**Title: AHA 22: EAST-AFNET4: Rhythm Control Therapy in Atrial Fibrillation**

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**Dr Shino Kany**

" - My name's Shino Kany. I'm a research fellow at the Broad Institute of MIT and Harvard and a cardiovascular fellow at the University of Hamburg. And today we'll be talking about the genetic substudy of the EAST-AFNET 4 trials.

**Substudy Rationale**

So the original EAST-AFNET 4 trial showed that early rhythm control in atrial fibrillation patients who have atrial fibrillation for less than one year is associated with a reduced composite outcome of cardiovascular death, stroke, hospitalisation for acute coronary syndrome or heart failure. And we know that atrial fibrillation is a highly heritable disease and we have been using polygenic risk scores to estimate this genetic burden that every one of us has for certain diseases. And we can do the same for atrial fibrillation and stroke. So we wondered what will happen if we look for the genetic risk in those patients and see the association with the outcomes of the trial.

**Study Design and Patient Population**

So the EAST-AFNET 4 trial enrolled patients who had atrial fibrillation for less than one year to be able to treat basically in the beginning of the disease. Most patients had atrial fibrillation for less than three months, and the design was a one-to-one randomization to early rhythm control, which included antiarrhythmic drugs, catheter ablation, or user care; which was mostly rate control based in terms of severe system, despite optimal rate control, rhythm control was allowed as well, but very, very rarely utilised in that arm of the study. And around 1600 patients gave consent to the biomarker substudy, where we got basically also genetic material that we could then analyse for common variants and estimate polygenic risk score in those patients. So in total, for the genetic sub-study we had 1,567 patients that were included and roughly half and half in each treatment arm, so it was quite balanced still.

**Key Findings**

So the key findings were we looked at two polygenic risk scores. So one for atrial fibrillation and one for stroke. And for the polygenic risk score for atrial fibrillation we found quite moderate association of that score with recurrent AF in the trial as a time to event analysis. That was to be expected. And for the stroke of polygenic risk score, quite unexpectedly, we found no association with stroke but association with heart failure. And to further validate this finding, which was unusual and unexpected, we also looked at the polygenic risk score for stroke in the UK Biobank. And there we found association with atrial fibrillation, stroke, and heart failure. And those basically validated what we saw and also explained the reasons why we didn't saw the association with stroke in our trial. The EAST-AFNET 4 trial patient cohort is very, very well treated. Anticoagulation is above 90% in each arm. And in the UK Biobank it isn't. So in a population that is not anticoagulated, we see a association with stroke with our polygenic risk score.

**Take-home Messages for Clinicians**

My take home messages are that early rhythm control is effective and safe across the genetic risk spectrum and that polygenic risk scores are only as good as the question that we ask and the tools that we create from them. So basically, that polygenic risk scores that are made in populations that form with no anticoagulation are not as powerful in patients who are anticoagulated. So I think the key messages here that we still have to learn a lot about polygenic risk scores, but atrial fibrillation should probably be treated early in disease history.

**Further Study Needed and Knowledge Gaps**

So I think one of the major, major problems in cardiovascular science, especially in the genetic field, but also in the clinical field, is the lack of diversity. The polygenic risk scores were made, constructed in European populations and used in a poor European population of the trial. And the reason for that is because we just don't include enough people from minorities, from other ethnic backgrounds which is a major gap in our current understanding of genetics and the application in clinical care. And what we don't have, despite the lack of diversity, is a lack of trial data that also includes genetic data. So we can understand the influence of genetics on treatments There are large Biobanks, but we need to do a better job in getting also bio information from our trial populations.”