

March 23, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16354-review.doc).

Title: Clinical relevance of clopidogrel-proton pump inhibitors interaction

Author: Stella D. Bouziana, Konstantinos Tziomalos

Name of Journal: *World Journal of Gastrointestinal Pharmacology and Therapeutics*

ESPS Manuscript NO: 16354

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers

Reviewer 00225353

Add a table reporting data on CV risk trend with coadministration of clopidogrel and PPI.

We added a relevant table.

Add a table schematizing known polymorphisms potentially affecting antiplatelet activity of clopidogrel.

We added a relevant table.

Reviewer 00504904

This is a good paper developing a topic still under debate with several controversials. However, just a comment. The authors affirm that "In conclusion, even though pharmacodynamic studies suggest that omeprazole can attenuate the antiplatelet effect of clopidogrel, this interaction does not appear to translate into increased cardiovascular risk in patients treated with this combination". This could make to be believed that lower doses of the drug may be administered with no increase in cardiovascular risk. How do the authors explain that?

We thank this Reviewer for stating "This is a good paper developing a topic still under debate with several controversials." Regarding the effects of lower doses of clopidogrel on cardiovascular events, it is quite possible that they might be as effective as the currently recommended dose of 75 mg/day. Indeed, the licensing of clopidogrel at this dose was provided based on pharmacodynamic studies and not on studies evaluating cardiovascular events. Moreover, the same is well-established with aspirin, which reduces cardiovascular events to a same degree at the dose of 80 mg/day and at the dose of 325 mg/day (BMJ 2002;324:71-86).

Reviewer 00742221

Very well written and important review.

We thank this Reviewer for her/his positive comments.

Reviewer 01430778

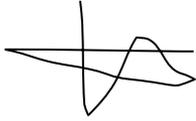
A high quality review paper covers wide range of important articles.

We thank this Reviewer for her/his positive comments.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Pharmacology and Therapeutics*.

Sincerely yours,

A handwritten signature in black ink, consisting of a vertical line on the left, a horizontal line across the middle, and a looped flourish on the right.

Konstantinos TZIOMALOS, MD, PhD

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