Title: MANIFEST-PF: First Real-World Experience of PFA in Commercial Practice
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Dr Vivek Reddy

"- I'm Vivek Reddy from Mount Sinai Hospital in New York City, and I'm going to be speaking on the Manifest-PF Registry one year results.

Evidence on the Pentaspline Catheter

Well, if you look at the current data with the Pentaspline Catheter, we're really looking at the first in human trials that were performed about two plus years ago, and there, the data was quite good. We have excellent durability data and excellent one year outcome data. With the paroxysmal population, in which it was tested, the outcomes were about 83% success at one year. With persistent patients, we do have some data, but really, in a very small number of patients. So now fast forward to two, three years later, now the Pentaspline PFA Catheter has approval. It has CE mark approval here in Europe and is now being used in clinical practice. So the purpose of the Manifest-PF Registry was to try to understand how it's being used in practice and what are the outcomes in practice. We had previously had a Manifest-PF survey. We published that about a year ago. That was really a centre level survey that was really focused on safety events and acute procedural success. We had no data on long term procedural success, and we didn't have patient level data. So we went back to the first 24 centres that started doing pulsed field ablation. We asked for information on the first group of patients that they treated after the device was approved in 2021. And overall, it was 24 centres, everybody participated, so 100% participation. We included just over 1,500 patients, who underwent first time ablation for either paroxysmal or persistent Afib. It was about 2/3 paroxysmal, 1/3 persistent, so a lot of patients, lot of centres, a lot of operators.

MANIFEST-PF Study Design

The Manifest-PF Registry was designed as a retrospective analysis of, at many centres, prospectively collected cohort of patients. It was a patient level analysis, so we had individual patient level data, and we wanted to understand the one year outcomes in clinical practice. So, and the primary endpoint for our study was looking at freedom from any atrial arrhythmia recurrence with a three month blanking period. So, one year time horizon. We had a secondary outcome of freedom from arrhythmia or also freedom from taking an anti-arrhythmic drug or undergoing a redo ablation procedure. That was our secondary endpoint. So, we got the information from all of the centres, and then we combined the data and then just recently presented the data.

Overview of Cohort Enrolled in MANIFEST-PF

If we look at the patient population enrolled in Manifest-PF, it was about 2/3 of the patients were paroxysmal Afib, 1/3 were persistent, very few long-standing persistent patients. Sort of, I think, the kind of patients that are typically treated in clinical practice. About 40% of the patients were receiving a class one or a class three anti-arrhythmic drug before entering the trial. The remaining were receiving beta blockers or calcium channel blockers. The ejection fraction was largely preserved in this population with relatively few heart failure patients. So, let's talk about the key findings in MANIFEST.

Key Findings from MANIFEST-PF

So the patients were followed for a median of 367 days, so about a one year follow up, and what we saw for the primary endpoint, freedom from atrial arrhythmia recurrence, in the full cohort, was a success rate of 78%. If we separate it by AF subtypes, the success rate was 82% in the paroxysmal population and 71% in the persistent population. If we look at the secondary endpoint of freedom from arrhythmia or redo procedure or anti-arrhythmic drug, the success rate dropped a little bit in the cohort to about 72-73%. We also did some analyses to try to understand what predicted success versus failure in terms of centres. We did analysis, looking at centres that did a lot of procedures versus few procedures, and basically, there was no difference in outcomes, and one thing that says is that using this catheter, people have pretty good outcomes pretty much the first time they used it. Now, I should note, these are 24 experienced

centres, so these are not novice centres, but the point is, with an experienced centre, introducing this catheter for literally the first time that they've ever used it, they're having good outcomes. On the safety side, what we saw was, just as we saw in the previous survey, there were no esophageal complications, no evidence of PV stenosis, and happened in literally one in 1,000 patients, actually less than one in 1,000. And we saw no other unusual side effects, so overall safety continued to look good.

Unknowns around PFA and Promises of this Technology

When we think about what's unknown about PFA, I think that Manifest really helped in trying to understand what is the efficacy in sort of clinical practice. I think that's very important. But there are other questions on the efficacy side. For example, what if we have an implantable loop recorder, and we are looking at short bursts or asymptomatic Afib, that may not otherwise be detected in clinical practice, will that track just as we see, for example, with thermal ablation? My guess is yes, but we don't have that data, and we need to assess that. On the safety side, look, this is over 1,000 patients, over 1,500 patients, and the safety looks excellent. Of course, I'll feel even more comfortable after 10,000 patients, to continue to see, number one, that these sort of complications that we're looking for continue to be either not happening or extremely rare. And number two, there's always the possibility of the unknown unknown, the complication we've never even thought about that may potentially occur after 10,000 patients. Again, it seems less likely, but it's something that we need to continue to watch for.

Next Steps Based on MANIFEST-PF Findings

Now, following up the Manifest-PF Registry, there are a couple of analyses that we've already had planned. It is interesting, for example, to try to think about how different populations fare with pulsed field ablation. For example, there's been some data that women, for example, may not do as well with catheter ablation of atrial fibrillation as men do. There's other data suggesting that may not be the case. I think it's very important for us to understand how different genders. I think it's very important for us to understand what the effect of pulsed field is on different genders, so that's an analysis that we're planning. We're also planning on looking at the redo patients and trying to

better understand why failures occur. And then following up MANIFEST, we are thinking about a different analysis, more based on a safety analysis, at even larger numbers of patients, but again, this is in the planning stages."