**Title: TCT 24: Transcatheter Aortic Valve Replacement in Patients with Heart Failure and Moderate Aortic Stenosis**

**Participants: Dr Nicolas M Van Mieghem**

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**What is the reasoning behind the trial?**

So the rationale behind the TAVR UNLOAD randomized study was that we have been seeing that in patients with moderate aortic stenosis, the event rate is quite high. And then if we then further look into it, it turns out that the event rate is even higher in the patients with depressed LV function. So that was the design of the TAVR UNLOAD. It is a heart failure study in patients with symptomatic HFrEF, so heart failure with reduced ejection fraction, moderate aortic stenosis on optimal guideline directed medical therapy, randomizing those patients to either TAVR or clinical surveillance with only treatment of the aortic stenosis when it progressed from moderate to severe.

**Could you tell us about the patient population and study design for TAVR UNLOAD?**

So the study design, the patients were symptomatic heart failure patients with moderate aortic stenosis and depressed LV function. They were on optimal guideline directed therapy. Mean age of the patients was 77 years old. One in five were women. The STS score was 4.4, meaning an intermediate operative risk, if you will. And these patients were quite symptomatic, so they had advanced heart failure. More than 50% of the patients were in New York Heart Class 3 or Ambulatory Class 4. Half of the patients had a heart failure hospitalization prior to study entry and the LVEDD. So, the LV dimensions were quite large, so dilated ventricles.

**What were the key findings?**

The key findings? Well, in a nutshell, it was a negative study. We missed our primary endpoint, which was a hierarchical endpoint and an assessment at longest follow up with a median follow up of 23 months. That came as a surprise. But if we would look at the primary endpoint at one year, we would have seen a significant difference in favor of pre-emptive TAVR. Why did we change or modify the sample size of the study? Because of slow enrollments, because of the COVID that hit us. And we had the belief that if we would prolong the time of the assessment of the primary endpoint, that we would end up being more significant. It turned the opposite way. To add to that, what we did see was a faster improvement in quality of life in the pre-emptive TAVR arm.

**How should these findings impact clinical practice?**

So, it is a neutral study, but there are quite some interesting findings here because if we just look at the clinical surveillance arm, 40% of the patients in the control arm, they progressed from moderate to severe aortic stenosis, and they required a TAVR procedure. 20% of those patients already had their TAVR done within the first year. Obviously, that affects the outcome.

Basically, one of the major findings of the study is that if you do a TAVR in heart failure patients with moderate aortic stenosis, you will immediately improve their quality of life. And on the other hand, if you do not treat the moderate aortic stenosis, you will see disease progression to severe aortic stenosis very rapidly. So, maybe we need to enhance the clinical surveillance of those patients, so bring them back earlier, for instance, after six months rather than after 12 months for additional echo follow up.

**What further research is needed?**

So this is definitely not the end of trials on moderate aortic stenosis. There are two large trials ongoing, the PROGRESS trial and the TAVR EXPAND II trial, focusing on patients with moderate aortic stenosis, but talking about cardiac damage, so they no longer focus on LV ejection fraction. So regardless of ejection fraction, patients will become eligible for the study if there is a signal of cardiac damage. And cardiac damage can be LVH, it can be atrial fibrillation, it can be mitral regurgitation, it can be pulmonary hypertension, and so on.

So, you will see a totally different phenotype of patients. And then the question is, obviously, okay, how will those patients behave after TAVR or TAVI for moderate aortic stenosis? And also, what would be the rate of disease progression in the control arm?