PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Predictive value of apelin-12 in ST-elevation myocardial infarction patients with different renal function: a prospective observational study
AUTHORS	Yang, Lingchang; Zheng, Ting; Wu, Haopeng; Xin, Wenwei; Mou, Xiongneng; Lin, Hui; Chen, Yide; Wu, Xiaoyu

VERSION 1 – REVIEW

REVIEWER	Alparslan Kurtul Ankara Education and Research Hospital, Ankara-Turkey
REVIEW RETURNED	01-Aug-2017

GENERAL COMMENTS	This is an interesting paper that is evaluating apelin-12 in ST-elevation myocardial infarction patients with different renal function. Although the paper is well written and designed, there are some minor limitations. Below are some of my comments: 1- Is there any data about clinical follow-up period? 2. The manuscript needs grammar editing and there are some language mistakes needs to be corrected. 3. The inclusion and exclusion criteria are not well-defined. It can be rearranged with a flow-chart. 4- All references must be revised on the basis of journal format standards.

REVIEWER	Plinio Cirillo Department of Advanced Biomedical Sciences, Division of Cardiology. University of Naples "Federico II"
REVIEW RETURNED	15-Aug-2017

GENERAL COMMENTS	In the present report, the Authors have investigated the potential value of Apelin 12 in predicting MACE in STEMI patients treated by primary PCI. They conclude that those patients with STEMI and treated with pPCI and lower apelin 12 levels are more likely to suffer MACE during hospitalization and at 2.5 years FU. The paper is well written and deals with a very interesting tool. However, this Reviewer has the following comments: 1. In the "Methods section" the Authors state that "all patients received aspirin....and postprocedure anti GPI". What does it mean? GPI are usually indicated as bail-out therapy in patients with high thrombotic burden and during procedure. How were the patients selected to receive GPI? and which GPI, tirofiban, abcximab or eptifibatide? In line with this question, how different GPI affected MACE, clinical outcome or post PCI apelin-12 plasma levels?

	2. In the discussion, the Authors speculate about the potential pathophysiological mechanisms by which apelin 12 might exert protective effects. They should add in this section a study recently published in Thrombosis and Haemostasis that strongly support their results becasue it shows the apelin 12 is able to protect pro-thrombotic effects of other Apelins in endothelial cells (Thromb Haemost 2015; 113: 363–372). 3. In the title the Authors claim about the vaule of apelin 12...in patients with different renal function. However, in the discussion, the impact of renal function on clinical outcome od STEMI patients is missed and its potential relationship with apelin is reported in conclusions only! 4. The Authors have followed STEMI patients for 2.5 years but Apelin-12 plasma levels were measured at baseline and after 72 hrs. It is hard to believe that a close relationship might exist between an "acute" plasma evaluation and a very long time FU! The Authors should carefully evaluate their results.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

1- Is there any data about clinical follow-up period?

2. The manuscript needs grammar editing and there are some language mistakes needs to be corrected.

3. The inclusion and exclusion criteria are not well-defined. It can be rearranged with a flow-chart.

4- All references must be revised on the basis of journal format standards.

Answer:

We appreciate Kurtul's constructive comments. Based on Kurtul's comments, we amended the relevant part in manuscript. Some of the questions were answered below.

Answer for question 1: we have added relevant statement in the first paragraph of results. 31 (6.7%) patients reached end point during hospitalization. 21 (4.5%) patients loss to follow up after discharge.

Answer for question 2: we improved the English writing according your advice.

Answer for question 3: we drawn the flow diagram of patients selection process and results and changed the former figure sequences

Answer for question 4: we reformat the references according to the journal standards.

Reviewer #2:

1. In the "Methods section" the Authors state that "all patients received aspirin....and postprocedure anti GPI". What does it mean? GPI are usually indicated as bail-out therapy in patients with high thrombotic burden and during procedure. How were the patients selected to receive GPI? and which GPI, tirofiban, abcximab or eptifibatide? In line with this question, how different GPI affected MACE, clinical outcome or post PCI apelin-12 plasma levels?

2. In the discussion, the Authors speculate about the potential pathophysiological mechanisms by which apelin 12 might exert protective effects. They should add in this section a study recently published in Thrombosis and Haemostasis that strongly support their results becasue it shows the apelin 12 is able to protect pro-thrombotic effects of other Apelins in endothelial cells (Thromb Haemost 2015; 113: 363–372).

3. In the title the Authors claim about the vaule of apelin 12...in patients with different renal function. However, in the discussion, the impact of renal function on clinical outcome in STEMI patients is missed and its potential relationship with apelin is reported in conclusions only!

4. The Authors have followed STEMI patients for 2.5 years but Apelin-12 plasma levels were measured at baseline and after 72 hrs. It is hard to believe that a close relationship might exist between an "acute" plasma evaluation and a very long time FU! The Authors should carefully evaluate their results.

Answer:
We appreciate Cirillo's constructive comments. Based on Cirillo's comments, we amended the relevant part in manuscript. Some of the questions were answered below.

Answer for question 1: We really appreciate your reminding , and we are very sorry to indicate not all the patients receive GPI medication during or after procedure, indeed, only patients with high thrombotic burden utilize the GPI, which was determined by our interventional physician, whereas no difference was found between MACEs group and non-MACEs group through chi-square test (table 1, 15,12.7% vs 52, 15.0% p=0.536), and all the GPI administrated in our center these years are all uniformly tirofiban.

Answer for question 2: we have added the study in our discussion section in the reference 28.

Answer for question 3: We hypothesis the potential explanation of the subgroup analysis according to different renal function is that patients with relatively normal level of eGFR fail to perform enough discrepancy to distinguish high-risk patients, to these patients, our novel index apelin-12 show its superiority in predicting MACEs.

Answer for question 4: our research focus on a comprehensive end point as MACEs, which consist of cardiac death, recurrent target vessel myocardial infarction (RMI), and clinically driven target lesion revascularization (TLR), cardiogenic shock or demonstrated congestive heart failure (DCHF). Just as our discussion, apelin-12 was proved to play its protective role from several aspects: prevent severe impaired cardiac function; anti prothrombotic; reflect some signal pathway to decreasing permeability of microvascular endothelial cells, improving neovascularization, offer nutrients and oxygen to the ischemic area, improves cardiac metabolism, down-regulation exacerbates ischemia-reperfusion injury and protects against cardiovascular fibrosis.
Several recent clinical studies have support our results and certified the predictive value of "acute" plasma apelin-12 following STEMI in long-term prognosis. Low apelin values were associated with a high rate of MACE, although in the non-acute phase. (PMID 28728608). Increased plasma concentrations of apelin at admission in patients with STEMI were associated with a higher risk of mortality at 6 months. (PMID 27889567) Liu et alhave certified the effect of serum apelin-12 in predicting 1-year outcomes following pPCI in patients with STEMI. (PMID 25634182) Abnormal level of apelin and a serious of adipokines observed in acute MI patients heralds high incidence of MACEs during 3-year follow-up. (PMID 24933198)
Although we follow up for 2.5 years, the first onset of each patient in MACEs group occurs more in the first half period. Among the 118 patients in MACEs group, 31 suffered MACEs during hospitalization, a total of 68 suffered MACEs within the first year follow up period.

We are grateful for the critical reviews, positive comments and constructive suggestions from the reviewers, and believe that all the suggestions and our corresponding revisions have significantly improved the manuscript. We hope that you will reconsider our revised manuscript for publication in BMJ open.

VERSION 2 – REVIEW

REVIEWER	Plinio Cirillo Dpt. of Advanced Biomedical Sciences. School of Medicine. University of Naples "Federico II". ITALY none
REVIEW RETURNED	20-Sep-2017

GENERAL COMMENTS	no other comments