Author’s response to reviews

Title: Equivocal tests after contrast stress-echocardiography compared with invasive coronary angiography or with CT angiography: CT calcium score in mildly positive tests may spare unnecessary coronary angiograms.

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Reviewer reports: Reviewer #1: Very interesting, clinically relevant paper. Well-designed study and well-written manuscript. Minor issue: In the Limitations section, I suggest underlining the fact that it is a single-center study.

Thank you. We added it. “Limitations: This is a retrospective and single-center study and the strategy suggested needs to be further tested in a prospective and multicenter validation cohort.

Reviewer #2: Interesting paper examining what clinical or additional non-wall motion imaging variables affect the ROC curves for equivocal dipyridamole stress echo wall motion results in detecting angiographically significant CAD. The authors retrospectively examine data from equivocal studies that subsequently underwent either CTA (n=137) or iCA (n=supposedly 314). Additional variables tested included patients symptoms during the stress test, EKG changes, reversible perfusion defects when perfusion imaging was performed, CFR data in the LAD when performed, as well as subsequent calcium score in those underwent CTA.

Interesting retrospective review, but there are some significant questions: 1. The definition of equivocal seems to be different in the Methods section when compared to the Results as well as Figure 1. In the Methods section on page 6, equivocal tests are only those who have a delta
WMSI of < or equal to 0.016, but in the ICA Results more than 0.06 change is described as a method of reducing the false positive rate of such studies to 29%. Why are WMSI changes of >0.06 appearing in the Results when the purpose of this paper was to discuss equivocal stress echo results?

The way we presented the selection of SE patients who underwent following iCA and CTA may have been in fact a bit confusing, sorry for that.

In the background the sentence “We selected all patients who were either indicated a) iCA after cSE (<90 days) for any clinical reason, whatever the cSE result, and OR b) multislice CTA specifically after equivocal cSE, defined as mild reversible WM abnormalities, or normal WM but abnormal findings among the other parameters assessed during cSE. We assessed diagnostic accuracy data of cSE in the iCA and CTA groups, to find hints helping modify our practice and minimize false positive cSE sent to iCA.” was modified with “either” “OR”, so that it becomes clearer that we selected both a)all patients undergoing iCA after stress, whatever the WMSI, plus the ones undergoing CT in this case only the ones with equivocal tests. This implies that in patients with a iCA available we had both pts with WMSI>0.06 and WMSI<0.06, while in the CTA group only WMSI<0.06.

We moved this paragraph at the beginning of the methods, which probably is a more appropriate place for it to be more clearly noted. Note that pts undergoing iCA within the time frame selected after SE were also included “for any clinical reason”, possibly independently from SE result.

Also, in the Methods section it states the 2 minor findings which are "extremely abnormal" would be considered a frankly positive cSE, but in Figure 1 it appears that EKG and chest pain would never be considered in the frankly positive category.

Yes, only myocardial perfusion or CFR-LAD had the possibility to function as “major” criteria when severely abnormal.

So the sentence has been changed to “The definition of a frankly positive cSE, encompassed either a more severe WMSI delta (>0.06) as a standalone criterion or, alternatively, WMSI delta ≤0.06 but associated with >2 other ancillary abnormal variables or only 2 of such variables, but showing extremely abnormal values, limited to myocardial perfusion or CFR-LAD.”

2. Are the authors presenting the results of both equivocal and non-equivocal cSE studies? Or just equivocal cSE studies? This is not specified in the Results section pages 9-12, but in the Results section in the Abstract it is stated that only equivocal cSE studies were retrospectively examined. Yet, in the Results, patients with reversible WMSI >0.06 appear to be included (although these are not considered equivocal). This must be clarified.

Yes, again this was apparently not very clearly presented in the manuscript. Sorry again. The fact is that, as we said, CTA was only for equivocal SE, while iCA was all SE pts sent to iCA within 3 months, irrespective of SE results.
So it is the abstract which is not clear enough, and we now clarified it with just few additional words, as follows:

“Objectives We assessed the diagnostic accuracy of contrast stress-echocardiography (cSE) in comparison with invasive coronary angiography (iCA), and CT angiography (CTA) only in case of equivocal tests, to find hints helping reduce falsely positive cSE in the suspicion of coronary artery disease (CAD).”

“Results 137 subjects with equivocal cSE and CTA and 314 with cSE (any result) and iCA were selected.”

3. The word "prospectively" should probably not be used on page 5. This is all retrospective analysis of data.

Sure, we now removed the word “prospective”. Now the sentence is “From our cSE database we retrospectively selected patients…”

4. Page 7, line 150: How can a slice interval be in mm? An interval is usually measured in msec.

No, that was intended as spatial interval; now we redefined (maybe to match English language better) “spacing”.

5. The specific reason the over 3000 patient exclusions should be detailed in a flow diagram.

Done. Secondarily I updated figure numbers since this new figure is named figure 1 (flow diagram) 6. Only 176 had myocardial perfusion information in the iCA group. Was this because the data could not be analyzed, or because the study was just using LVO? When myocardial perfusion could be analyzed, did it impact sensitivity and specificity? Should just those with both wall motion and perfusion data be analyzed separately?

Both reasons contributed.

The starting stressecho pool of exams was fully unselected, to maximize the number of patients undergoing iCA that could be retrieved, nowadays a limited percentage.

This implied that stressecho studies performed by operators not using myocardial perfusion (all but myself..) needed be included and only a percentage of patients had myocardial perfusion data retrievable. Moreover we wanted such data to be interesting for most echocardiographers worldwide, currently not using myocardial perfusion, unfortunately.