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Jia-Ping Yan  
Science Editor, Editorial Office  
World Journal of Orthopedics

**RE: Revision of Manuscript No. 49724: Effect of clopidogrel in bone healing. Experimental study in rabbits.**

Dear Dr. Jia-Ping Yan,

We are grateful to you and to the reviewers for both the consideration and the recommendations given for strengthening our manuscript. All due changes to the text have been accordingly incorporated into the manuscript and have been highlighted using red font. Two extra histological images with higher magnification have been added to the revised manuscript, as proposed by one of the reviewers. Below, you will find point-to-point answers to the comments and suggestions provided by you and the reviewers.

Thank you for giving us the opportunity to submit a revised version of our manuscript, as well as for your positive feedback to our submission.

Sincerely,



Professor Zoe Dailiana, MD, PhD  
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Greece

## **SPECIFIC COMMENTS FROM THE EDITOR**

**1. Please provide language certificate letter by professional English language editing company.**

The revised manuscript was checked for typing, grammar and language errors by a professional English language editing company in order to achieve grade A in language quality evaluation. A certificate letter is provided.

**2. Please provide the approval file of Institutional review board, and state it on the title page.**

Our study was reviewed and approved by the Institutional Review Board of the Medical Faculty of the University of Thessaly, Larissa, Greece. The statement has been incorporated into the manuscript (Page 1), and the approval letter is also provided.

**3. Please offer the audio core tip.**

An audio core tip file in mp3 format has been prepared by the first author and uploaded to the submission system.

**4. Please provide an Article Highlights section.**

An Article Highlights section has been written and incorporated duly into the manuscript (Page 14-15).

**5. Please check and confirm that there are no repeated references and add PMID and DOI citation to the references.**

All references have been checked again for typing errors, format, repetitions and PMID & DOI numbers.

**6. Please provide the decomposable figure of figures, whose parts are all movable and editable.**

All figures are provided in the re-submission in PowerPoint format (.pttx) in order to be movable and editable.

**7. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published. (Comment for figure No.2)**

Figure No.2 was completely prepared by us and it is not copyrighted. All drawings and examples (radiographic images from our material) are based on the scoring proposed by Patel et al., which is described in detail in the main text. We had put this citation reference in the Figure legend in order to avoid repeating the main text details about the scoring scale. We agree that the citation in the Figure legend leads to misunderstanding about the copyright of the Figure; therefore, we have removed the citation reference in the revised legend of Figure No. 2.

## **SPECIFIC COMMENTS FROM THE REVIEWER #1 (CODE: 00505755)**

**1. Figure 2 may be revised to indicate or explain the state of the radiographs in each score number.**

Figure 2 has been revised properly in order to indicate clearly the scoring scale. However, no extra text has been added to the Figure, as the detailed description of every number is provided in the main text.

**2. The title of the table 1 may be revised into Secondary histomorphometric parameters shown in mean  $\pm$  SD etc. Number of samples may be indicated.**

The title of Table 1 has been changed accordingly and all numbers of the samples have been added into the table.

**SPECIFIC COMMENTS FROM THE REVIEWER #2 (CODE: 02728252)**

**1. The result section should be extended especially the descriptive one.**

The results section has been extended considering the descriptive histological interpretation (Page 10).

**2. A scale bar should be calculated on the images.**

Scale bars with the results of the radiographic scoring have been added to the Figure 4.

**3. Images with high magnification should be added if possible.**

Two extra Figures (5 and 6) with histological images of higher magnification have been added to the submission.

**4. Why the authors didn't use Micro-CT to obtain their quantitative data?**

Availability and cost reasons didn't allow us to obtain Micro-CT examination. However, the method of defect regeneration assessment (combination of radiographic and histologic interpretation) is well described in the literature and provides reliable results (Spicer PP et al. Evaluation of bone regeneration using the rat critical size calvarial defect. Nat Protoc. 2012;7(10):1918-29). Nevertheless, we added the lack of Micro-CT data in the limitations section in the manuscript (Page 13).

**SPECIFIC COMMENTS FROM THE REVIEWER #3 (CODE: 02446061)**

**1. The introduction should be clear about previous studies suggesting a beneficial role of clopidogrel. You suggest this is a controversial topic, but all sentences suggest it act as a nocive agent.**

The second paragraph of the introduction (Page 5) has been revised properly in order to point out more clearly that the results from the few studies on the effect of clopidogrel on bone metabolism are contradictory. However, we have not further analyzed these studies, as a more detailed discussion of their results is taking place in the discussion section.

**2. Further discussion of four articles provided by the reviewer.**

Two of the articles (Jorgensen et al. 2017 and Coimbra et al. 2015) have been added in the discussion section (Page 12), as the reviewer suggested. However, the other two articles haven't been added in the discussion, as we believe that they are out of the scope of the present study, do not contribute to the better understanding of our results, and may further confuse the reader of the article. The study of Kim et al. 2017 refers to the treatment of arthritis and not in bone healing. Moreover, clopidogrel is in combination with aspirin and not alone, and, for this reason, the exact effect of clopidogrel in bone cannot be pointed out. We also haven't included the study of Medeiro et al. 2016 in our discussion, because it refers to ticagrelor and not to clopidogrel. Although ticagrelor is also a thienopyridine antiplatelet drug, it acts differently than clopidogrel. Moreover, in the vast majority of cardiovascular patients in clinical practice, ticagrelor is used in

combination with aspirin following coronary stenting, which is a different clinical scenario than the hypotheses of our study mentioned in the introduction section.