is no reference study examining PK of ticagrelor in STEMI or NSTEMI patients, we decided to perform an internal pilot study of approximately 30 patients (15 patients for each arm) for estimating the final sample size. Means and standard deviations of AUC$_{(0-12)}$ for ticagrelor in the first 33 patients assessed for the overall population, for patients who received morphine and patients who received placebo were 8805 ± 5723, 6917 ± 4920 and 10379 ± 5996 ng·h/ml respectively. Based on these results and assuming a 2-sided alpha value of 0.05, we calculated using the $t$-test for independent variables that enrolment of 68 patients would provide a 80% power to demonstrate a significant difference in AUC$_{(0-12)}$ for ticagrelor between patients who received morphine prior to a loading dose of ticagrelor and those who received placebo prior to ticagrelor loading dose.

Blood pressure should be recorded, and patients in shock may be an interesting subgroup analysis.

Blood pressure is one of many parameters which are recorded upon screening for eligibility. Patients who are in shock during screening for eligibility are not included in the study (exclusion criterion "Killip class III or IV during screening for eligibility"). Obviously, any cases of patients developing shock during their participation in the study will be recorded, however no such case has occurred so far.

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The typing mistake has been corrected.

Quality of written English: Needs some language corrections before being published.

Minor language corrections have been applied to the manuscript as suggested.