**Title: AHA 22 Late-Breaker Discussion: The PRECISE Trial**

**Participants: Dr Harriette Van Spall and Dr Pamela S Douglas**

**Date: 7 Nov 2022**

**Dr Harriette Van Spall**

- I'm Harriette Van Spall Associate Professor of Medicine, and Scientist at McMaster University, and I'm delighted to have with me today, Dr. Pamela S. Douglas. Who is the Ursula Geller Professor of Research in Cardiovascular Diseases at Duke University. And we are here at AHA 2022 to discuss her PRECISE trial. Welcome Dr. Douglas.

**Dr Pamela S Douglas**

- Oh, thank you. It's a pleasure to be here.

**Dr Harriette Van Spall**

- I am so excited to talk to you about this trial, which was a prospective randomised trial of the optimal evaluation of cardiac catheterization. In which you tested a risk tool to stratify decision making around patients who presented with cardiac symptoms. Tell us about the rationale for the work.

**Dr Pamela S Douglas**

- Absolutely. Well, as you know, new onset stable chest pain is incredibly common. And in the United States alone, every year accounts for over 4 million tests. What's worse is that we don't have a validated prospectively validated strategy to optimise testing, even though guidelines agree that our goal should be to reduce unnecessary testing, improve diagnostic yield, reduce complications and costs of invasive testing, and optimise preventative medical treatment. So we know what we want to accomplish, we just don't know how to get there.

**Dr Harriette Van Spall**

- Right so, who were your patients of interest? Were these ambulatory patients who presented to the emergency department, or seen in a cardiac clinic?

**Dr Pamela S Douglas**

- We wanted to test in stable chest pain patients, so mostly in the clinic, and they were new onset disease. We didn't want people with known coronary disease or who had, you know, had tests after tests of a workup, but no answer. We were enrolled actually 2100 patients like this, stable patients, and randomised them to either a precision strategy, or usual testing. So these were people that their physicians felt needed a test, so a stress test, a catheterization or whatever. In the precision strategy, which of course was the intervention arm, we gave as you mentioned, a risk tool, a quantitative risk assessment, using the PROMISE minimal risk score, which has been validated both internally and externally of the PROMISE trial to take the 20% at lowest risk, and assign them to deferred testing. And the other 80% to CT coronary angiography with selective FFR CD if they had an intermediate stenosis.

**Dr Harriette Van Spall**

- Dr. Douglas, tell us about the PRECISE tool that you used in your intervention. What were its performance characteristics and the external validation cohort?

**Dr Pamela S Douglas**

- The PROMISE minimal risk score was derived from the 4,600 patients in the PROMISE trial who had CP testing, and we modelled those with essentially no risk. 27% who had no calcium, no plaque, no events, and we wanted it to be readily available, clinical datas, clinical variables so that you have the data in the office that you needed to make a decision. Externally, it was validated in SCOT-HEART and Dan-NICAD, a total of over 3400 patients. With an AUC of 0.76, which is better than either a Framingham risk or a dominant forester.

**Dr Harriette Van Spall**

- Fantastic. And what did you choose as your primary endpoint for this trial?

**Dr Pamela S Douglas**

- The primary endpoint was a composite of all cause death, nonfatal MI, and catheterization, without obstructive disease. And we chose this composite to give a net clinical effectiveness. We've got the efficacy of the cath without obstructive disease, and we've got the safety of the death, and MI. And cath without obstructive disease, a little unusual as an endpoint but it has been used as endpoint in trials, and it's associated with better quality of life, fewer complications, and lower costs. So we felt in this low risk population, with few hard endpoints, this was a significant metric as to the quality of the chest pain evaluation.

**Dr Harriette Van Spall**

- Fantastic, tell us about your trial population. What were their baseline characteristics?

**Dr Pamela S Douglas**

- The baseline characteristics of our population we had a mean age of 58, and there were half women. 94% had at least one major cardiac risk factor. In our diamond forester pretest, probability was 16%, so squarely in an intermediate range with a pooled cohort equation, tenure risk of 8%. A quarter of our patients had typical chest pain.

**Dr Harriette Van Spall**

- So tell us about your result.

**Dr Pamela S Douglas**

- Our primary endpoint, which as you remember, was a composite, was strikingly positive. Supporting the precision strategy with an unadjusted hazard ratio of 0.35 adjusted 0.29 very close. We also, as a secondary analysis did a hierarchical win-ratio analysis, which favours death and MI over the softer cath endpoint. And this had a similar degree of strong positivity supporting the PRECISION strategy.

**Dr Harriette Van Spall**

- Okay, and in your primary analysis, tell us about the component endpoints rather. You talked about the secondary win-ratio but how about the component endpoints of death versus the obstructive coronary disease?

**Dr Pamela S Douglas**

- So death and nonfatal MI, or death or MI, were much less common than the cath without obstructive disease, and they weren't significantly different in the two arms. There was a trend towards a larger difference if non-fatal MI, but the confidence intervals crossed one. The cath without obstructive disease was much more common accounted for about half of the precision strategy endpoints and most of the usual testing endpoints. So it was 2.6% in precision, and 10.2% in the usual testing.

**Dr Harriette Van Spall**

- So a big reduction in that endpoint. What do you make of the hint of increased risk in the intervention group with regards to nonfatal MI? Why do you think that might have been?

**Dr Pamela S Douglas**

- Well, that's a complex issue as you might guess. We looked very hard at that. A third of our MIs were prior to the randomised tests, so could not be due to the test intervention. And similarly, when we did a per protocol analysis the difference was much smaller. We did note that the majority of the difference was in type two MI'S, and peri procedural MI's. And for this reason, we did a post-hoc analysis using a sky definition for a procedural, peri procedural MIs, which again removed three MIs in the precision group, and none in the usual testing group. So again, suggesting somewhat related to protocol adherence. The MI definition, making it difficult to, I think make too much of it. Obviously we are very concerned about safety of the strategy, but we didn't see anything that pointed to a worse outcome related to the trial intervention of CT and FFR CT. I should say here, very importantly, there were no deaths, and no MIs in the precision strategy patients assigned to deferred testing. So there's absolutely no safety concern at all in that group, which is an important point.

**Dr Harriette Van Spall**

- Sure, and your median follow up was about 12 months, right? It was just under 12 months

**Dr Pamela S Douglas**

- Correct, the trial duration was 12 months. Our median follow up was 11.8, 96% completed the study.

**Dr Harriette Van Spall**

- And were there any crossovers before you measured your endpoints?

**Dr Pamela S Douglas**

- There were some crossovers in that people received either the other test, or in the groups that were supposed to be tested. A few did not test, but overall 92% of the population received the evaluation strategy to which they were assigned.

**Dr Harriette Van Spall**

- Right, and were there consistent treatment effects across subgroups, or did you find any variation?

**Dr Pamela S Douglas**

- There was great consistency across subgroups, or just one or two that the confidence intervals crossed one, but by large everything, age, sex, risk score and so on, were all in favour of the precision strategy.

**Dr Harriette Van Spall**

- Sure, I wonder if you could comment on the uptake of lipid lowering or antiplatelet therapies in both groups?

**Dr Pamela S Douglas**

- Yeah, that was a really interesting finding. We found that at 12 months there was a substantially significantly more lipid lowering therapy, as well as antiplatelet medication compared to the usual testing arm. The magnitude of this increase was similar to what has been reported in other trials like SCOT-HEART and PROMISE, and as you'll recall is about to be the mechanism of benefit of CT in the. SCOT-HEART trial, as a sort of a control. There was no difference in anti-hypertensive medication.

**Dr Harriette Van Spall**

- So in summary, your intervention was effective with a big treatment effect in reducing the composite of death non-fatal MI, or catheterization without obstructive CAD, largely driven by the benefit in that endpoint of cardiac cath without obstructive CAD at one year follow up. How do you think this is going to change patterns of risk stratification, or investigation in patients with stable CAD?

**Dr Pamela S Douglas**

- I'm hoping that this provides physicians with two things. One, a randomised trial evidence that you can safely defer testing using a quantitatively determined risk score. And we haven't ever had that. We've had assessments of low risk patients who were tested in trials like PROMISE, SCOT-HEART, who did well, but of course their care was informed by the testing that they received. Here we have the prospective validation of that. We're very excited. And in fact, we reduced the amount of testing overall in the precision arm and increased the yield, tests were more likely to be positive. We also reduced catheterization in the prescision arm compared to the usual care arm. The second thing that, that is the take home point is, that the use of CTA with selective FFR CT, was superior to usual testing, was any stress test of the physician's choice, or directed catheterization. So I think those two points, the safety of a carefully performed deferred testing strategy and the use of CTA as a first test, are the real take home messages of PRECISE.

**Dr Harriette Van Spall**

- And how do you put these findings in the context of other investigations in this area?

**Dr Pamela S Douglas**

- Well, regarding the safety issue and deferred testing that has never been tested in a randomised prospective trial. In fact, all of our risk scores are based on retrospective data and none of them have been, I have cut points that have been actually examined prospectively in a randomised way. So that is a, you know, first of its kind. We have and regarding the use of CT as a first test, we have numerous observational studies, some of which I've done, many of which have been done by others, like advances, a large one platform, that suggests that CT with FFR CT is beneficial in reducing catheterization, in enhancing preventive treatment. But this is the first randomised trial evidence that we have comparing it to usual care testing.

**Dr Harriette Van Spall**

- Any plans to do cost effectiveness analysis?

**Dr Pamela S Douglas**

- Yes, we, yes, we think that that's very important. Both the cost effectiveness analysis and a drill down details in the low risk group, the results in the outcomes in the low risk group are planned, hopefully for ACC, but not in, not in time to include here at at AHA.

**Dr Harriette Van Spall**

- Wonderful. Well, thank you so much for spending time with us to go over the results of your important trial. And congratulations, on your late-breaking clinical trial presentation. That's just a few days away.

**Dr Pamela S Douglas**

- Thank you so much. It's such a pleasure to be here with you today.