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PEER-REVIEW REPORT

Name of journal: World Journal of Cardiology

Manuscript NO: 42289

Title: Subclinical carotid atherosclerosis predicts all-cause mortality and cardiovascular events in obese patients with negative exercise echocardiography

Reviewer's code: 03465354

Reviewer's country: United States

Science editor: Fang-Fang Ji

Date sent for review: 2018-09-28

Date reviewed: 2018-10-01

Review time: 3 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The proposed manuscript entitled "Subclinical atherosclerosis predicts all-cause mortality and cardiovascular events in obese patients with negative exercise echocardiography" by Vidal-Perez and co-authors is a retrospective cohort study



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involving 226 patients with BMI \geq 30 kg/m² without significant heart or vascular disease and suspicion for coronary artery disease, and with negative exercise echocardiography, who were submitted for stress and carotid ultrasonography in a single medical center in Spain. Aim of the study was to determine the association between carotid disease and adverse events in obese patients who are negative for exercise echocardiography. This is an important question, because current research is still not clear about the role that the obesity and obesity-accompanied conditions may play. The main finding is that subclinical atherosclerosis defined by carotid plaque in obese individuals with negative exercise echocardiography predicts adverse events. Besides the limitation of this study that the authors state in the Discussion section (retrospective character and one center-based), in my opinion, this study brings additional important knowledge in the field. As a peer reviewer, I do not have any further concerns.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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PEER-REVIEW REPORT

Name of journal: World Journal of Cardiology

Manuscript NO: 42289

Title: Subclinical carotid atherosclerosis predicts all-cause mortality and cardiovascular events in obese patients with negative exercise echocardiography

Reviewer's code: 03846820

Reviewer's country: Netherlands

Science editor: Fang-Fang Ji

Date sent for review: 2018-10-13

Date reviewed: 2018-10-13

Review time: 6 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input checked="" type="checkbox"/> Onymous
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Dear author, The paper represents results of the retrospective study (N=2000) which is aiming to examine the association between asymptomatic carotid disease and adverse events in obese patients with negative stress echocardiography. The article is written



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with the good English-speaking adduction of the arguments. The article is sufficiently novel and very interesting to warrant publication. All the key elements are presented and described clearly. The most discussable options in the article are: 1) Please, optimize your general concept with the proper Introduction and definitions: a) There must be clear understanding about the link between subclinical atherosclerosis and obesity. Please, elaborate it according to the previously published papers such as 10.1016/j.atherosclerosis.2017.03.035, 10.1161/JAHA.114.001540. b) Do you think it could be better to use a definition of "subclinical carotid atherosclerosis" in the title and throughout the manuscript c) page 3 - you write "As we previously described" without any reference! I would remind that the only novelty of your manuscript is that dimension of the CV events in patients with obesity and subclinical carotid atherosclerosis with healthy stress echo. Please, harmonize it. d) IMT - this is one of the most challenging options in the article. Please, be careful and accurate with your judgments and comments. I would suggest you to harmonize your Introduction and Discussion in accordance with the modern-day understanding of its clinical significance - utilize for instance the link 10.1371/journal.pone.0191172. e) What "carotid plaque" truly means in your case - with a stenosis below 50% (ultrasound-revealed), asymptomatic patients - please, define it transparently. f) Should you talk about "adverse events" or about "clinical outcomes"? Please, optimize your definitions in accordance with the common sense and your initial idea. 2) Please, provide the reader with the understanding about your sample size calculation and therefore about your statistical power. Furthermore, there is a room to elaborate your Limitations dramatically. Please, be critical - this is a way for your paper to survive. 3) Another option is a degree of the obesity and a per cent of the patients with a morbid obesity. How many of them were severely obese? As you know a degree of the obesity plays the certain role in prediction of the clinical outcomes. 4) Methods: what are about medications? Did they take aspirin



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due to carotid atherosclerosis or by any other reason? Please, elaborate it. It could be nice to have even simple analysis of any associations between medications and outcomes. 5) Can you draw any conclusions with your statistical power whereas the design of the study? 6) Methods: please, explain how your ultrasound analysis was organized in sense of the expert examination - how many investigators were involved, did you re-assess it. Did you have any independent adjudication of both ultrasound data and clinical outcomes? Please, reflect these details in Methods.

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PEER-REVIEW REPORT

Name of journal: World Journal of Cardiology

Manuscript NO: 42289

Title: Subclinical carotid atherosclerosis predicts all-cause mortality and cardiovascular events in obese patients with negative exercise echocardiography

Reviewer’s code: 03702209

Reviewer’s country: Greece

Science editor: Fang-Fang Ji

Date sent for review: 2018-10-13

Date reviewed: 2018-10-16

Review time: 3 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input checked="" type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer’s expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This is an interesting study showing that Subclinical atherosclerosis defined by carotid plaque predicts AE in obese patients with negative EE. However, a number of issues need to be adressed: 1. Some of The patients included in the study may have healthy



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metabolic obesity i.e. have a lifestyle that involves exercise activitiew. The level of exercise in the cohort is not recorded. The only clue of "fitness" is a negative EE. 2. In page 2 (abstract) and page 7 define "metabolic equivalents-METS 3. In page 3 line 27 replace this by these 4. In page 6 line 14 clarify the phrase "expert cardiologists blinded to the angiography results". Did all subjects undergow invasive angiorgaphy??? 5. in page 8 line 29 clarify the phrase "similar findings were obtained in ischaemic patients". How was ischaemia defind in the patients of the study 6. in page 12 line 1 define what PTP stands for i.e. pre-test probability

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PEER-REVIEW REPORT

Name of journal: World Journal of Cardiology

Manuscript NO: 42289

Title: Subclinical carotid atherosclerosis predicts all-cause mortality and cardiovascular events in obese patients with negative exercise echocardiography

Reviewer’s code: 02465908

Reviewer’s country: Italy

Science editor: Fang-Fang Ji

Date sent for review: 2018-10-13

Date reviewed: 2018-10-18

Review time: 5 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

I read with interest the paper entitled “Subclinical atherosclerosis predicts all-cause mortality and cardiovascular events in obese patients with negative exercise echocardiography”, the idea is clever. However, some points need to be discussed. In the



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methods sections, authors reported precisely reasons for exclusion of patients from this study in the text as well as in figure 1, however they summarized in a few words parameters listed in table 1. In my opinion how and when clinical characteristics were collected and calculated should be explained, especially considering that glomerular filtration rate and metabolic equivalents were found to be independently associated with adverse events. I could understand that about 20% of patients were diabetic being more prevalent in the group of patients with plaque. Was diabetes included in the multivariate analysis model? Moreover oral antidiabetic drugs and insulin treatment should had been prescribed before exercise stress echocardiography (as stated in table 1). Paragraph relating kidney function and adverse events could be improved . It has been reported that ultrasonographic evaluation of carotid arteries damage is related to coronary atherosclerotic damage also in dialysis patients (Int J Artif Organs 2007; 30 (444): 315-320). Moreover relationship between adverse events and kidney function should include evaluation of proteinuria (the latter could be related to presence of diabetes). Diabetic patients with proteinuria have high risk for cardiovascular events. Finally atrial dilatation was not included in the analysis. I wonder if all these points could be included in the discussion section as limitations of the study. Minor remarks Abbreviations should be explained in all tables Dependent variable should be reported in table 3 and table 4.

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