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'There Is Work To Do:' Sean Salmon Discusses Medtronic's Recent Hard-Won Cardio Breakthroughs

by Reed Miller

Medtech Insight caught up with Sean Salmon, the president of Medtronic's cardiovascular business, to talk about the long-awaited FDA approval of the Symplicity Spyral renal denervation system, recent approvals of the PulseSelect pulsed field ablation system and extravascular ICD, and the company's plans for transcatheter aortic valve replacement.

Medtronic's cardiovascular business achieved at least three important long-term goals in the last three months, highlighted by the long-awaited US regulatory approval of its Symplicity Spyral radiofrequency renal denervation (RDN) system.

In November, the US Food and Drug Administration approved Symplicity Spyral along with *ReCor Medical*'s Paradise ultrasound RDN system to help lower blood-pressure in patients whose hypertension cannot be controlled with medications or lifestyle modifications alone. (Also see "*Medtronic Lands Surprise Approval On Symplicity Spyral*" - Medtech Insight, 20 Nov, 2023.)

The approval arrived about three months after an FDA advisory panel voted narrowly against affirming the benefits of Symplicity Spyral outweighed its risks. But the analysis of the clinical evidence is nuanced, and the agency agreed it should be an option for patients with uncontrolled hypertension. (Also see "*Cardio Catch-Up: Medtronic Still Has Work To Do On RDN After FDA Advisory Panel*" - Medtech Insight, 30 Aug, 2023.)

Symplicity Spyral is one of three major *breakthrough device* approvals Medtronic's cardiovascular business has announced in the last six months.

In October, the FDA approved Medtronic's Aurora EV ICD, the first extravascular implantable cardioverter defibrillator available in the US. It provides anti-tachycardia pacing, cardioversion

and defibrillation therapies through a lead placed under the breastbone, outside of the heart and veins.

It is competing with *Boston Scientific*'s Emblem subcutaneous ICD (S-ICD), which delivers shocks through a lead above the sternum and does not provide anti-tachycardia pacing. (Also see "*FDA Approves Medtronic's 'Extra-Vascular' ICD, The First Of Its Kind*" - Medtech Insight, 23 Oct, 2023.)

More recently, *the FDA approved Medtronic's PulseSelect pulse field ablation technology*, making it the first PFA device to be commercially available in the US. That distinction was short-lived as the agency approved Boston Scientific's Farapulse PFA in early February and will likely approve *Biosense Webster*'s Varipulse PFA soon. (Also see "*Updated: J&J Moves Closer To PFA Approval; New Data Presented At Boston AF*" - Medtech Insight, 7 Feb, 2024.)

Medtech Insight recently interviewed Sean Salmon, Medtronic's executive vice president and president for the company's cardiovascular portfolio, to understand how the company got Symplicity Spyral over the 'goal line' and how it plans to compete in the rapidly growing PFA market.

He also talked about the significance of the EV-ICD approval and provided an update on Medtronic's progress in the increasingly competitive expanding transcatheter aortic valve space.

This interview has been edited for clarity.

Q ***Medtech Insight*: One of Medtronic's recent big successes was finally getting FDA approval for the Symplicity Spyral renal denervation system after at least a *decade of effort* that began with *some setbacks*. Although it was close, the FDA advisory panel did not vote in favor of it due to some questions about why the pivotal trial missed its endpoint.**

Why do you think the FDA was comfortable with approving it despite those questions?

A Sean Salmon: It sounds like you've been on the ride for almost as long as I have. The first investment we made in that startup company, *Ardian*, was *in 2009*.

And we've been through this, what we called the original trials and then the '*reboot' of it all*, where we took a lot of precautions. It is hard to study something that the patient can measure themselves at home [like blood pressure].

They can go into their medicine cabinet and do something about it. It is really hard to do trials in the presence of medications. I guess that is the short story.

But we learned a bunch of things, including that it is important to be able to prove whether you have drug metabolites in patients – yes or no – and to know which ones they took. That wasn't the case in the first studies and that was among the things we changed.

We also changed the patient population, the site of ablation, and we changed the catheter design. We changed a bunch of things, but what you can't change is prescriber and patient behavior, per se, so it was pretty clear and understandable where the challenges were.

That conversation was going on way before and will go on way after that meeting.

Q **After all of those discussions, the *indication FDA approved for Symplicity Spyral* is fairly broad. Is that what you were seeking?**

A I think you get the indication that follows what you proved. And what we proved is that people who weren't able to control their blood pressure with lifestyle and drugs were able to get to a lower blood pressure with Symplicity Spyral – and in a clinically meaningful range.

That degree of blood pressure lowering confers nearly a 20% reduction in heart failure, stroke, and all-cause mortality, cardiovascular disease. The discussion got a

little bit in the weeds about ‘Are you sure it’s making things better?’

But the incumbent situation is you've got eight classes of drugs approved, but only one in four people with high blood pressure is controlled. And that's a massive problem, as one out of every two people has high blood pressure and nine out of 10 of us are going to have it in our lifetime. And it is the leading modifiable cause of death and disability.

SEAN SALMON, EXECUTIVE VICE PRESIDENT AND PRESIDENT FOR MEDCTRONIC'S CARDIOVASCULAR PORTFOLIO *Medtronic*

The FDA had a perspective that [understood] that it's a meaningful difference that we can make for patients.

We did patient studies with a formal instrument that can measure whether patients would rather take another pill or have an intervention. And that in that choice that they get to make, you give them different ranges of what the procedure complication rates will be.

Even when we proposed a crazy-high rate – nothing close to what we actually ever observed – still, one in three patients would prefer a one-time procedure, over having to take just one more medicine [every day].

We did two trials, we did one in the presence of medications and one in the absence of medications. And in the one the absence of medication, we took them step by step by step through more medicine until we got to blood pressure control. And we were able to get about 92% of patients to go without a diuretic, which is among the most hated and the hardest to adhere to medication for high blood pressure.

We also didn't have to dose escalate them from the starting dose of amlodipine,

which was the first step of our drug titration algorithm followed by an ACE inhibitor or an ARB – all generic drugs, all easy to take, with low side effects.

The difference between the starting dose of amlodipine and the doubling of that dose is more than doubling the level of side effects that the patient has from things like flushing and palpitations and edema.

The point is that they prefer not having to take pills that cause side effects. This one-time procedure, that appears to last forever, and you don't have to remember to do anything, and it lasts all day and all night? It's a pretty compelling value proposition when pulling back from questions like 'Did you hit this threshold or that measure?'

So, it was complicated, but suffice to say, we got there with Symplicity Spyral and it is gratifying.

Q **How will you identify which patients who should be offered RDN, and how do you get those people into the referral chain so that they get the therapy?**

A There's going to be plenty of patients with high blood pressure, obviously – one in every two people.

So, finding the ones that are most appropriate for this is going to require [discretion.] Rule out about 10% of the people with some secondary cause of hypertension that's not going to be treated with this procedure – you could have *hypothyroidism*.

You could have a tumor in your adrenal gland. There's a whole litany of those things. So, you've got to screen those patients out and then you get to the other patients where it becomes a question of the label indication, which is pretty broad, as you said.

Then it's about the judgment of the treating physician guided by a lot of

professional-society guidelines. And what those are saying predominantly is that, for patients who are unable or unwilling to control their blood pressure by taking more medications, [that RDN is a good option.]

The treatment guidelines are very pragmatic; if you're not going to take your blood pressure medicine, it's not going to work. But they really look for risk-enhanced people whose problem is going to be a lot worse if they've already had cardiovascular disease, already had a heart attack, or evidence that their organs are being damaged by that long-standing hypertension, such as left ventricular hypertrophy or enlarging of the heart.

They might have atrial fibrillation caused by high blood pressure or maybe excreting urinary protein, which is an early sign that your kidney is on its way to failing.

So, organ damage, risk factors, and people who are having a difficult time controlling their blood pressure. But even if I put all of those filters on it, it's still about 30% of the potential patient population and it's still a large number of patients – approximately 10 million.

Just to put that in perspective, you know, coronary intervention is a hugely successful global procedure that we do about four million or so a year around the whole world.

The more important question now is 'Will it get paid for?' And that's the biggest lift that we've got right now. There is a lot of activity there. We've started [talking to payers] well before the regulatory approvals.

We have a little help there since this has the FDA's breakthrough device designation. That confers some help with the steps and hurdles we have to get over to get add-on payments. … And then we can use that transition to get a full national coverage determination from Medicare.

And then that would be coverage with evidence development – coverage for five

years while gathering incremental evidence to satisfy concerns or questions that CMS may have. CMS wants to know, 'Is this reasonable and necessary in the enhanced-risk population?'

We studied this in a pretty narrow population. Then we start adding in things like kidney disease or diabetes – or whatever it may be that they're interested in.

That's the pathway for evidence development to secure a national coverage determination from Medicare. Once we have a national coverage determination, all the commercial payers that participate in *Medicare Advantage*, will have to follow the national coverage determination, and that opens sort of a mandate that they have to also cover it with their commercial insurance – they can't have one policy for one beneficiary and another for another.

So, in the near term, we will go state-by-state, payer-by-payer to compel their medical directors and coverage policies to cover this as well. But that's always made easier when Medicare's made their decision.

Q **Whenever there's a study like this that shows that some patients benefit from the therapy a lot more than others, the next obvious question is how can you identify the patients who are most likely to benefit from this. *Geneticure* is developing something like that, for example. Is there pressure from payers to develop risk-stratification tools or diagnostics like that?**

A It would be great to know who this is going to work for, beforehand.

The other complication is that blood pressure is like the weather. It changes often, so for any study you must know 'what did they really measure when starting? Was that a good day or a bad day? Did they respond or not respond?' It's complicated.

If we had a continuous blood pressure measurement for everybody's lifetime like the

EKG long-term recorders, [that would help], but the best we can do is 24 hours.

So, sometimes, 'Do they respond? Yes or no?' is a complicated question.

But the safety profile for RDN makes us feel that we've got time to sort this out. Are there other predictors that could say if this person would or wouldn't respond to the therapy?

There's been a bunch of proposed ideas that are quite promising that then fall apart in larger studies. But we're on the hunt for it. We've got a lot of effort against that, including the use of things like predictive modeling and AI. But right now, we just don't know.

Q **Moving to Medtronic's development of pulsed field ablation technology – Medtronic's PulseSelect PFA system is now FDA-approved, and CE marked, and all of the trials of PFA systems show it's safer and faster than existing ablation modalities with a fairly short learning curve.**

How has the roll out of that gone so far and what can Medtronic do to speed up the adoption of PFA and be competitive with the other electrophysiology companies introducing PFA systems?

A There's work to do.

It's not it's not the same as what we were just talking about – the reimbursement is all there for the category. But there's some training that we have to do to make sure people know that they should not use this like you're using the 'last thing.'

The golf analogy is, you don't hit a three iron like you do a pitching wedge. This is not so different.

But it's important to understand that PFA creates an electrical field – like the *lightsaber* in *Star Wars*. It's not a knife. So when you get close to the tissue, it will ablate with electroporation. And when you're touching it, it'll do so even better.

In the early days of PFA, people thought you just needed to get it in the 'zip code' of the tissue you're ablating, and you don't need to be in contact, unlike RF where you have to push and apply pressure to create more effective lesions – but you also have to be certain that you aren't pushing too much because you'll risk perforating or poking through the heart wall. With PFA, the catheter does have to be in contact to get the best results but the required force is different than with traditional RF ablation.

And so, we need to make sure people know and understand why that's important. PulseSelect has a circular array of electrodes that is almost identical to what electrophysiologists use all day long to do the electrical mapping while they're doing point-by-point ablation. So the handling of that catheter is really familiar to them.

PulseSelect is used to exclude just the pulmonary arteries, which are the source of the majority of, but not all of, where the arrhythmia is coming from. In more complex persistent atrial fibrillation patients, they typically create a more extensive lesion set to address the electrical sources of the arrhythmia.

Our next-gen catheter, the Affera Sphere-9 catheter, is a point-by-point solution that is integrated with a mapping and navigation system.

The point-by-point ablation segment is the big one. It's 85% of the market right now. What we call 'single shot' which our PulseSelect and cryoablation products participate in is the other 15% of the market.

We have put a lot of emphasis on ensuring that our catheters are really familiar and easy to handle. We have also placed a lot of emphasis on ensuring that our safety profile is very good – less than 1%. And under the auspices of an FDA trial, we have

two indications for both paroxysmal and persistent AF with that first launch of PulseSelect.

And then right on its heels, we'll have a persistent AF indication coming for the Affera catheter and system. What's really unique about Affera is that we utilize one device to create beautiful, high-density maps that tell you where you want to go and what you've ablated already – mark what you've done. That same catheter can do the mapping and it's also the therapeutic device. There's nothing else like that in the market.

And it can use either pulsed field ablation energy or it can use traditional radiofrequency energy. And that's important because, when you're in certain anatomical locations that are close to the coronary arteries and when you use PFA you can cause coronary spasm.

This has been seen in *Boston Scientific's PFA data set*. We haven't seen it yet. But to be fair, I'm not sure we've done enough ablations in close proximity to the coronary anatomy. If you want to use RF energy in those places you have that choice, and if you want reduce the risk of damaging the esophagus or the phrenic nerve – the things at the back of the heart that cause a lot of consternation and complications – you can choose to use PFA instead without having to change out your catheter.

With Affera, you can have those choices. The Sphere-9 catheter itself is small at just 8.5Fr. but the catheter tip of it is really big, though – 9mm. A typical ablation catheter for point-by-point is 3mm. So, think about the efficiency of that. You get three lesions for every one ablation that you do and the mapping system is beautiful – very high density.

It is like going from *MS DOS* to an *Apple* computer – super easy with a 'gamified' look.

The Affera mapping and navigation system will be the platform that all our catheters

with eventually work with. Cryoballoon, our traditional RF catheters, and PulseSelect will all be in that ecosystem. So, we'll have that whole thing.

The other last thing I'll say about PulseSelect is that it can work without a mapping system. You can just use regular visual guidance and intracardiac ultrasound with flouro and it can work. And, in our trial we did it with all the mapping systems. It worked with Boston Scientific's, it can work with Abbott's system and Biosense Webster's one.

And what's really interesting is that with this circular electrode array, you can clearly see the position of the electrodes on a mapping system to ensure that you are making tissue contact.

So, there are a lot of catheter-to-catheter differences that will be there, but being first and having the safety and efficacy profile that we do and having a pipeline to treat the entire array of arrhythmias with point-by-point or focal ablation, that's really where we see our competitive advantages.

Q **Is there anything unique or 'magical' about the specific pulse delivered by PulseSelect?**

Or, will electrophysiologists just compare your overall offering to the competitors' PFA systems?

A We do believe there's something important about the way you deliver energy in a pulse train. We spent about 15 years perfecting exactly that.

Can you just throw 2000 volts of electrical current into somebody's heart? Yes, you absolutely can and people are doing that. But we spent a ton of time on all the circuitry protection to make sure you couldn't overlap electrodes and cause an electrical short. We gate to the R wave – EKG gating to make sure you're not putting an R wave on a T wave – which can induce a fatal arrhythmia.

We were really intentional about titrating our energy delivery that so that we would be specific to cardiac muscle and not affect other structures, including nerves, the esophagus and lung structures and all those other things that are in close proximity to the site of ablation.

Maybe we were overcautious. But that's part of the reason for the excellent safety profile we demonstrated in our clinical study. We always put a high priority on patient safety.

What's interesting about pulse field ablation is that it can do a lot a lot of very quick ablations. So you can take the procedure time down significatly. That's important, especially for the complex cases that eat up a lot of lab time. And with our safety profile, it compels people to come in and try ablation as a first-line therapy before failing antiarrhythmic drugs, which are not very benign.

There's a market expansion opportunity here. One problem that every EP center will tell you about is that they've got a three-month waiting list.

And that's here in the United States. Access to care is a problem because of the inefficiency of today's solutions and efficiency of pulse field ablation procedures can help address those constraints.

Q **Speaking of transcatheter valves, Medtronic and Edwards especially have made so much progress in transcatheter aortic valve replacement (TAVR). Where do you see your CoreValve platform TAVR going in the future?**

A We've got more coming out in the first half of this calendar year – longer-term data comparing CoreValve directly to surgery in those low-risk patients. There's been a bit of equipoise there. We know that TAVR results look good for 30 days, and up to a year, compared to surgery.

That early data has looked pretty good for TAVR. But the questions have been will the early benefit persist in late follow-up? Will the patients continue to do well?

Our low-risk data – we *just reported our four-year data at the TCT conference* – and the delta between surgery and our CoreValve Evolut value is widening in our favor, and it's widening on all-cause mortality and disabling stroke – hard endpoints.

Four years is more of an intermediate time point, but we are certainly heading in the right direction compared to surgical valve replacement with our Evolut TAVR platform.

Our Evolut valve performance looked better, and we have a super-annular valve, so we get a bigger hole, basically. The valve will last longer if the hemodynamics are better. That's kind of the short story of our advantage over surgery. So, compared to surgery, Evolut looks really good.

Now we still have to, as I said, prove benefit over longer-term follow-up periods because surgery has got a long history. Following the lessons learned in that long surgical history, we do know that a bigger valve area with lower gradients is better. It portends better outcomes for patients and longer lasting valves too.

We will have a new study, the *SMART* trial, reading out soon, which is the head-to-head trial against the Edwards' Sapien valve, the market leader, in patients with small annulus. *And those are patients (often women) that have been underrepresented in these trials.*

Women don't make it into clinical trials as often. So, this is almost and exclusively women trial – it would be appropriate for any small annulus patient as well – we're taking on the market leader head-to-head in valve performance and hard endpoints in a very important cohort of patients.

> And we'll follow those patients for five years after the primary one-year endpoint as well.

"Waiting is not a benign thing – waiting for the valve to get tighter and tighter and tighter – that means you're losing heart muscle along the way." – Sean Salmon

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Q **Medtronic is sponsoring trials looking at other indications *beyond the severe symptomatic patients*, correct? What is the next frontier for the TAVR indications?**

A What you were referring to is what we call moderate aortic stenosis (AS). There's trepidation to treat a patient with AS, so you wait until they are really severely symptomatic, because surgery can be scary and risky.

But waiting is not a benign thing – waiting for the valve to get tighter and tighter and tighter – that means you're losing heart muscle along the way.

So, the hypothesis is that earlier TAVR intervention for those patients, versus not doing something, should improve ventricular health and other outcomes. So that's the next potentially big indication that's probably as big if not bigger than the low-risk indication and the two prior indications – severe and intermediate risk patients. So, the TAVR market has got a lot of legs left and will continue to be a growth driver for us.

Q **Beyond those pateints, could TAVR also be developed for people whose native valve is just too big?**

A Typically, that's referred to as a leaking valve or aortic regurgitation. There are a few

solutions. We don't have a dedicated one right now.

There are a couple of companies trying to pursue that. It's a little rarer. It does not have the same fundamental patient risk as untreated aortic stenosis which has a 60% two-year mortality rate.

These patients aren't so far into heart failure and don't always feel as sick. But regurgitation a valid pathology. A leaking valve is more common in the mitral side, rather than a stenotic one. It's sort of the inverse for the aortic valve.

Q **Is there any other new development within your business that you want to highlight?**

A We've had approvals of three breakthrough device designations. Symplicity Spyral, PulseSelect and the other one was the *Aurora extravascular implantable cardiac defibrillator (EV ICD).*

Having leads in the heart is great because you can use those leads not just to shock the patient out of their arrhythmia, but you can also use the leads to pace the heart and avoid the need for that painful and scary shock. The prior solution for not having leads in the heart [the Emblem S-ICD] doesn't solve that.

It can only provide a shock to terminate an arrhythmia and it's a really big device. It's twice the size of our device and its battery doesn't last as long – the battery life is 60% less than Aurora. With Aurora we discovered this way that you could get underneath the breastbone for this 'epsilon-shaped' lead that you put place above the heart.

And from that position, we can attempt to pace, rather than shock to terminate the arrhythmia. So that is really a breakthrough opportunity to take leads out of the heart to avoid things like infection risk and or some movement limitations that younger

patients particularly worry about.

We do all that with a device that is really going to compete in the traditional single-chamber ICD market. So today that market size for the subcutaneous ICD is about $300m, but we think it's more like a billion-dollar opportunity as we reinvent ourselves again in the ICD space just like we did with leadless pacing.

We've disrupted ourselves with leadless pacing and we're doing that again with conduction-system pacing. So our oldest business, CRM, is alive and well with compelling innovation too.

Q **It's noteworthy that EV-ICD was approved in the US before it got a CE mark in Europe. That used to be very uncommon but seems to be happening more often now. Is that a permanent trend?**

A The *medical device regulation, MDR, is a harder road.* They really ask for a lot.

We are seeing transcatheter valves in the United States almost a year ahead of the CE mark approval. It's really different than in years past.

Q **With the advancement of leadless pacing and ICDs, where will lead technology go? Will they eventually be obsolete?**

A I think what we do with those leads is also going to change a lot, whether that is leads for brady pacing or leads for resynchronization in heart failure.

We're starting to use the hearts native conduction system more and more now. *We currently have the only approved lead for conduction system pacing in the United States.*

You can place a pacing lead anywhere in the heart and it can make the heart beat, but

> it can happen in a discordant fashion that can induce heart failure for patients who are susceptible to that. This whole concept of conduction system pacing – you'll hear that also described as left-bundle branch pacing or HIS bundle pacing – is where we are going with our lead technology.
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> On the leadless pacing front, our current *Micra* iteration features battery technology that lasts 40% longer than our last iteration. So that means that for 80% of patients, in their lifetime, they'll only need one vitamin-sized device that's put in with a catheter.
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> In the future I can envision us providing completely leadless devices for cardiac rhythm management that do a great job for patients while reducing the inherent risks associated with placing leads in the heart.