Title: View from the Thoraxcenter: TCT 23 Late-breaking Science Preview

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Prof Van Mieghem:
Dear colleagues, ladies and gentlemen, welcome to the View from the Thoraxcenter for Radcliffe Cardiology.
This time we preview the late breaking trials for the upcoming TCT 2023 meeting. As always, my name is Nicolas Van Mieghem and I'm doing this preview together with my good friend and colleague Joost Daemen. Joost, there's a lot of lot of structural data coming up.

Dr Daemen:
Absolutely. As usual, a lot of focus on structure at TCT and one of the key trials we wanted to present was the PARTNER 3 Low Risk trial.

Prof Van Mieghem:
Yes, and this is immediately a two-piece trial because there will be a presentation by Martin Leon on the clinical outcome of PARTNER 3 Low Risk at five years. And then there is back-to-back, also a presentation by Becky Hahn on the echocardiographic follow-up. This is very relevant because we are talking about low-risk patients.
This was the pivotal trial together with the EVOLUT Low Risk Randomized Control trial. The mean age of the patients is 73 years old, with an STS score below 2%. Then, the patients were randomized one-to-one to either the S3 or surgical aortic valve replacement.
Mind you, in 2019, the original publication showed really favorable results for TAVI because TAVI outscored surgery in terms of a one-year composite outcome of mortality, stroke, and rehospitalization. So, it's going to be very interesting to learn what the situation is at five years. Is there a catch-up? Is this difference between TAVI and surgery maintained? We don't know.
And then, obviously, we know from the PARTNER 2 that the previous generation of the balloon-expandable valve, the Sapien XT, may have been lagging behind surgery in terms of structural valve degeneration. But then the SV registry showed that structural valve degeneration was basically in line with what you could expect from surgery.
So, this is the first time a randomized comparison between S3 and surgery in terms of structural valve degeneration at five years. That is very interesting data coming up. At the same time, when you mention PARTNER 3, you also have to mention EVOLUT Low Risk. The EVOLUT Low Risk is the other pivotal randomized controlled study in patients at low operative risk. But this time, patients are randomized to either TAVI with an Evolut system, the self-expanding supra-annular functioning system, and in the control arm, again, surgery with a mean age of the patients at 74 years old. Again, low-risk patients. This presentation by Mike Reardon will be on clinical follow-up at four years. I don't think we will see any echo data out to four years. I think the echo follow-up will be at five years. So, we zoom in on clinical follow-up, but we already know from the recent ESC meeting that out to ten years, this supra-annular platform is performing quite favorably compared to surgery. Because out to ten years in the NOTION trial, TAVI was outperforming, at least the self-

expanding supra-annular TAVI platform was outperforming surgery in terms of structural valve degeneration. So, the question is, is there a class effect in TAVI, or is this more device-specific? Well, I think we will get the first answers to that question.

Dr Daemen:
Absolutely, interesting. JenaValve.
Prof Van Mieghem:
Yeah, JenaValve is a totally different concept, right? All the designs of these TAVI platforms are specifically focusing on calcific degenerative aortic stenosis and JenaValve is really introducing a different anchoring mechanism: The native leaflets will be used for anchoring of a new device. it's a clipping mechanism. And that's why JenaValve is also focusing on pure aortic regurgitation without calcific disease. And this is very compelling.
The ALIGN-AR trial is the first prospective study that will look at the safety and feasibility of JenaValve at one years in patients with pure AR. We're talking about 180 patients. Quite a robust patient set for patients with aortic regurgitation. And the primary endpoint is valve performance in terms of aortic regurgitation, but also hemodynamic, mean gradients.
And then also I'm interested in the neurological events and the need for new pacemakers because it seems to be those patients with pure AR, they have a higher risk for pacemakers.
And so, because it's a different animal, it's not calcific aortic stenosis. So, you will see more often dilated ventricles. There will be more tension on the conduction system, if you will, so that might translate into a higher pacemaker rate. But let's figure that one out in that presentation at TCT.

Dr Daemen:
Yeah, I think it's important data, right? I mean, this is the first robust, larger scale trial on the performance of the JenaValve. This will tell us a lot about this technology, which really is developed for patients with AR, which makes it a unique product and a device that we'll hopefully see more and more in the future.

Prof Van Mieghem:
And obviously the market of pure AR is much smaller than aortic stenosis, but at the same time, this device also lends itself for treatment of aortic stenosis. So more to come on that.

There is also the VIVA trial. The VIVA trial is yet another trial by Josep Rodes-Cabau from Quebec in randomised study comparing TAVI with surgery in patients with small anatomies.
And this is relevant because there is an indication that TAVI may outperform surgery in terms of hemodynamic valve performance.
Patients now are eligible if they have small anatomies. Small anatomy here is defined as a mean annular diameter less than 23 millimetres and a minimal diameter equal or less than 21.5 millimetres.
300 patients will be randomised one to one. And then the question that I have is what kind of surgery is recommended and is encouraged. Will we see root enlargement and will we see a high uptake by the surgeons to perform root enlargement?
Because that would be a game changer, because if a surgeon would just implant small surgical bioprosthesis, then we know that TAVI will likely outperform surgery, because the TAVI devices that are being used in VIVA are either the Sapien valve, but also the supra-annular functioning EVOLUT and ACCURATE platforms.

I think the main takeaway for me here will be the surgical arm. How effective will the surgeons be in implanting larger valves?
This is a very important discussion if you consider lifetime management and if you consider that the patient might outlive the bioprosthesis, because then obviously you are thinking in the future about a valve and valve procedure. And if you start with a patient prosthesis mismatch from the get-go, that's hard to correct with a TAVI procedure. Interesting from a concept point of view.

Dr Daemen:
Definitely interesting and I also looking forward to seeing the screening log, to see a little bit to get a little bit more of a flavour on percentage of patients that were not enrolled simply because of an upfront preference for maybe a percutaneous strategy because of the small anatomy.

Prof Van Mieghem:
And you expect, obviously, patients at lower operative risk, otherwise why would you still randomise? Because for high or inoperable patients, there is no point in considering surgery.

So, let's switch now to the coronary space: A lot to do about drug coated balloons. This is basically the theme of the last couple of interventional cardiology meetings. So also, TCT 2023.

Dr Daemen:
Absolutely, so again, a lot of hype on drug coated balloons. And I think at TCT there are some interesting trials to highlight. Also acknowledged to be as one of the late breakers and perhaps the most important one is the AGENT IDE trial.
AGENT IDE is the pivotal trial of Boston Scientific for their AGENT Paclitaxel-Coated Balloon. As you know, DCBs are not available yet in the US and this trial could be the first really dedicated IDE trial that could change that availability.
This trial is a randomised controlled superiority trial. Randomising approximately 500 patients to either the agent DCB or standard POBA for the treatment of instant restenosis and lesions between 2 to 5 and 4 millimetres of stents that were either BMS or a drug eluting stent. No selections for just BMS or DES restenosis. Any patient with instant restenosis can be enrolled.
And with that, I think the trial is very interesting because with this and the primary endpoint of target lesion failure at one year, you really dilute the exact added benefit of the paclitaxel on the balloon as compared to standard POBA. The trial is very ambitiously powered with an assumed event rate of almost 11% in DCB arm versus 21% in a POBA arm. So, with that the investigators expect a 50% reduction in target lesion failure. I think it's a little bit ambitious, but that said, I think the trial is conceptually one of the most interesting trials I've seen to date.
Simply because you really dilute the effect of the drug on top of the balloon. This is not a comparison of a DCB versus a stent, which is conceptually completely different, but in this case, just the added benefit of the drug coating will be tested.

Prof Van Mieghem:
I think there's a lot at stake here. If this is a negative study, then we need to really question the on the programme.

Dr Daemen:

There are at least three or four deep dive sessions on this topic, so that typically suggests that there will be some data to digest afterwards.

Prof Van Mieghem:
There will be multiple perspectives, for sure.

Dr Daemen:
More on DCBs is a DCB-ACS trial, which is a prospective, multicenter randomised control trial from Harbin in China.
So this is a trial comparing DCBs versus Zotarolimus eluting stents in patients presenting with ACS. So either STEMI or non-STEMI patients need to have a proper restoration of flow after standard POBA in a vessel with a reference diameter of 2 to 5 to 4 millimetres and a lesion length shorter than 28, which fits with the available length of the DCB, primary endpoint is interesting: FFR at nine months.
With that, the trial conceptually follows the PAPA trial. I don't know if you recall that small trial from Amsterdam almost ten years ago, in which our Dutch colleagues tried to assess the feasibility of a paclitaxel coated balloon strategy in patients presenting with the ACS. They proved the feasibility, but also demonstrated a bailout stenting rate of 40%.
I'm curious to see what this trial will show us. I don't know what to think about it because you would expect that with 40% bailout and a stent in which the acute gain is much higher than with the balloon, that would affect the FFR at nine months.
That said, I could not find that many details on the trial. Let's see what the Chinese investigators will tell us on this trial at TCT.

Prof Van Mieghem:
So, as a principle, I'm a little bit worried because we're talking about an all-comers study in the context of ACS, but in my mind it's still okay. But ballooning, there is always a risk of recoil, and recoil is not being solved with a drug coated balloon. I think, from a conceptual point of view, these trials, I'm wondering whether it's viable.

Dr Daemen:
I agree. I'm very reluctant to believe that this will become a feasible, realistic strategy for patients with ACS and properly sized arteries. I'm not talking about a small 2 millimetre obtuse marginal branch, but there are two thing: One, how this drug will dissolve in a ruptured plaque, to me, is a thing I find a little bit problematic to envisage. And the other item is that, again, as you say, this is a big vessel, the plug has already ruptured, so the recall concept might be different as compared to a fibro-calcific plug in a big artery, which is stable.
So, from that perspective, I do believe that some patients may have sort of a benefit of ballooning alone, but with a lot of bailout rates, I don't know. We'll see it's a lot to speculate, but let's wait for the results.

Something completely different is T-PASS, which is a large, randomised control trial from Korea studying an abbreviated DAPT regimen in patients presenting with ACS. So again, STEMI and non-STEMI patients, 2850 patients, randomised one to one to either an abbreviated DAPT strategy of DAPT and then the interruption of aspirin at the time of discharge, after which ticagrelor monotherapy will be pursued, versus a standard DAPT regimen of aspirin ticagrelor for one year.

One year endpoint, net clinical endpoint being any death, MI, stent, thrombosis, stroke or major bleeding. I expect honestly non-inferiority.
This follows a little bit the results of the GLOBAL LEADERS trial in which Patrick Serruys and colleagues presented a sub-analysis also in ACS patients in which they demonstrated no difference in the efficacy endpoints in terms of thromboembolic complications. But what they did show was a significantly lower risk of BARC 3 or 5 bleeding at two years in the patients in which aspirin was stopped early.
So that could be well. I think it's realistic that we'll see the same least trend in T-PASS. That said, this again is an Asian trial. Korean patients, which we know, and you've heard that from us already, a lot of times, have a little bit of different ischemic bleeding profile as compared to Western populations.

Prof Van Mieghem:
Well, it fits with this recent trend to trimming down the antithrombotic regime in the context of chronic, but also acute coronary syndromes. I'm a believer in abbreviating the duration of DAPT and I like the concept of continuing with aspirin out to discharge and then monotherapy from that moment on.
But there are some signals of an increase in definite or probable stent thrombosis in single arm, in single antiplatelet therapy, early single antiplatelet therapy. So, I'm going to be on the lookout for that. Is there a signal somewhere where we see an increase in early MIs or in definite or probable stent thrombosis?

Dr Daemen:
Yes. All right. So more on bleeding, but then switching gears a little bit.

Prof Van Mieghem:
We go back to the TAVI scene. There is an interesting, randomised study in patients who undergo TAVI but have atrial fibrillation and an indication for oral anticoagulant therapy.
In WATCH-TAVR 349 patients will be randomised to either TAVI with a concomitant LAA occlusion with the WATCHMAN device and the control arm is TAVI with regular medical treatment.
Samir Kapadia is going to present a study, I think from a trial design or concept there are some questions because; are these patients going to be blinded, yes, or no? And if so, will all these procedures be under general anaesthesia? So, then you can basically blind the patients for the treatment arm, but if so, what kind of antithrombotic regime is associated with the respective therapy? So are patients in the WATCHMAN arm, are they taking off oral anticoagulants? Are they continuing aspirin or clopidogrel? Probably clopidogrel. Is there a follow up echo to confirm whether you have a successful LAA closure? So, multiple questions there in terms of trial design.
At the same time, the primary endpoint is quite reasonable and as expected, it's a composite of death, stroke and major or life-threatening bleedings at one year.
So, you hope that implanting a WATCHMAN device will reduce the bleeding events. I think this is not a definite win.

Dr Daemen:
I have no high expectations, honestly. Let's see.

Prof Van Mieghem:

Well, but, you know, the other issue here is that patients are eligible if they can be treated with an LAA closure device according to the labelling of the device.
But labelling in the US is different from labelling in Europe and different from labelling in the Netherlands. As a matter of fact, there is no reimbursement in the Netherlands for an LAA closure with a percutaneous device. So, it's going to be interesting to see what kind of patients were enrolled in this study and again, what was the screening rate and were patients screened out because of anatomical variation and so on. So, there's more to that study than just the comparison of the two treatments.

Dr Daemen:
TRILUMINATE.

Prof Van Mieghem:
Yeah, so we now move to the tricuspid space. There are two interesting trials that we want to highlight on the treatment of patients with tricuspid regurgitation:
The first is the TRILUMINATE Pivotal trial, already discussed, presented and published in the spring of this year. This was a randomised controlled study that was published in the New England. 350 patients with severe TR and then randomised to tricuspid tear with a TriClip or control. And the results were somewhat underwhelming because people were expecting a homerun in favour of TEER.
But that didn't turn out to be the case, although there was a more improvement in quality of life and a significant improvement of twelve points in favour of the TEER arm, but there was no effect on six-minute walk test. And also, there were more numerically more rehospitalizations in the TEER arm, so that was definitely not a homerun.
There was definitely a need for more data to support treatment of tricuspid regurgitation. And I think the next randomised trial is TRISCEND II that basically fills in a gap. This is a different trial. This is a trial that will enrol many more patients, but it has several sub-studies, if you will, embedded into that study.
So there is a randomised control trial component, including 1070 patients who will be randomised one to one to either control or transcatheter tricuspid valve replacement with the EVOQUE system. And high expectations there, because as opposed to treatment with TEER with a tricuspid valve implant, the ambition is to really abolish the TR. You want to get rid of the TR so that might affect clinical outcome and might have a more comprehensive impact on clinical and functional status of patients.
So that is the randomised control trial arm, but I think that they are not going to present the randomised or the full randomised control data because if you look at clinicaltrials.gov, the trial will last until next year in the summertime.
So I think it's a bit early to get the full trial results. But there is a single arm study of patients who were turned down for the randomised trial: Those were in a nested registry. And there is another registry that continues access. At the end of the study, the patients in the US can still benefit from treatment of TTVR, but then in a continued access arm.
So what Susheel Kodali is going to present? I don't know. I tried to reach out to him, but he must have been too busy. So I don't know yet.
But definitely something to look for because we do need scientific data, randomised control data to provide support for treatments of severe tricuspid regurgitation.

There are some other concepts that also are being presented in terms of randomised controlled studies. One of them is the PICSO-AMI-I trial.

Dr Daemen:
So PICSO-AMI-I is a small randomised controlled trial under the leadership of our friend Adrian Banning. So, as you know, PICSO for those of you who are not familiar with the concept is pressure controlled coronary sinus occlusion, which is a technology developed by Miracor, which was designed to decrease infarct size following acute myocardial infarction.
The feasibility of the concept was recently tested in some relatively small studies, but this is an important one because this is the first randomised control trial enrolling 144 STEMI patients with large anterior myocardial infarction.
The patients really need to have proximal or mid-LAD occlusions, after which they will be randomised to either standard of care or standard of care plus the PICSO treatment algorithm. Small registry arm will also be added to the trial of around 30, if I'm correct, non-STEMI cases, just to test the feasibility of the concept. Primary endpoint: MRI based infarct size, as you would expect, at five days.
And with that, I think this is a trial to look out for there's. By now, I think a large pipeline of PICSO-AMI, I, II, III, I think even IV has been announced. On the website of Miracore, you find 33% infarct size reduction based on the data they have. But if you look into the details, this is based on 1422 patients propensity matched.
So, with that, I think this trial is going to be very important for the company, but even more for us as physicians to see if this technology is going to really make a really going to be a game changer in terms of treating large anterior MIs.

Prof Van Mieghem:
The concept is about trying to survive. Right. And I think this trial, with 144 patients with an MRI infarct size endpoint. This is a lead out to other more robust trials that should be coming in the future. But let's first see what the data will be from this study.

Obviously, an interventional cardiology meeting cannot end without a study on renal denervation. So Joost, what do we have here?

Dr Daemen:
Yes, that's correct. So also, here this year at TCT, some interesting RDN data to be expected.
One is the or maybe the most important one is the six-month pool data of the RADIANCE trial programme that will be presented by the study PI Michel Azizi.
So please recall, the RADIANCE programme encompasses three randomised sham-controlled trials. Now, 506 patients that were randomised to either ultrasound based RDN or sham for the treatment of mild to moderate hypertension in RADIANCE Solo and RADIANCE II, or patients with therapy resistant hypertension on a standardised triple pill combination in RADIANCE Trio.
Recall, all these three trials met their primary endpoint at two years in terms of efficacy, showing a significantly larger blood pressure reduction following ultrasound RDNs compared to sham.
But as you know, these patients were followed for six and twelve months in which a stepwise antihypertensive drug regimen was applied in those who were not on target, physicians at this stage, and that's important to realise, were blinded to the treatment allocation. And with all the

discussions about the durability of the treatment, the safety of the treatment and the longer term, I do believe these data are important because they will tell us a little bit more about the durability of the treatment, the difference of the ultrasound based RDN effect on top of drugs and also in terms of the safety, at least up to six months in this largest ultrasound RDN trial programme thus far.

Prof Van Mieghem:
But will we see any new data, like extended follow up?

Dr Daemen:
Yes, six-month data is new, at least for RADIANCE II.

Prof Van Mieghem:
Okay. But it's not that we will have like three, four, five-year outcome data for the entire cohort.

Dr Daemen:
Not for this entire cohort, because RADIANCE II obviously is now at one year and that is something that is ongoing.

Prof Van Mieghem:
Okay. So, it's more an integrated perspective on the thing on thank you very much, Joost.
So, with that, we will see you there and we'll come with a wrap up after TCT. Stay well.