

Dear reviewers,

We have corrected the different recommendations that you have communicated to us. The changes are highlighted in yellow in the new version of the manuscript.

Reviewer 1 – 00227375

This editorial is nicely structured and well written. I have no question about this manuscript.

Thank you very much for your appreciation about our paper

Reviewer 2 -

1. I am generally satisfied by the content of the submitted article but would suggest elaborating on a few options.

Thank you very much for your constructive comments.

2. Would you please avoid a slide style in the main text particularly when you are writing about key limitations of previous trials.

The paragraph addressing the key limitations of previous trials has been rewritten according to your suggestions.

3. Is that possible to underline the role of CCTA in your schemes and how you offer the routine clinical practice to determine what is more preferable CCTA or ICA in figure 2?

After the ISCHEMIA trial results, we should probably offer optimal medical treatment as a first option to patients with severe ischemia once left main (LM) coronary artery disease (CAD) has been excluded. Therefore, if the goal is just to exclude LM CAD (i.e non-diabetic middle-age women with severe ischemia but non-severe angina) you might wish to perform a CCTA, and if LM is free of disease, continue OMT. If the goal is to revascularize (ie. old-

male diabetic, severe ischemia, limiting/severe symptoms) you might start with angiography.

According to your comments we have modified Fig 2, stating that we could perform CCTA in these subjects with severe ischemia if we are thinking on excluding LM CAD and angiography if we are thinking more on revascularization.

4. I have a big question about kidney function when discussing contrast-associated interventions such as both CCTA and ICA. What are about G3b CKD? From ISCHEMIA trial we know very well higher rates of death and initiation of dialysis. The recommendations for such patients with chronic coronary syndrome especially in the group with GFR 30-44 are not obvious.

That is a good point. From the data provided by ISCHEMIA-CKD we know that the invasive arm in patients with severe kidney dysfunction led to more combined death/new dialysis. Therefore, in these subjects less is more, and that's why we recommend starting the workflow with ischemia test in them (Fig 1), and proceed accordingly but trying to avoid angiographies and revascularizations.

The eGFR threshold employed in the ISCHEMIA trial was 30 ml per minute per 1.73 m², and most patients underwent CCTA. However, the main exception for the use of CCTA was renal dysfunction, and it is not clear how many patients with eGFR between 30 and 45 were included and underwent CCTA.

According to your comment, we have added this sentence: Another important remark for a better comprehension of our approach is that according to the ISCHEMIA-CKD results, starting up with an ischemia testing and trying to avoid coronary intervention seems desirable for patients with kidney dysfunction.

5. Ischemia testing - what do you exactly mean. I ask because there SPECT and CMR with a contrast as well. It becomes again critical for kidney function. Just imagine the story if by this scheme the patient should take three test including first CCTA, with indications CMR or SPECT and then if necessary ICA with possible PCI. All of these procedures are with a contrast. Please elaborate on it.

We agree that not all tests are equal and besides some of them are radioactive, but in the end, users are going to perform them according to local availability and expertise. For ischemia testing we refer to stress echocardiography, magnetic resonance imaging or SPECT. We do not consider exercise ECG testing due to low sensitivity/specificity (but we consider it as a wonderful and cheap test for evaluating symptoms in patients with known CAD).

Regarding to your comment on the risk of kidney dysfunction with imaging test, this is obvious for CCTA/angio, as referred elsewhere. This risk is much lower with functional tests. MRI might rarely induce severe kidney dysfunction after gadolinium injection, whereas as far as we know, no kidney dysfunction has been reported with SPECT and SPECT has even been performed for risk stratification before kidney transplant.

We have modified figure 1 to specify that a non-contrast technique (Stress echo or SPECT) for evaluation of ischemia should be the preferred option in patients with renal dysfunction. Also, according to your comments, we have included a footnote in Figures 1 and 2, stating that ischemia testing refers to stress echocardiography, magnetic resonance imaging or SPECT, in addition in figure 2 some remarks have been written to clarify the use of test according to renal function