Title: ACC 23 Late-breaking Discussion: The COORDINATE-Diabetes Trial
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Dr Van Spall
- I'm Harriette Van Spall, Associate Professor of Medicine and Cardiologist from McMaster University in Canada. And I'm delighted to be here at ACC 2023 with our friends from Radcliffe and the PIs of the COORDINATE-Diabetes Trial, Dr. Neha Pagidipati, who is Associate Professor of Medicine and Cardiometabolic Disease at Duke and Chris Granger, who is Professor of Medicine and Director of the Cardiac Care Unit at Duke. Welcome.

Dr Pagidipati
- Thank you.

Dr Granger
- Thanks, Harriette, great to be here.

Dr Van Spall
- It's lovely to be here with you and we are so excited about your late breaking clinical trial presentation that is scheduled for a couple of days from now. I wonder, Dr. Granger, if you would provide the context and the rationale for this implementation trial?

Dr Granger
- Well, Harriette, you're a perfect person to discuss this with 'cause this is, I know this is also a passion of yours, that there's nothing more important now in all of medicine to improve health than to more consistently apply those treatments which have proven benefit. And sadly, if we look at all the major treatments that we use in cardiovascular disease, they're only used in about half the time or less in a way that would really improve health. So, what we intended to do with this trial, was to generate high level evidence to demonstrate whether a multifaceted intervention in cardiology clinics in the United States could meaningfully improve the use of these treatments for patients with atherosclerotic cardiovascular disease and diabetes to improve health. And those include simple things like high-intensity statins, only used in about 25% of patients with atherosclerotic cardiovascular disease, ACE or ARB, which have the proven benefits for vascular and renal protection for diabetes and ASCVD. And then the new diabetes drugs with such impressive proven benefits, GLP1 receptor agonists and SGLT2 inhibitors.

Dr Van Spall
- Yes, important work indeed. And these trials are difficult to execute. Tell us what your principal hypothesis was.

Dr Granger
- So, we used a cluster randomised approach. We enrolled... we randomised 43 clinics that ended up participating in the trial, cardiology clinics and about a thousand patients. And our goal was to improve the proportion of patients that were on all three of those treatments. And to start with, none of the patients were on all three of those. There was a little bit of a nuance that if patients

had a haemoglobin A1C of less than seven and were on metformin, we counted that in the beginning of the trial as fulfilling the need for the diabetes treatment. But basically we wanted to show that we could improve the proportion of patients that were on all three of those treatments.

Dr Van Spall
- Okay, so your primary outcome is a proportion of patients on the three therapies that you discussed. Dr. Neha, perhaps I'll pivot to you and ask you to give us a deeper dive into the research methods. This was a cluster randomised trial. Tell us about the unit of randomization and the patients that you included.

Dr Pagidipati
- Absolutely, so the unit of randomization was cardiology clinics across the United States. So these clinics, we really wanted a diverse group of clinics. These clinics needed to have at least three cardiology providers of any type. They could be MD, DO, APP, and they needed to be able to identify someone who is a diabetes care provider that they could collaborate with. So that could be anyone in their orbit really who, kind of, specialises in or cares for patients with diabetes. That could be an endocrinologist, a primary care clinician, or other, and they needed to be interested in participating in the trial. And that was about it. So we really tried to keep this as general as we could. And then the patients that they enrolled also were meant to reflect the patients that we see every day in clinic. So those were patients with type two diabetes and atherosclerotic cardiovascular disease, whether that was coronary, cerebrovascular, or peripheral arterial disease and they needed to be adults. And that was basically it. We really, as I said, wanted to keep it as generalizable of population as as possible. So we ended up randomising 43 clinics that enrolled patients, 20 to the intervention arm, and 23 to the usual care arm. And on average the clinics enrolled about 24 patients per site.

Dr Van Spall
- Okay and tell us about your intervention.

Dr Pagidipati
- Yeah, absolutely. So, this was as Chris mentioned, this was a multifaceted intervention because we know that just one thing doesn't necessarily work to change provider behaviour. It's not that easy of a thing to change. And so, the six components that the intervention had were really delivered by what we're calling a coordinate trio. And that included a cardiologist, an endocrinologist, and an implementation specialist from the study team. And initially, the team went to each site in person at the start of the intervention but then when COVID hit, everything transitioned to virtual. And so, the entire intervention was delivered remotely. And the six components that were delivered was; one, there was a clinic level assessment of barriers to what are the challenges to prescribing these evidence-based therapies in that particular clinic. And then the second aspect was trying to develop pathways to overcome those challenges. Maybe it was including a pharmacist because some of the issues were around prior authorization, maybe it was educational pathways because there were issues with understanding the use of the drugs. The third component was really coordination of care. And so, as the name suggests, a really big emphasis of the intervention was to coordinate the care of patients between the cardiologist and the diabetes care provider, and the primary care provider, because we know that a lot of times these patients are seeing multiple providers and they can get lost in the mix. The fourth component was education. And so there was a strong emphasis

on education through online videos and modules and monthly discussions to talk about tough cases that they might be experiencing. And then importantly there was audit and feedback. So we thought it was really important that the sites understood how they were doing in terms of prescription of these therapies for their patients, and how they were doing in comparison with other sites in the intervention arm with anonymized data. And then lastly, we did include some participant facing educational tools as well to help the clinicians in discussing the trial and in discussing these medications with their patients. So those were the six components of the intervention.

Dr Van Spall
- Right, so a complex health service intervention that may have looked a little different across the sites. How did you measure adherence to the intervention or fidelity to the intervention?

Dr Pagidipati
- Yep, it's an excellent question and I will say that with the pandemic, things definitely took a difficult turn overall in terms of the way that we were delivering the intervention and also the way that we were measuring the fidelity, as you mentioned. What we did was, we tried as much as we could to keep the delivery consistent and the benefit of our intervention was it was all being delivered by the same team. So, it wasn't multiple teams delivering the intervention across sites. And so, we could keep metrics in terms of the number of meetings that we had, the number of modules that were completed by each site and by the clinicians, the number of times we gave grand rounds, lectures, things like that. So that is how we basically kept track of the fidelity of the intervention.

Dr Van Spall
- Okay, but some of the intervention surely involved an algorithm or prescriptions tailored to the therapies that you were aiming to improve uptake in, yes?

Dr Pagidipati
- Yes, I mean, and the outcome was the prescriptions themselves.

Dr Van Spall
- Right, tell us about the baseline characteristics of your patients.

Dr Pagidipati
- Absolutely, so we had 1,049 patients, ended up enrolling across the 43 sites. We had about 30% women, obviously would have loved to enroll more but compared with a lot of cardiovascular trials, it was relatively reasonable. I will say that the proportion of patients from diverse backgrounds was about 20% if you include patients who were self-identified as black or who had hispanic origin. And they all had atherosclerotic cardiovascular disease and their baseline characteristics were pretty well matched across both of the arms. The majority of the patients had coronary disease more than cerebral vascular or peripheral arterial disease. And about half of the patients in both arms were on approximately two of the target medications at baseline, but not on all three.

Dr Van Spall
- Okay, tell us about your primary outcome.

Dr Pagidipati
- Absolutely, so in short, the intervention worked. So, at the end of the intervention, which was a follow up of 6 to 12 months for both arms, there were 14.5% of patients in the usual care arm who had prescriptions for all three groups of therapies. And in comparison, there was 38% of patients in the intervention arm that had prescriptions for all three therapies. So that was an absolute difference of about 23% and a fourfold increase in the likelihood that patients would be prescribed all three therapies in the intervention.

Dr Van Spall
- Now, would you say that at baseline the intervention group had a higher proportion of patients who had a composite medication score of two, so close to the target, or were they completely balanced in the uptake of medical therapies at baseline?

Dr Pagidipati
- Yep, that's an excellent question. So, there was a slightly greater proportion of patients in the usual care arm that had a, I'm sorry, in the intervention arm that had a composite score of two. So, it was about 59% of patients in the intervention arm had a composite score of two at baseline, whereas 51% had a composite score of two at baseline in the usual care arm. And so, in order to account for that difference, we did several things. One, we adjusted for that difference in the modelling which was our pre-specified primary analysis. And the other thing we did was we looked for an interaction to see whether or not what your baseline medication score was impacted whether the intervention was effective. And in short, we found that there was no difference. So, whether the baseline composite medication score was zero, one or two, there was really no difference in the effectiveness of the intervention.

Dr Van Spall
- Okay, and was the uptake of any one group of therapies greater than the other in your primary endpoint measurement?

Dr Pagidipati
- Absolutely, and that's a great question as well. And yes, so there was a significant increase in the use of the antihyperglycemic agents with cardiovascular benefits. So the SGLT2 inhibitors and the GLP-1 receptor agonists. There was patients in the intervention arm were three times more likely to be prescribed an SGLT2 inhibitor or GLP-1 receptor agonist compared with the patients in the usual care arm. And there were significant improvements in prescription for the other classes as well, the high-intensity statins and the ACE inhibitors or the ARBs. But the magnitude of that difference and the magnitude of the effect of the intervention was greater in the SGLT2 inhibitors and GLP-1 receptor agonists.

Dr Van Spall
- Would you like to tell us about any of your secondary endpoints and the results pertaining to those?

Dr Pagidipati

- Absolutely, so some of the secondary endpoints we're looking at, the change in prescription for each of the medications in particular. And as I just explained, there was a significant improvement for SGLT2 inhibitors and GLP-1s. We also looked at the proportion of patients who had a score of at least two, and that was significantly improved in the intervention arm as well. And then we did look at any changes in atherosclerotic cardiovascular disease risk factors, and specifically blood pressure, haemoglobin, A1c, and LDL cholesterol. But because this was a pragmatic trial, we didn't mandate that these labs be checked at the end of the study. And so only less than half of patients had an LDL cholesterol or an A1c at the end of the study. But among those who did have these metrics checked, there was no significant difference in those physical assessments at the end of the study. We also did look at heart clinical outcomes and our composite outcome was all cause mortality or hospitalisation for an MI stroke, decompensated heart failure, or urgent revascularization. And we did see a numerical decrease in the number of composite events in the intervention arm versus the usual care arm. And the hazard ratio was 0.79, but this was not statistically significant. And again, this trial was not powered to show differences in clinical outcomes, but it is in line with what we would expect to see based on the large clinical trials for these medications.

Dr Van Spall
- Yeah, and we always struggle as trialists in selecting our primary outcomes and whether to go with clinical outcomes or surrogate measures. And so, I think there's a balance between some of the clinical focus that we have with the burden of enrolment, particularly during a pandemic and the need to be pragmatic and get a trial completed with a primary outcome or endpoint that has been shown to improve clinical outcomes. So even though you didn't choose a clinical outcome as your primary outcome, I think, you know, aiming to improve medication uptake is a worthwhile aim. And you've nicely demonstrated that a complicated complex health service intervention could be effective when implemented at the clinic level, albeit through a central team of clinicians that stayed stable across sites.
Chris, would you tell us what the next planned steps are to implement the findings of your implementation trial in everyday clinical settings?

Dr Granger
- Harriette, there's so much work to do, right? And, but I think what this trial reminds us is that we cannot be satisfied with the status quo. We're simply failing to consistently use treatments which will improve health. And now we're getting these randomised trials which are showing us ways that we can better implement proven, effective therapies. And there're many of them, but I think this, you know, we think this is an important one for an important condition in an important setting. And I would hope that cardiology clinics would take these findings, would review our study, would review the materials that we used. And would think, how can they use these principles to measure how they're doing and then take deliberate systematic steps to identify and overcome barriers to have the coordinated care team, including the coordination between clinicians and pharmacists and then to measure how they're doing. Because what we've shown is it is clearly possible to make a major improvement in how we're treating these patients and that will result in improved outcomes.

Dr Van Spall
- Yes, particularly if follow up is long enough and events accrue, and as you said, your trial wasn't powered to demonstrate a difference in clinical outcomes, but surely that would follow with better

uptake of medical therapies. Well, let me congratulate the two of you on executing this trial so well and also on your publication in JAMA. Thank you so much for sharing your late breaking clinical trial results with us. And we will be in the room to watch you present it at ACC. Thank you both.

Dr Pagidipati
- Thank you so much.

Dr Granger
- Thanks Harriette.