- My name is Dr. Maria Min-Young Kim and my research interests are primarily looking at the role of the autonomic nervous system in various cardiac conditions, including atrial fibrillation.

Please summarise the main aims, study design and endpoints of this trial?

So the main aim of the Ganglia-AF trial was to understand the mechanism behind the cardiac autonomic nervous system in atrial fibrillation. We know that the most common cause of AF is from the pulmonary veins, where a single PV ectopy can actually cause atrial fibrillation as well. And there's a very important structure surrounding the pulmonary veins, as well as being in the epicardial fat pad of the human atria called the ganglionated plexuses, which are very dense nerve structures, and hyper excitability of these nerve structures can trigger pulmonary vein ectopy and atrial fibrillation. So we hypothesised in the Ganglia-AF trial, that perhaps by targeting these specific ectopy triggering GPs can prevent atrial fibrillation long-term. So Ganglia-AF was a prospective randomised controlled study across three different centres in the United Kingdom. We randomised 116 patients into two different groups. So pulmonary vein isolation by radio frequency ablation, or ganglionated plexus ablation without pulmonary vein isolation. And we were primarily targeting, ectopy triggering GPs as well. And then patients who we recruited had paroxsymal atrial fibrillation with good LV systolic function. who was symptomatic and clinically indicated for AF ablations. And in order to look for these specific ectopy triggering GPs, we've mapped all around the left atrium using a technique called high frequency stimulation or HFS. By delivering these short bursts of HFS within the atrial refractory periods. By doing so, we could ensure that we are not capturing the myocardium, and only stimulating the cardiac nerves. And then we would look for specific responses such as PV ectopy or non PV ectopy, which would also sometimes trigger atrial fibrillation. And then we would ablate around the ganglionated plexus sites at these particular points in a cluster formation. And we would ablate until no further functional response to HFS could be induced. But if there was any further ectopy, further AF with retesting, we would do touch up RF ablation in that site until it was rendered negative. However, it wasn't always... The patients weren't always maintaining sinus rhythm during the HFS mapping protocol because of the trigger ability of AF with GP stimulation. And some cases we had to convert with different HFS protocol to look for a different type of GPs called the AV dissociating GPs. And what these GPs are is if you stimulate them, it produces a vagal response or an asystole or significant bradycardia. So in some instances where there was a lot of incessant AF, these AV dissociating GPs have to be targeted in addition to the ectopy triggering GPs. So all patients were followed up using ambulatory Holter monitors at three, six, nine and 12 months after their ablation. We had a blanking period of three months where we ignored any atrial arrhythmia that occurred during this time. And the primary end point was greater than 30 seconds of AF, or atrial tachycardia recorded in Holter monitors or in the ECG. Patients were allowed any additional ECGs and Holter monitors in between these designated three monthly time points. If they were symptomatic with AF as well. The secondary endpoints that we also looked at were significant complications, and also need for redo AF ablations.

What were your key findings?

So in total, we had 52 patients randomised to GP ablation group, and 50 patients in the PVI group. And this was in the per protocol analysis. All patients completed 12 months follow up, and at the end of the 12 months follow-up, we found that 64% of patients in the PVI group were free from atrial fibrillation and atrial tachycardia compared to 50% in the overall GP ablation group without pulmonary vein isolation. Now, this was not statistically significant, however, when we looked at the subgroup of the GP ablation group, so looking at only the patients who received ectopy triggering GPs ablations without any incessant atrial fibrillation requiring additional AV dissociated GP ablation, then the success rate was actually higher at 58% compared to 50% in the overall GP ablation. Interestingly, the GP ablation group required less than half the amount of radio frequency ablation used on average in the PVI group. However, the procedure time was approximately an hour longer in the GP ablation group compared to PVI. And this was primarily due to the dense mapping with HFS in the mapping stage of the left atrium in order to try and identify as many GPs as possible. In the secondary end points, there was one peri procedural complication in the GP ablation group. This was a cardiac tamponade which result with pericardiocentesis with no further complication. The rate of re-do AF ablations was very similar in PVI, as well as GP ablation group.

What are the take-home messages?

So ectopy triggering GPs can be safely mapped and ablated in patients with AF to prevent AF long term. But its current success rates isn't good enough to be an alternative to pulmonary vein isolation procedures. But ET GPs, the ectopy triggering GPS are around the conventional areas where we do pulmonary vein isolation ablation lines. So PVI does tend to inadvertently ablate these ectopy triggering GPs, and perhaps contributing to their success. But importantly, these ectopy triggering GPs are also found outside these conventional regions, such as down the middle of the anterior wall, inferiorly to the left atrial appendage, and across the middle of the left atrial roof. And very importantly, I'd like to highlight that actually the specific anatomical distribution of ectopy triggering GPs, and the number of GPs that we find in patients, it is very widely variable between patient to patient. So high-frequency stimulation is the only way we could have selectively identified these specific types of GPS in all of these patients. I know that a lot of autonomic studies to date favour the use of anatomical GP ablations sometimes, with or without adjunctive pulmonary vein isolation procedures. But I hope that this ganglia AF study results can demonstrate to clinicians all around the world that selective GP ablation can be performed with half the amount of ablation required for pulmonary vein isolation, and that it is very necessary to differentiate the ectopy triggering GPs to atrioventricular dissociating GPs, because the patients who received additional atrioventricular GP ablation has actually a lot poorer outcomes in this trial. And by being selective with our ectopy triggering GP ablations, at minimising ablation, we were able to avoid any macro re-entry atrial tachycardias, which can be quite common in anatomical GP ablations with additional lines as well. And it was definitely less common than we have seen in pulmonary vein isolation procedures. So I think one of the reasons why pulmonary vein isolation, durable PVI, works so well in first-time AF ablation patients, is that it provides the electrical barrier and preventing any triggered pulmonary vein ectopy or fibrillation from conducting into the left atrium. But on top of that, it also inadvertently ablates important ganglionated plexuses around the pulmonary vein sites, and perhaps even other types of substrates that we don't know quite what they are yet. So I think it will be really interesting to see whether doing an adjunctive ectopy triggering GP ablation in addition to pulmonary vein isolation, because then that would provide almost like a double barrier to atrial fibrillation. Not only would this be taking out the source, the autonomic source of pulmonary vein ectopy, but also targeting non-pulmonary vein ectopy triggers. It would also provide that extra barrier of preventing any of these triggered ectopy from conducting into the atrium.

How should this study influence further research into GP ablation for AF, and influence practice?

So I think we might be able to see some superior outcomes than performing ectopy triggering GP ablation alone, or PVI alone by combining the two procedures. And I think it's an important area to investigate because more and more, we are seeing patients with more advanced forms of AF disease who require multiple repeat AF ablations. And sometimes, we see patients with completely durable PVI, and yet still they have a lot of symptoms and AF recurrence. So in these patients, I think an additional substrate, this adjunctive procedure targeting these specific ectopy triggering GPs could be very useful.