J Hochman

Should interventionists be afraid of ISCHEMIA?

The ISCHEMIA Trial will assess whether an early invasive strategy with catheterization and optimal revascularization is superior to continued intensive optimal medical therapy and lifestyle changes, with catheterization reserved for those who fail medical therapy, in patients with moderate or severe ischemia.

Confluence spoke to the Study Chair, Professor Judith Hochman, Co-director, Clinical and Translational Science Institute, New York University School of Medicine, New York City, about how this trial might impact clinical practice.

Clinically, what does ischemia mean for patients?

From a patient perspective, it doesn't mean a lot if they don't have symptoms. However, we know a lot of ischemia is associated with an increased risk of death or myocardial infarction (MI). In terms of what it means for a patient, once again, it means something if it's associated with angina, but we know that not all the ischemia is associated with symptoms.

How is ischemia currently managed? What kind of drugs are used? Are all patients treated with just basic medical therapy, or are other interventions used?

There are a range of medications that are used to treat stable coronary artery disease (CAD). Firstly, there are risk factor modifiers, the secondary preventive medications that are meant to change the natural history of plaque, plaque rupture, atherothrombotic disease and to protect against arrhythmias precipitated by unstable plaque. This includes statins and other lipid-lowering agents to lower LDL cholesterol, agents that control blood pressure, and medicines that help to control HbA1c. Lifestyle factors are also important including the management of obesity and sedentary lifestyle, etc. Secondly, there are the drugs that reduce the risk of sudden death and also reduce exercise-induced ischemia, beta-blockers, for example. This also includes ACE inhibitors, which are especially efficacious in patients with left ventricular dysfunction, diabetes and hypertension. Finally, there are others medications that help manage ischemia and angina, including calcium channel blockers, nitrates and ranolazine.

In addition to medical therapy, we have data on the use of strategies such as catheter-based revascularization. Right now, in clinical practice, despite the fact that when you talk to people at academic centres and they think that all these patients with ischemia are getting cath, this is not the case: it is about 50/50, even in patients with at least moderate ischemia. Rory Hachamovitch has investigated referral data in 5,833 patients with moderate or severe ischemia on myocardial perfusion imaging from nine different US studies.[1-4] Within 90 days of testing, the rate of referral for catheterization was only 35–65%. We can see there really is quite a variety in treatment, and equipoise about whether they need upfront, early invasive management after a positive stress test.

What will the ISCHEMIA trial investigate and why is it important?

The landmark COURAGE and BARI 2D trials demonstrated that an initial management strategy of revascularization and optimal medical therapy (OMT) did not reduce the risk of death or MI in stable CAD patients compared with initial OMT alone. However, the COURAGE trial was not without its drawbacks. There was possible selection bias (all patients underwent coronary angiography so the role of selection bias based on perceived risk/benefit is difficult to assess). It is also unknown how much baseline ischemia was present in many patients.

The ISCHEMIA trial will investigate stable patients with moderate or severe ischemia on nuclear (e.g., ≥10% left ventricle ischemia), echo, or cardiac MRI stress testing. The trial will assess whether an invasive strategy with cardiac catheterization

and optimal revascularization plus OMT reduces cardiovascular death or MI compared with a conservative strategy comprising OMT with catheterization reserved for patients with refractory angina despite maximal medical therapy, or those with acute coronary syndrome, acute ischemic heart failure or resuscitated cardiac arrest. It is a superiority trial, so the hypothesis is a positive one: that the routine, (early invasive strategy with catheterization and what we call optimal revascularization) will be superior to continued intensive OMT and lifestyle changes.

The ISCHEMIA trial is going to be very important for interventional cardiologists, because since COURAGE was published, the use of PCI in stable ischemic heart disease (SIHD) has been decreasing because of the lack of evidence for a reduction in death or MI when added to medical therapy. A key aim of the ISCHEMIA trial is to try to redress some of the limitations of those landmark trials. The trial is also important because it will have implications for guidelines, performance metrics and reimbursement. In the current economic climate, there is a huge focus, both nationally and internationally, on cost. Following the two negative trials, COURAGE and BARI 2D, payors are likely to say 'well, why are we paying for this?'. The trial is really designed to be well-powered and well-positioned to demonstrate that there is superiority for an invasive strategy if in fact the hypothesis is correct. Patient quality of life will also be assessed throughout the study. The withdrawal of medications due to side effects and the numbers of patients who require catheterization for angina will also be recorded.

How will ISCHEMIA address the limitations of these previous studies?

The first attribute is that we intend to recruit 8,000 patients, which is over three times as many as COURAGE and BARI 2D, meaning the study is very well powered. Another critical issue is that randomization will take place following a stress test but before cardiac catheterization. Patients (without renal failure) who qualify on the basis of ischemia will undergo blinded coronary CT angiography (CCTA) to exclude left main disease and to confirm the presence of obstructive coronary artery disease prior to randomization. This is a concern from many previous trials, not only COURAGE and BARI 2D (RITA-2 was another stable CAD study that randomized after catheterization). Once you see the angiogram, it has been argued that those who would have seen the most potential benefit from revascularization may have already been excluded. There may be a lot less bias in terms of who you include if you randomize before catheterization. The next potential limitation of the prior trials is that they did not require a specific threshold of ischemia to get into the study. They required an anatomic definition of coronary disease but not necessarily ischemia. The ISCHEMIA trial will actually require at least moderate ischemia in all patients that are enrolled, and therefore it should be adequately powered for the sub-set patients that got into COURAGE and BARI 2D that had moderate or more ischemia.

The other key variable is that the protocol for the ISCHEMIA trial focuses on complete revascularization of all the ischemic segments, that wasn't specifically emphasized in COURAGE and BARI 2D. The PCI is going to be guided by the functional testing, stress imaging, or fractional flow reserve and SYNTAX score. We believe it to be important that this is not just anatomical revascularization, it is revascularization based on functional testing. Also, our definition of MI is going to be very conservative in terms of the peri-procedural MI. We will have a high threshold, meaning specificity in terms of clinically important infarcts.

Also, the techniques and devices have continued to evolve over time, and we are going to use the most up-to-date practice and materials. All stents will be drug-eluting stents unless it is indicated to use a bare metal stent. They will be the most recent stent types that have shown at least equivalence or superiority to older generation stents.

The last thing is that there is a group of leading interventional cardiologists and surgeons (representing the 'Heart Team' concept) who are leading this study. As there is going to be bypass surgery in this trial as opposed to COURAGE, all of these specialities have had substantial input into all aspects of this trial. The Leadership Committee includes interventional cardiologists, Gregg Stone, David Williams, Bob Harrington, and a cardiac surgeon, Bruce Ferguson. Bill Boden is Chair of the OMT Committee and I am acting as Study Chair, working with David Maron as PI and Study Co-Chair. It is a very well-balanced Leadership Team and we have been working hard.

Do you think there are any limitations to this present study design?

A major limitation of this study will be if people don't support the trial and patients don't get enrolled; we need to enrol people that represent a broad cross-section of patients with SHID and at least moderate ischemia, so long as they don't have symptoms that are refractory to medical management. We know that PCI and CABG improve angina. If a patient needs revascularization to improve their angina they are not going to be targeted for this trial as they will only end up crossing over from the conservative group to the invasive group, which is something we want to avoid. It is really in the best interest of the whole cardiology community to enrol a broad cross-section of patients, so we have the true answers and we are able to test the hypothesis of superiority. The study will therefore exclude: 1) patients with an unacceptable level of angina despite maximal medical therapy (i.e., requiring revascularization) and 2) patients who are very dissatisfied with medical management of angina at present.

As study Chair, what does your role involve?

Overseeing all the moving parts! As I mentioned, it is our intention to include 8,000 patients in this study and recruitment will start in approximately 500 centres in over 30 countries this summer. We also have a clinical coordinating centre that I run at New York University (NYU), in our Cardiovascular Clinical Research Centre; we have a statistical and data coordinating centre at Duke (DCRI); an Ischemia Imaging Coordinating Centre at Emory, that Leslee Shaw will oversee; and a stress nuclear core lab, a stress MRI core lab, and stress echo core lab. We have a coronary angiography core lab, we have a CCTA core lab, and of course we have all of our country-leaders and academic research organizations – and most importantly – our sites. I am coordinating all of these facilities together with David Maron.

How do you think the results of this study are going to change clinical practice and benefit patients?

If the trial shows superiority of an early invasive strategy, more patients should be getting it and we would have another proven strategy for these patients. If it is a positive trial, the increased use of an invasive strategy would be the goal.

Obviously, if the trial does not show superiority, it shows that you can wait and make judgements about catheterization based on how patients respond to therapy: this would of course lead to a reduction in unnecessary procedures and a significant cost saving. As cost is as huge a concern in the US as elsewhere, the study will make a notable contribution in this area. There will also be a lot of education for the sites regarding the quantitative analysis of ischemia, which will be directed by members of our leadership group. I think there are going to be a lot of positive things that will come out of this study, beyond just answering of the primary question.

Do you think interventionists are going to have something to fear from the outcomes of the study? Do you think the results could prove controversial?

I suggest they look at the design of the trial, see that it's very well-powered and positioned to test the hypothesis, and they should not be afraid of the trial. It is possible that COURAGE and BARI 2D were limited in their ability to show a benefit for revascularization because interventionists refused to offer trial participation to their higher risk patients. ISCHEMIA has been designed to show a benefit from revascularization in SIHD if one exists, but if interventionists do not offer trial participation to their higher risk patients, they could unwittingly undermine the ability of the trial to prove the hypothesis.

Every clinical trial has some controversy! We have worked very, very hard on designing this study – a process which has taken three years. Also, a lot of people have had input into the planning stages and we hope that people will acknowledge their depth of expertise and knowledge. Therefore, I feel the results here will stir up a lot less controversy than many other trials.

Are you assessing differences between patient groups?

We will certainly look at sub-groups, including the usual sub-groups: by age, by sex, by diabetes, by ischemia location, for example. We are most particularly interested in patients with anterior ischemia and patients with more extensive coronary disease. We have noted that most patients, aside from those with chronic kidney disease, will have a blinded CT coronary angiogram, so as we will have baseline information

about the coronary anatomy, we have a sub-group based on those data as well.

What are you looking for in prospective study sites?

It should be stated that we have very strict criteria to determine which sites can participate because we want to make sure that the quality of the intervention and the quality of the surgery is very high. We believe that the outcome, obviously, will be very sensitive to how well the procedures are performed. This is something else that should be reassuring to the interventional community: that we are only selecting for sites that have high quality interventionists and excellent surgical outcomes. We are, therefore, looking for those kinds of sites to participate in the study.

How can people contact the Leadership Team if they would like further information or are interested in participating?

They can visit the study website, **http://ischemiatrial.org/** or they can email the study at **ISCHEMIA@nyumc.org**.

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