RESPONSE LETTER

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Title: Ticagrelor therapy and atrioventricular block: do we need to worry?

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POINT-BY-POINT RESPONSE

1) A copy of the **revised manuscript** has been submitted.

2) **Answering reviewers.**

a) Reviewer 02469584. Classification: Grade B (very good). Language evaluation: Grade B (minor language polishing). Conclusion: Accept. Comments to authors: I have no objections to this editorial.

RESPONSE TO REVIEWER: We agree. We have improved English Language at our best.

b) Reviewer 01483111. Classification: Grade B (very good). Language evaluation: Grade A (priority publishing). Conclusion: Accept. Comments to authors: none.

RESPONSE TO REVIEWER: We agree.

c) Reviewer 02446589. Classification: Grade B (very good). Language evaluation: Grade A (priority publishing). Conclusion: Accept. Comments to authors: Several P2Y12 receptor inhibitors such as clopidogrel, prasugrel and ticagrelor have been widely used for prevention of thrombotic events and provide substantial clinical benefit. However, as it was presented in this case, they may exert some serious adverse effects. Therefore, dissemination of such cases by publication of papers is highly important for professionals.

RESPONSE TO REVIEWER: We agree.

d) Reviewer 02446698. Classification: Grade C (Good). Language evaluation: Grade B (minor language polishing). Conclusion: Major revision. Comments to authors: In this paper Authors report about two personal cases of paroxysmal bradyarrhytmia associated

with Ticagrelor, a recently introduced non-thienopyridine P2Y12 platelet receptor inhibitor and hence a potent antiplatelet drug. The two patients involved were affected by an acute coronary syndrome (ACS): one of them was also treated with a beta-blocker, and the other one developed persistent AV block needing positioning of a pacemaker. The description of the two cases is supported, in the paper, by the description of five additional, similar cases, already described in the literature by other Authors. Comprehension and explanation of the problem is sound and the case-report is interesting. However, I have some comments and suggestions, whose answer will enhance the value of this paper - For chapter subdivision and denomination I suggest to follow the indications of the Editor. - I suggest also to avoid the impression that Authors describe 7 cases. The 5 cases of the literature should be presented more concisely, and in somewhat less detail, perhaps in some chapter with the "overview". - Clearly, in the discussion the 5 additional cases may enforce the observations made in Authors' own cases. - It is evident that all (5+2) cases had ACS. Most, if not all, were on beta-blockers (bisoprolol), and could therefore be considered at high risk of bradyarrhythmic complications. Please comment. - Authors could widen their reasoning by considering at least three more papers, two of which so recent that could probably not be seen, but that can now be quoted: a) Johnston SC et al NEJM 2016 (on patients after stroke or TIA); b) Ariotti S et al, Curr Cardiol Rep 2017 (on patients with previous AMI); c) Hiatt WR et al. NEJM 2017 (on patients with PAD). - In this way Authors could enrich the discussion including the observation of these adverse effects in populations with more stable cardiovascular conditions. In fact, the bradyarrhythmic adverse effects are likely less frequent in more stable or less severe cardiovascular patients. Authors could comment about this possibility that might influence the clinical use of the drug.

RESPONSE TO REVIEWER: dear colleague, for chapter subdivision, we followed the format suggested by the Editor, considering that this article is an invited editorial in which we also describe some case reports. Now we have renamed the first chapter ("introduction"), and, just to avoid the impression of describing 7 cases, we have a second chapter named "Five published case reports…." and a third chapter named "Two further cases managed at our hospital". Moreover, the five published case reports have now been presented more concisely, with a bit less details. In the discussion, we have underlined the fact that most patients were on beta-blockers, thus increasing the risk of bradyarrhythmic complications. We also have enriched the discussion by including the observation that

relatively more stable patients treated with ticagrelor (after stroke/TIA, chronic stable CAD, PAD) can have a lower risk of bradyarrhytmias. However, it has to be noted that the three interesting articles you suggested did not specifically address the risk of bradyarrhythmic complications. Finally, we have improved English Language at our best. Best regards, Elia De Maria.

3) **Copyright assignment.** It has been submitted with the other required documents.

4) **Audio Core Tip.** It has been submitted with the other required documents.

5) **Institutional review board statement**. This case report/editorial was exempt from the Institutional Review Board standards at our Institution.

6) **Informed consent statement**. The patients involved in this study gave their *oral* informed consent authorizing use and disclosure of their protected health information. At our Institution informed *oral* consent is regarded as sufficient for case reports/editorial.

7) **Conflict-of-interest statement.** Submitted with the other required documents. The authors report no relationships that could be construed as a conflict of interest.

8) **Google Scholar.** We checked the title and stored a screenshot of the results.

9) **Grant Application form**. The manuscript is not supported by any foundation.

10) **Language certificate.** Even if I was born in Italy I am a Native Speaker of English as it was usually spoken in my family since I was born.

Carpi, February 19th 2017 Signature