



**SDI Review Form 1.6**

Journal Name:	<b><u>Advances in Research</u></b>
Manuscript Number:	<b>Ms_AIR_29264</b>
Title of the Manuscript:	<b>FIXED DOSES COMBINATIONS ACTING ON CARDIOVASCULAR SYSTEM - UTILIZATION AND GENERIC COMPETITION</b>
Type of the Article	<b>Original Research Article</b>

**General guideline for Peer Review process:**

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(<http://www.sciencedomain.org/page.php?id=sdi-general-editorial-policy#Peer-Review-Guideline>)



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**PART 1: Review Comments**

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<b>Compulsory</b> REVISION comments	<p><b>In introduction:</b> Paragraph 1, line 3: ...and adult mortality (17%) [Ref]. Please cite reference.</p> <p>Paragraph 3; ....75% of patients with hypertension (Ref). Please insert reference.</p> <p><b>Paragraph 5, last sentence:</b> "Some combinations of antihypertensive agents exhibit additive or even synergetic effect" please give examples and cite references.</p>	<p>The reference of this information is cited after the end of the paragraph 1 as follow: Allender S, Scarborough P, Peto V, Rayner M, Leal J, Luengo-Fernandez R, Gray A 2008, European cardiovascular disease statistics, European Heart Network, Brussels, England. Available: <a href="http://hdl.handle.net/10536/DRO/DU:3002050">http://hdl.handle.net/10536/DRO/DU:3002050</a></p> <p>The reference of this information is cited after the end of the paragraph 3 as follow: Gradman A. Strategies for Combination Therapy in Hypertension. Curr Opin Nephrol Hypertens. 2012;21(5):486-491.</p> <p>The text is corrected as follow: Treatment by combination therapy offers some advantages compared to monotherapy. The combination therapy sometimes can influence the compensatory mechanisms induced by one of the drugs and prevents the adverse reactions. Some combinations of antihypertensive agents could exhibit additive or synergic effect. Additive blood pressure reduction has been documented with the combination of an ACE-Inhibitor, ARB, or DRI with a CCB. [9] A recent study has shown that ACE-Inhibitors are more efficacious than ARBs in decreasing peripheral oedema associated with CCB therapy. [10] Meta-analysis 42 trials (10,968 participants) To quantify the incremental effect of combining blood pressure-lowering drugs from any 2 classes of thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers over 1 drug</p>



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	<p>The title of the figures should be placed below the figure. Only Tables have their title placed above.</p> <p>On page 7; ...higher response rates than either of the treatments alone [19]. <b>Pls include more reference.</b></p> <p>On page 9;...did not cause low potassium level or any adverse effects on the lipid profile. Did you carry out any biochemical analysis of Lipid profile and Potassium?</p> <p><b>The reference lists are inconsistent and should be properly formatted.</b></p>	<p>alone and to compare the effects of combining drugs with doubling dose. The extra blood pressure reduction from combining drugs from 2 different classes is approximately 5 times greater than doubling the dose of 1 drug. [11].</p> <p>The title of the figures are corrected</p> <p>In this paragraph more references and data were included. The text is amended as follow: FDCs of ACE- inhibitor and calcium channel blocker diminish number of exhibited adverse event of CCB - legs oedema. The combination of calcium-channel blockers and ACE inhibitors could have a synergistic effect. The results shows that the combination of nitrendipine and captopril appears to be a very effective and well-tolerated for the treatment of mild to moderate primary hypertension [18,19, 20, 21].</p> <p>The text is amended as follow: The combination renin–angiotensin–aldosterone system (RAAS) inhibitor and a diuretic in low-doses shows higher reduction of blood pressure and response than the medicines administered separately as well as will compensate the increased plasma renin activity provoked by the diuretic. [22, 23, 24, 25].</p> <p>Corrected</p>
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<p><b>Minor</b> REVISION comments</p>	<p><b>Result Section of Abstract: Methodology.</b> What is INN?</p> <p><b>Result section of Abstract:</b> The 1<sup>st</sup> two sentences should be removed as it is not a result. "Many new generic molecules as FDC entrance the PDL and generally, the gene . . . therapeutic groups"</p> <p>In abstract, what is DDD? Abbreviation should be defined at first used.</p> <p><b>In Introduction section:</b> paragraph 3, line 4, What is BP? "Blood Pressure" Please define abbreviation at first use.</p> <p>Although the authors stated that T-test was applied for statistical analysis. No such statistic was seen anywhere in the manuscript. <b>The degree of significance should be stated categorically. Very important.</b></p>	<p>Corrected/ The list of abbreviation was added</p> <p>The text is amended as follow: The number of the new generic medicines included in PDL is the highest for the group of ACE -inhibitors and diuretics, angiotensin receptor blockers (AT receptor blockers, ARBs, sartans) and diuretics. Many new generic molecules as FDC entrance the PDL and generally, the generic competition leads to decrease of the reference price</p> <p>Corrected</p> <p>Corrected</p> <p>The results from t-test were added (page 12): The results from the T-test shows that there are no statistically significant changes in the utilization and reference prices. In the analysis were compared DDD/1000 inh/day and reference price per DDD for each group between 2009 - 2013. The highest change in utilization is found for the group of ACE - inhibitors and Ca antagonists, <math>p = 0.113</math>. The highest change in reference price is found for the group of ACE - inhibitors and Ca antagonists, <math>p = 0.167</math> and b-blocker/ diuretic (we observe combination bisoprolol/HCTZ only), <math>p = 0.113</math>. Despite the great change in the utilization for some of the products included in PDL, as a whole there are no statistically significant differences between 2009-2013 year for the groups. The same is found in regards to the variations of the reference value. The reference value reduces significantly for some products, but within the group it is not statistically significant.</p>
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	<p>Why didn't the authors use a regression analysis as part of their statistics? This would have enables one to appreciate the beauty of the study.</p> <p>Clarify the plagiarism issue:</p> <p><b>The similarity text check is however insignificant. The related links are:</b> <a href="http://www.medscape.com/viewarticle/7726">http://www.medscape.com/viewarticle/7726</a> <a href="http://www.aafp.org/afp/2008/0501/p1279">http://www.aafp.org/afp/2008/0501/p1279</a> <a href="http://www.oalib.com/relative/269062">http://www.oalib.com/relative/269062</a> <a href="http://europepmc.org/articles/PMC2686259">http://europepmc.org/articles/PMC2686259</a> <a href="http://www.aafp.org/afp/2000/0515/p3049">http://www.aafp.org/afp/2000/0515/p3049</a> <a href="http://dmsjournal.biomedcentral.com/arti">http://dmsjournal.biomedcentral.com/arti</a> <a href="http://www.tribune.cz/clanek/13206">http://www.tribune.cz/clanek/13206</a></p> <p><b>I strongly suggest that the Authors perform a check of the revised manuscript and store screen shot images of the results before resubmission. CrossCheck analysis program is available at</b></p>	<p>We have been working in this issue. Because of the great volume of the information included in this publication, we will prepare the regression analysis for future publication. We will provide it for review, when the data is ready. We hope that will be interesting for your readers</p> <p>The most of the paragraphs were revised, removed or amended. We hope that now the information is clear and without the marks of plagiarism.</p>
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	<a href="http://www.crossref.org/crosscheck/index.html">http://www.crossref.org/crosscheck/index.html</a>	
<b><u>Optional/General</u></b> comments	<p><b>It is an interesting article that should be consider for publication after a critical revision.</b></p> <p>The manner of use of paragraph is seriously irrelevant.</p> <p>The references cited in the discussion section are less than 7. An article like this should have not less than 20 citations. Most importantly that it an observational study between 2009 and 2013. More references should be cited in the discussion section.</p> <p><b>The reference lists are inconsistent. This should be properly taken care of.</b></p>	<p>The limitation and contribution of the study were added: In Bulgaria it is the first study comparing DDD/1000 inh/day, reference price per DDD, and number of the approved trademarks and generic medicines for fixed doses combinations between 2009-2013 . Limitation of the study is calculation of DDD only for DDD/1000 inh/day. The WHO has approved also DDDs per inhabitant per year for estimation of the average days for treatment annually of each inhabitant.</p> <p>More references were added in the discussion section.</p> <p>The reference list is corrected.</p>