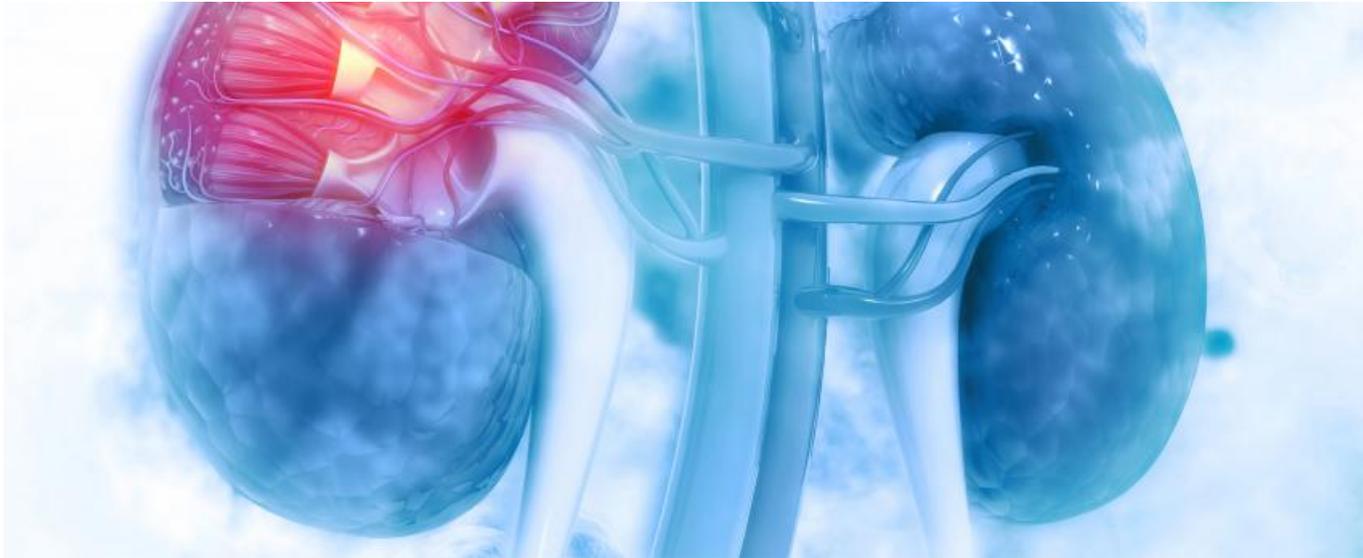


The future of renal denervation



[Elizabeth Cairns](#)



The pivotal trial of Medtronic’s hypertension device came out more than a year ago, yet the company has still not sought approval.

Data presented last week by both Otsuka and Medtronic on their respective renal denervation systems suggest that the technique is viable after all as a means of reducing blood pressure. But despite enormous expectations for this technology – Medtronic believes the market to be worth over \$3bn by 2029 – and a plethora of trial results no submissions to the FDA have yet been made.

This is in spite of the approval trial of Medtronic’s device, named Symplicity Spyral, having [hit its endpoints in March 2020](#). The company is waiting for data from a non-pivotal sister trial, expected in the autumn, before filing. In the meantime questions remain about how acceptable this intervention will be to patients and cardiologists, and whether the blood pressure reductions are large enough to justify its use.

Renal denervation involves threading a wire through the vasculature from the groin and, from within the renal arteries, ablating the surrounding nerves. It had been thought a dead technology, more or less, until a surprise interim hit was reported in a sham-controlled trial called [Spyral HTN-Off Med](#) ([The corpse of renal denervation starts twitching, August 28, 2017](#)). Subsequently Medtronic expanded the trial and recast it as the US pivotal study.

So why no filing, bearing in mind that Off Med succeeded more than a year ago? Medtronic declines to state explicitly, but the answer likely has to do with the label it wants.

Patients in Off Med were, as the name suggests, taken off their hypertension medication to show the effect of the denervation. A similar trial, [Spyral HTN-On Med](#), does allow enrollees to take their pills, permitting one, two or three antihypertensive medication classes. This ought to resemble more closely how the technology will be used in practice.

“Our belief is that with a broader dataset we’re going to be in a better position,” says Jason Weidman, president of Medtronic’s coronary & renal denervation.

Should On Med hit too when data emerge, probably at the TCT meeting in November, a filing will follow swiftly, Mr Weidman says. “Provided that happens, we would see approval sometime next calendar year.”

Downward Spyral

While Off Med must be regarded as a success by the trial’s parameters, some have questioned whether the reductions are steep enough to make the procedure worth undergoing. So far, none of the three systems vying

for US approval have managed to muster a sham-adjusted blood pressure reduction of more than 6.5mmHg.

The renal denervation players

Company	Device	Ablation tech	US clinical trial data	
			With drugs	Without drugs
Medtronic	Symplicity Spyral	Radiofrequency	<u>On Med</u> : Data expected Oct/Nov	<u>Off Med</u> (pivotal): 24-hour SBP drop of 3.9mmHg; office SBP drop of 6.5mmHg
Recor/Otsuka	Paradise	Ultrasound	Trio*: median daytime ambulatory SBP drop of 4.5mmHg	Solo*: median daytime ambulatory SBP drop of 6.3mmHg
Ablative Solutions	Peregrine	Alcohol	-	<u>Target BP I</u> (pivotal): data expected 2022

*Different cohorts of the [Radiance HTN](#) trial. SBP: systolic blood pressure. Source: company releases & *The Lancet*.

Professor Felix Mahfoud of Saarland University Hospital in Homburg, Germany, who presented data from an uncontrolled registry trial of Spyral at the EuroPCR meeting last week, says this ought to be sufficient.

"5mmHg in office systolic, when achieved by pharmaceutical agents, corresponds to significant improvements in cardiovascular outcomes," he tells *Evaluate Vantage*. "You can reduce stroke, cardiovascular events, such as heart failure, heart attacks, chronic kidney disease, by 10-15% with 5mmHg."

No direct effect on cardiovascular effects had been proven with denervation, though Professor Mahfoud presented an analysis at EuroPCR that used data from the registry trial to estimate a 26% relative risk reduction in major cardiovascular events for all patients treated with Spyral, and a 34% reduction for those with drug-resistant disease, over three years.

Estimates are as good as it is going to get. Mr Weidman says no trials of denervation with CV events as the endpoint are on the cards.

"If you were going to do a true outcomes trial ... you'd end up with a with a clinical trial that could be well over 10,000 patients, and we're looking at events that sometimes occur 10 or 20 years down the line. That's impractical."

He points out that trials like this have not been done for hypertension drugs either. These have been approved simply on the magnitude of blood pressure reductions, with the effect on patients' health being taken as read.

Lofty

Approval, then, appears to be a distinct possibility. Living up to Medtronic's lofty commercial hopes for renal denervation might be a bigger unknown. On the group's last quarterly call in February its chief executive, Geoff Martha, said Spyral could get to the \$3bn mark with just 1% market penetration.

To be fair, hypertension is widespread. Around two billion people worldwide have the disorder, and in half of them it is poorly controlled by medication.

Mr Weidman believes that patients are keen. Most who enrolled in Medtronic's trials did so because they heard about it and volunteered, he says, rather than doctors telling specific patients to enter the study. "You've got a lot of patients that just feel like the current options out there aren't sufficient." The once-and-done nature of the technique is particularly appealing, he says.

For the technology to reach its full potential, cardiology societies such as the ESC, ACC and AHA will have to recommend denervation in their guidelines, and insurers will have to agree to reimburse it.

Mr Weidman denies that the potentially large upside if the technology does take off is balanced by a correspondingly large downside if it does not.

"There's generally a lot of excitement around renal denervation. But there's also a lot of excitement around many things in Medtronic's pipeline," he says. "When you make a lot of high-risk, high-reward bets across a large portfolio it's just like any investment portfolio, in that you're protecting yourself in case one of them doesn't work." Good to know.

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