Author's response to reviews

Title: Predicting Clinically Unrecognized Coronary Artery Disease: Use of Two-Dimensional Echocardiography

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Author's response to reviews: see over
To the Editor,
Cardiovascular Ultrasound
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Dear Editor,

We are submitting a revision of our original article entitled “Predicting Clinically Unrecognized Coronary Artery Disease: Use of Two-Dimensional Echocardiography” (MS ID: 1461256362236381) to your esteemed journal.

We are grateful to the editorial team and the reviewers for their thorough review and vital comments. Changes have been made and the editor’s reviewers’ concerns have been addressed on a point by point basis below.

The revised manuscript has been carefully read and edited by all the authors who approve of its current form. There are no conflicts of interest or disclosures for any of the authors. This manuscript is being submitted exclusively to Cardiovascular Ultrasound and is/has not been under consideration by any other journal.

Once again we thank you for your comprehensive evaluation of our work. We hope you will give our revised manuscript a careful review and consider it for publication in your esteemed journal.

Thank you and we look forward to hearing from you soon,

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Reviewer 2:
1 Patient selection: authors should provide more details on the patient population selection criteria. This is a major flaw in the study since authors do not justify on what basis patients underwent SPECT and coronary angiography.

Changes incorporated in Method Section.
Our institution is a large tertiary referral hospital and the testing (echo and SPECT) were ordered as per discretion of the treating physicians. We cross-searched our SPECT and Echo database to identify patients who have both tests done within one year of each other. The most common indications for SPECT were assessment of chest pain or CAD or preoperative evaluation. Patients then were referred for coronary angiography by their treating physician based on the clinical presentation or SPECT findings.

2. Level of risk: In the analysis authors have included patients with reduced EF (<50%), with previous MI identified by rest wall motion abnormalities. These patients per se have a higher risk of death and this may pollute the statistical analysis by increasing the mortality rate. The real novelty of the study relies on the ability of few, simple echo parameters in the prediction of CAD. Therefore, authors should exclude from the analysis patients with reduced EF and/or history of MI and restrict the analysis to the real prognostic value of MAC, aortic calcification, LVH + conventional risk factors.

We agreed with the reviewer’s comments of resting wall motion and low EF are predictors of fatal events. The aim of our study was limited to prediction of presence of CAD by myocardial perfusion imaging or coronary angiography. We did not investigate the prognostic value of the echo findings. Low EF and WMA could be also secondary to non ischemic cardiomyopathy, myocarditis, valvular disease or subjective interpretation. None of our patients have history of CAD, therefore we thought appropriate to include any echo findings that could help clinicians to identify patients at high risk of unrecognized CAD and proceed with further testing that could change the management.

3 SPECT may have a high number of false positive results as outlined in the study limitation but recognise a reduction of coronary flow reserve also in the absence of significant coronary artery disease as in diabetics, hypertensives or hypertrophy as the expression of microvascular disease. Please address.

Changes incorporated
Provide also separate data on outcome between perfusion abnormalities in the absence of CAD but with MAC, aortic calcification and clinical risk factors from those with significant CAD.

No clinical outcomes were obtained for current study.

4. On this same line not all coronary arteries are haemodynamically significant and may therefore, not induce perfusion abnormalities. Please address.

Changes incorporated

5. Please specify the definition of aortic calcification vs. aortic stenosis. Again, also aortic stenosis patients should be excluded from the analysis.

Changes incorporated in Method Section.
The definition of aortic calcification vs. aortic stenosis is based on the CW Doppler information across the aortic valve.
We thought appropriate to include also patients with aortic stenosis since they might share some common pathophysiological process as sclerosis and CAD

6. The discussion is too long and should be more focused on the clinical impact of calcification recognised by 2D echo when more sophisticated and expensive techniques such as CT are routinely employed to assess the same parameters but at much higher health and environmental costs.

Change incorporated
Reviewer 1:
There are some methodological aspects that should be underlined: the definition of LV enlargement as LVEDD > 50 mm, as well as the definition of LV hypertrophy seems questionable, as they do not refer to any existing Guideline. This reviewer is sure that Authors must have convincing reasons for this: they already comment on LV hypertrophy in the Limitations section. Please address also on LV enlargement and explain reasons for these choices.

We used the 2D methods for measurement of the LVEDD at the chordae level intersect the interventricular septum below the LV outflow tract mentioned in the ASE Chamber quantification document. They normal dimension mentioned in the guideline was between 4.7 to 5.2 cm. Therefore we chose 5 cm as the arbitrary cutoff for simplicity of use in clinical setting (see page 1444 of the Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-1463.

A 2D method, useful for assessing patients with coronary artery disease, has been proposed. When using this method, it is recommended that LV internal dimensions (LVIDd and LVIDs, respectively) and wall thicknesses be measured at the level of the LV minor dimension, at the mitral chordae level. These linear measurements can also be made directly from 2D images or using 2D-targeted M-mode echocardiography. Direct 2D minor-axis measurements at the chordae level intersect the interventricular septum below the LV outflow tract and, thus, provide a global assessment in a symmetrically contracting LV, and evaluate basal regional function in a chamber with regional wall-motion abnormalities. The direct 2D minor-axis dimensions are smaller than the M-mode measurements with the upper limits of normal of LVIDd being 5.2 versus 5.5 cm and the lower limits of normal for fractional shortening (FS) being 0.18 versus 0.25. Normal systolic and diastolic measurements reported for this parameter are 4.7 ± 0.4 cm and 3.3 ± 0.5 cm, respectively.
Authors properly underline that they would not advocate use of TTE as screening
test for unsuspected CAD. Anyway, it would be appropriate to suggest an
eventual diagnostic pathway for patients referred to TTE for other reasons, in
which WMA, MAC and AS are found.

Changes incorporated in Discussion section.

Reference 1 and 9 should be updated.

Done

Some minor reports:
- Page 5, line 10: a full-stop should be added before “Abnormal”
- Page 5, line 15: Accuson should be Acuson

Done