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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Cardiology

ESPS manuscript NO: 31152

Title: Ivabradine in the treatment of systolic heart failure - A systematic review and meta-analysis

Reviewer's code: 00259032

Reviewer's country: United Kingdom

Science editor: Fang-Fang Ji

Date sent for review: 2016-11-04 08:28

Date reviewed: 2016-11-16 02:16

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Thank you for asking me to review this systemic review and meta-analysis o Ivabradine + betablockers (BB) versus BBs alone in the Treatment of Systolic Heart Failure. The authors studied 25,659 patients were included and looked at the primary end point of mean heart rate reduction. On a general note the paper read very well and was clearly written. The main concern that I have is with the methodology. I can't see how you can include the main study and then the substudy which includes patients form the main study again as the patients are being counted twice creating significant bias. I think the BEAUTIFUL SHIFT and the other non SHIFT and BEAUTIFUL substudies only should be included. The second issue I have is with the primary endpoint that has been used in this paper. Why make the primary endpoint mean heart rate reduction when you are powered for mortality and other more robust end points? You don't need 25,659 patients to work out that the heart rate reduction is better with ivabradine vs a BB alone and this data adds only little. I think the paper is undersold and would make the primary endpoint as close to the original trials as possible and hence the composite of cardiovascular mortality or HF hospitalizatio The second issue I had



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was with the secondary endpoint which is listed as a combined end point of cardiovascular death and rehospitalization for worsening heart failure. Why is rehospitalisation rather than hospitalization? This would suggest that only patients with a previous hospitalization were included in the analysis yet the inclusion criteria does not state this. A number of additional endpoints were studied but why did the authors not look at Heart failure hospitalization separately as was done in both sHIFT and BEAUTIFUL Studies? There seems to be an important error in the conclusion which states that 'In summary, the results of our systematic review and meta-analysis of the published literature supports use of ivabradine in patients with chronic HFrEF in sinus rhythm and with HR of <70 bpm per guidelines however the strength of evidence supporting this recommendation is weak'. Should this not be >70 per minute?



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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Cardiology

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Reviewer's country: Japan

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input checked="" type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The authors reviewed the effect of concomitant administration of ivabradine and beta-blocker on heart failure. The beneficial effects are limited, but reduction of heart rate is significant and plays a crucial role in treatment of heart failure. Unfortunately, the most important endpoint, cardiovascular or all cause mortality cannot reach to significant level. The authors described reasons of limited effect in LIMITATION such as difference of target heart rate, hypotension and other bias. The authors cannot show enough evidences of effects of ivabradine in this review, but can suggest necessary factors for further study. The manuscript is worth publication.



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ESPS PEER-REVIEW REPORT

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Science editor: Fang-Fang Ji

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

A useful and interesting paper that should be published after authors make some changes to ensure the article is clearer, easy to read and not too technical statistically. 1. In abstract and text, risk ratio should be written as RR instead of "Mantel-Haenszel(MH)risk-ratio(RR)". An explanation can be then made in the methodology on how Mantel-Haenszel RR differs from the RR presented in other reports. 2. Table 1 contains too much information and should be better presented. 3. Abbreviations used in figures 6MWD and EF should be explained.