Title: View from the Thoraxcenter: ESC Congress 24 Hot Line Preview
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NVM: Dear colleagues, ladies and gentlemen, welcome to the View from the Thoraxcenter for Radcliffe Cardiology. This is the preview of the 2024 ESC meeting. My name is Nicolas Van Mieghem, and as always, it is my great pleasure to introduce to you my good friend and colleague, Joost Daemen. Together, we will start reviewing the ESC meeting. There are quite some interesting trials coming up, Joost.

JD: Absolutely, absolutely. There are some trials we want to discuss, perhaps not as many blockbusters as we saw last year, at least in the interventional space, but there are some trials that caught our attention, and I think are worthwhile discussing.

NVM: Yeah, multiple studies were long overdue, if you will. One of them is the **RESHAPE-HF2** randomised controlled study. This was a trial that originally started in 2015, a multicenter initiative in Europe, and Stefan Anker is now going to present the results of this study for the first time.

505 patients will be, or should be, included in the trial, and patients will be randomised to MitraClip on top of standard of care versus standard of care. Obviously, this is a trial focusing on patients with heart failure and secondary MR.

You might be familiar with the COAPT trial and the MITRA-FR trial. Those two trials generated more or less different results, if you will, and the interpretation of both trials was different because COAPT was considered to be a positive study in favour of TEER for secondary MR and heart failure, whereas MITRA-FR was neutral and some even say a negative trial.

Now, the question is, what is RESHAPE-HF2 going to be? Is it going to be positive or negative? At least the primary endpoint is similar to COAPT, so it's a composite of recurrent heart failure hospitalisations and cardiovascular mortality at 24 months. But they also look at total heart failure hospitalisations at two years and a change in KCCQ in quality of life at one year.

For me, this is going to be an important study. It's not going to be a game changer, but it might be good to have another positive trial for the space of TAVR and secondary MR.

JD: Yeah, I totally agree. I think, on the one hand, it's a trial that has the potential to be the second positive trial supporting the use of TEER in the mitral space. Conversely, it's a German trial, it's somewhat smaller. It's perhaps a trial with not that much scrutiny, as, for instance, was in place in COAPT. So I'm not sure what the trial will show, but it will definitely generate discussion.

NVM: Well, it's not just Germany; it's really throughout Europe, multiple countries in Europe. But I think one of the limitations is the time window of study enrolment. So, the study started in 2015, and we're now in 2024. So, I think the results can go either way.

JD: Yeah, we'll see.

MATTERHORN. That's another trial that started already in 2015. This trial is comparing surgery with MitraClip in patients with symptomatic secondary mitral regurgitation at high surgical risk. It is, for me, unclear whether this is a single-centre randomised controlled study or a multicentre study. Fair to say that the core of the study is in Köln, Germany, and the aim was to enrol 210 patients. The primary endpoint is a composite of death, rehospitalisation for heart failure, reintervention and assist device implantation, and stroke at 12 months. This is a little bit of a different study. It might be more reflective of the EVEREST II randomised controlled study back in the day. So, that was a study in 2009 where they compared MitraClip versus surgery predominantly in patients with primary MR. This study is exclusively focusing on secondary MR, so it's a little bit different. But I think the fact that we are now talking about patients at high operative risk might be an interesting feature of this trial.

JD: High operative risk, but operable. But operable.

NVM: But still, if you are at high operative risk, the price of the surgery can be significant and might be a driver of the endpoint. This is an interesting study.

JD: Yeah, I agree. And a study that I think has somewhat more likelihood to become positive. But let's see. Yeah, Tri.fr Yeah.

NVM: So, also another trial in the tricuspid space. We have seen a lot of attention in tricuspid regurgitation in the last couple of years. We also already have one randomised controlled study, the TRILUMINATE, which was presented in 2023. Mixed results, mixed reactions to that trial. So, a follow-up study or a new study on patients with secondary tricuspid regurgitation was definitely worthwhile. And this is where this French study comes in. Up to 300 patients with severe TR, confirmed by an echo core lab and also confirmed by a screening committee, will be randomised one to one to either TriClip on top of standard care or standard care. The primary endpoint is a composite endpoint that they deem to be the Milton Packer clinical composite score, which is basically an integration of symptoms, New York Heart Class, quality of life, but also major cardiovascular events. There are three categories: either the patient improved, worsened, or everything remained unchanged. So, an interesting study design, and I'm looking forward to a positive trial result here.

JD: I hope so, I hope so. Yeah. But.

NVM: Okay, enough of the structural for now. Let's move to the coronary space.

JD: Yeah, the coronary space, but still a little bit of surgery, is the **SWEDEGRAFT** trial. SWEDEGRAFT is a multicentre randomised controlled trial that will be presented by Stefan James. It was a trial actually designed to investigate if vein grafts harvested and implemented with the no-touch technique are superior to conventionally harvested vein grafts with respect to medium-term graft patency.

So, as you know, harvesting the saphenous vein graft with a particle of surrounding tissue and without graft distension is called the so-called no-touch technique. It has been shown in the past that this technique may have advantages in terms of graft patency, in the sense that it significantly improves patency as compared to conventional techniques in the short to medium term. This trial will randomise 900 patients, with the primary endpoint being graft patency as determined on a CTCA at two years, or obviously signs or evidence of revascularisation within the two-year primary endpoint timeframe in patients randomised either to the conventional or to the no-touch technique. I think it's interesting there's still a considerable number of patients that are not eligible for bilateral grafting. The saphenous vein graft is perhaps still one of the most widely used conduits. It's promising.

PREVENT IV was a multicentre trial that already showed that vein grafts tend to become either significantly stenosed or even occlude in 27% of the cases within a timeframe of one to two years. So, that's substantial and I think warrants further optimisation of the technique. By avoiding graft distension and the complete adventitial stripping of the vein graft, one could argue that this technique has the potential to increase graft patency.

NVM: I'm wondering whether this still is a timely trial, to be honest. Obviously, you will see bypasses to the circumflex and the right coronary, but not so many to the LAD. Obviously, there we're talking about a LIMA to the LAD, and that definitely is a superior grafting technique. We have seen multiple trials in the CABG space, if you will, with off-pump, on-pump, minimally invasive or not, and the introduction of radial grafts and so on, which didn't make a lot of difference. In my opinion, it's all about the LIMA to the LAD and all the rest. In principle, if it's technically feasible, it should be PCI. But okay, that might be a controversial statement, but I don't have high expectations for this study.

JD: I agree with you, but a 27% graft occlusion rate is high.

NVM: That's what we know.

JD: That's what you know, but it also means there's a lot to gain. So if this works, I think with 1000 patients you have the potential to show something.

NVM: So you expect spectacular benefits of this no-touch technique?

JD: It could be. There is a tendency to believe that the trial will end up positive, showing a small but statistically significant benefit in terms of the no-touch technique. What that eventually will do to the outcome of the patient is obviously the question. And that’s the I predict no effect. So, we'll see.

NVM: Let's see.

JD: Perhaps more interesting, at least from my perspective, is **OCCUPI**. OCCUPI is a large, again Korean, multicentre randomised controlled trial to assess the superiority of OCT versus angio-guided PCI in patients with complex lesions. As you know, this is perhaps familiar. It's a study that actually focuses on CHIP patients. So, patients with complex lesions being either acute MI lesions, CTOs, long lesions, bifurcations, small vessels, patients presenting with either in-stent restenosis or thrombosis, even vein grafts can be enrolled.

So, a very broad spectrum of patients, but all patients with lesions with a higher risk of repeat events. A trial that is substantially powered with 1600 patients randomised one to one to either OCT or angio-guided PCI. But interestingly, in the OCT arm there is a sub-randomisation to either a completely OCT-guided revascularisation, meaning both pre and post-PCI OCT, as well as a second stratum in which the OCT is only used post-PCI in order to assess stent position, stent expansion, edge disease and potential room for optimisation. So, that I think is the second question that the trial will address.

The primary endpoint is MACE at one year. As mentioned, the trial is somewhat familiar in the sense that it has a design which very much reflects IVUS CHIP and IMPROVE, which are similar trials that are on the way to present their findings with IVUS also in a similar setting. For sure, this data, in my opinion, will generate a lot of debate, specifically in light of the recent somewhat neutral OCTOBER trial and the new guidelines for stable coronary syndromes that will be presented also at this ESC.

NVM: But how do you define complex lesions? Is it complex from a procedural point of view, or is it complex, as you were alluding to, because of the higher risk for reinterventions or vessel failure? So that, I mean, is an important driver because a STEMI or a venous bypass can be complex from the point of view of the need for reinterventions down the stretch, but from a procedural point of view, could be very easy. So I will be interested to see how many of those relatively easy lesions are being treated in the trial, because the more you move to the real complex lesions in terms of a procedural point of view, then you also will see more and more failures to get your OCT catheter down and to do a proper assessment. We have been involved in multiple trials even today, where we are doing OCT systematically in patients with, for instance, hypercalcific coronary artery disease. And how often do we end up not being able to do a series of OCTs in that same patient? It's not rare.

JD: No, that happens. But I think at the end, this is a bit of a double-edged sword. You know, at one time, you don't want a trial with only type A lesions and event rates of 3%, because then you need 10,000 patients to power the concept of imaging-guided PCI. So at some point, you want to select patients, which is obviously the combination of patient and lesion characteristics that result in higher event rates and a potentially higher likelihood of showing a, let's say, 10, 20, 30% benefit that you may expect with imaging-guided PCI.

NVM: But the point that I want to make is that the more complex the lesion is, for instance, the more calcium, the more tortuosity, the lower the likelihood that you will be successful in doing multiple OCT evaluations of that vessel. It becomes very difficult to get your OCT catheter down if there is a lot of tortuosity and a lot of calcium. And it might also be very difficult to have multiple OCTs, because obviously, in an ideal world, you would like to do an OCT upfront and at least at the end of the procedure.

JD: We'll see if that is something that pops up in this trial. I don't think in general, in lesions like this, that will be a big issue, but we'll see. So, what kind of lesions are they enrolling?

NVM: If they would only enrol hypercalcific lesions, then I guarantee you.

JD: I agree, but that's not the scope of the trial. Right. Let's see, let's see.

NVM: Interesting.

JD: Very good.

JD: **REC-CAGEFREE I** is the second trial that will be presented. This is, again, an Asian trial, Chinese in this instance. It's a large randomised controlled non-inferiority trial of drug-coated balloons versus drug-eluting stents for de novo coronary artery lesions. So, I think that's why the trial caught my attention. It's a trial that randomised 2270 patients in 40 Chinese sites to either a DCB or a drug-eluting stent strategy. Also, quite a broad eligibility spectrum of patients, including those presenting with stable as well as acute coronary syndromes, even including STEMI. So that's quite interesting. The primary endpoint is the device-oriented composite endpoint at two years, if I'm correct. This is a large randomised controlled trial in patients with de novo lesions, and that makes it, to me, interesting because it's one of the first really large trials to assess the concept of DCB in de novo disease, and not just in side branches of bifurcations or in-stent restenosis and so on. So that, I think, is interesting.

Two words of caution. It's a Chinese trial. We know these trials typically show relatively low event rates, and also it's a trial with Chinese technology. I looked at what kind of DCB was used, and it appeared to be a paclitaxel-coated balloon by Shenqi Medical called the Swide Paclitaxel-coated balloon, which, as far as I know, is not available in Europe. But I think conceptually, it's a trial that will show some interesting findings.

NVM: There's a lot of interest in drug-coated balloons these days and people are considering drug-coated balloons for all comers and so on. I think it's very important to note here that there is an important case-based selection. Non-complex coronary lesions.

JD: It's a relatively broad patient population. What is non-complex? I mean, stable, unstable, bifurcations. We'll see.

NVM: But also, you know, if you have a proximal LAD and a simple LAD lesion, it's quite a big step for me to move away from drug-eluting stents in 2024.

JD: But that's why I think it's interesting. I totally agree, and I also have conceptually a problem with that. But, yeah, we'll see. I think that's why the trial is interesting to me. You need to prove the gut feeling that this doesn't feel right and that there will not just be small diagonals included in this trial. So, we'll see.

NVM: SENIOR-RITA.

JD: **SENIOR-RITA**. So, we go to the elderly. This is a trial, SENIOR-RITA, a multicentre randomised controlled trial sponsored by the NHS. So, as such, conducted in the UK and Scotland, designed to compare an invasive versus a conservative strategy in elderly patients, defined as those 75 years and older presenting with non-STEMI. It's a trial that randomised over 1500 patients with a clinical primary endpoint as well as quality of life to see what would make sense in an early invasive strategy in elderly patients presenting with non-STEMI. So, quite a provocative concept, but not a new concept. This is a concept that was tested already in 2016 in the After Eighty trial in The Lancet that showed a 50% lower event rate if you go for early invasive. It was confirmed in the SENIOR and STEMI trial, also sponsored by the NHS and published in The Lancet in 2020, again showing the same thing. So, a significant benefit of early revascularisation. But those studies were open label,

propensity matched, so not really proper randomised controlled trials, and that makes this trial different. But honestly, I do not expect any different findings.

NVM: Well, you know, I think patients above 75 years old are a population that I no longer consider to be very old, right?

JD: Correct.

NVM: I think above 90 would be a different story. Maybe above 85, but these days, 75 years old in 2024?

JD: There's huge, as you say, there is huge heterogeneity in the type of patients and age is usually no longer the determining factor. I totally agree. All right. Alrighty.

JD: Finally, more on elderly patients is **EARTH-STEMI**. So, EARTH-STEMI is a meta-analysis. It's not a prospective, randomised controlled trial as we typically expect in the hot lines. This meta-analysis, led by Gianluca Campo from Ferrara, pooled data from various trials comparing complete versus staged or incomplete revascularisation in patients presenting with STEMI. These trials include FIRE, COMPARE-ACUTE, DANAMI-PRIMULTI, CVLPRIT, and COMPLETE, pooling all the patient-level data. It aims to address whether the benefit of complete revascularisation also applies to elderly patients, those aged 75 and older. From my perspective, I don't expect to see any heterogeneity in the treatment effect with age in these previous trials. I doubt this meta-analysis will suggest that complete revascularisation doesn't make sense for those 75 or older, but we'll see.

NVM: This is somewhat different from the previous trial, obviously. I think nobody doubts that you need to treat a culprit lesion. In the previous study, they were also discussing a non-STEMI patient, where there is also a culprit lesion. Avoiding the culprit lesion is a different story. You always need to treat the culprit lesion, regardless of the patient's age. Whether complete revascularisation in elderly patients makes the same difference as in younger patients is an interesting question, making this meta-analysis worthwhile.

JD: It's intriguing material. I have two concerns. Firstly, the study designs are not properly comparable. One study uses FFR, another doesn't. One does planned staged revascularisation, another has patients go home and return later. The control arm is quite heterogeneous. Secondly, if the benefit of the complete revascularisation approach in younger patients is to be supported, it should translate into a long-term outcome benefit. Most of these trials don't have a five-year follow-up. We'll see what's included and what conclusions can be drawn.

NVM: Okay, we return to the structural space with three more TAVI studies. The first is the **POPular PAUSE TAVI** trial from Jurrien ten Berg and his group in Nieuwegein. This multicentre study included 858 patients with atrial fibrillation on a NOAC or OAC undergoing TAVI. The question is whether these patients need to interrupt their anticoagulant therapy or if they can continue without interruption. This is very relevant, especially as we know from the EP space that interruption is unnecessary for safe procedures like pulmonary vein isolation. The study includes both transfemoral and transaxillary/subclavian access and randomises patients in Belgium, the Netherlands, Denmark, Italy, and Ireland. The primary endpoint is a composite of cardiovascular death, stroke, myocardial infarction, major

vascular complications, and significant bleeding according to the VARC-3 criteria. It's a timely topic and might be a practice-changing trial, if not, it's still highly relevant.

JD: Absolutely. This design, under the leadership of Jurrien ten Berg, addresses many relevant questions with practical and pragmatic approaches. Kudos to them.

NVM: Next, we have **NOTION-3**, the third in the NOTION family of TAVI trials. NOTION-1 and 2 focused on low-risk or all-comer patients. NOTION-3 follows the same approach but includes patients with coronary artery disease. It examines whether single or multivessel coronary artery disease should be treated when addressing aortic stenosis. This trial randomised 454 patients with significant coronary artery disease to either TAVI plus PCI or TAVI alone. Previous studies, like the ACTIVATION trial in the UK, included only 235 patients with a mean age of 83 and found no benefit from PCI, resulting in more bleeding. NOTION-3 may include younger patients, but it's not certain that revascularisation will be beneficial. The primary endpoint is all-cause mortality, myocardial infarction, and urgent PCI at one year. As previously mentioned, a one-year follow-up may not be sufficient; a five-year follow-up might provide more significant insights. Nonetheless, it's an interesting study to look forward to.

JD: Positive outcome?

NVM: I think it will be a negative study.

JD: I agree. The one-year follow-up is a key issue. These are not ACS lesions but stable coronary artery disease. Patients will feel better after their TAVI.

NVM: Exactly.

JD: By definition, they will feel better and say, "Oh, wow, now I can climb stairs again." Who cares about this 50% lesion that will be randomised in the concept of this trial with an FFR of 0.80?

NVM: But some may argue, "Okay, now the patient has the valve replaced or treated, becomes more active, and then becomes symptomatic." So, we'll see. It's an interesting and important study.

JD: The only problem here is that it's open-label, right? If you want to properly test the concept, and also consider the small sample size. Small sample size is a consistent feature in the NOTION trials.

NVM: Finally, we have the **RHEIA** trial. This is a randomised, controlled study focusing on women with symptomatic severe aortic stenosis. This all-comer study, as far as women are concerned, will randomise patients one-to-one to TAVI or surgery to treat their symptomatic severe aortic stenosis. The TAVI platform to be used is the Sapien valve, compared to any commercially available surgical bioprosthesis. The composite primary endpoint is all-cause death, stroke, and rehospitalisation, a familiar endpoint from the LOW RISK trials.

Honestly, I'm a little critical of this type of trial because women are not underrepresented in the TAVI space. All the randomised controlled studies have roughly a 50% split between

men and women. In fact, the latest trial, the SMART trial, had 87% women and only 13% men. While I understand the importance of generating sufficient research for both men and women, I'm not sure if this is really needed in this area. However, I expect a positive trial result because previous studies suggest that TAVI may be even more effective in women than in men. So, nothing new, I think.

JD: No comments with respect to this trial.

NVM: With that, we come to the end of our preview of ESC 2024. It's something to look forward to, and we will be wrapping up these trials at the end of the month. Thank you for staying with us.

JD: Thank you. Bye-bye.

NVM: Goodbye.