Evaluate Vantage

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Renal denervation goes from Symplicity to complexity

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Renal denervation works. The question is, does it work enough? Data from one sham-controlled study of Medtronic's Symplicity Spyral catheter and from another of its only rival, the Paradise device made by the much smaller group Recor Medical, show that both lower blood pressure.

But the sham-adjusted drops in blood pressure, at 7.4mmHg with Spyral and 6.3mmHg with Paradise, might not be great enough to convince doctors to put patients through a non-surgical but still somewhat traumatic process. If the battle for market share comes down to company reps working to persuade customers, Medtronic is surely positioned to be the winner.

Medtronic's data, presented this morning at the EuroPCR meeting in Paris, came from Spyral On Med. This is the companion study to Spyral Off Med, whose positive three-month results electrified the then-moribund renal denervation arena when presented at the European Society of Cardiology congress last year (*The corpse of renal denervation starts twitching, August 28, 2017*).

The difference between the trials is that the On Med patients were taking up to three antihypertensive medications, including diuretics, calcium channel blockers, ACE/ARB inhibitors or beta blockers. This is thought to reflect the real-world population better – as is the fact that only around 60% of the patients in the trial were adherent to their drugs at any time.

Interim six-month data from the first 80 patients in On Med show statistically significant drops in blood pressure across all the efficacy endpoints, including 24-hour ambulatory systolic blood pressure. Safety was clean, too, with no severe adverse events in either arm of the trial.

There was an increase in the size of the effect from three months to six, which the investigator, Dr David Kandzari of the Piedmont Heart Institute in Atlanta, Georgia, said underscored the need for longer-term follow-up to understand "the trajectory of benefit with renal denervation".

Interim Spyral HTN On Med (NCT02439775) data

	Mean decline in BP from baseline (mmHg)			
	Renal denervation (n=36)	**Sham control (n=36)**	**Sham-controlled reduction**	**P value**
24-hour systolic ambulatory BP*	9.0	1.6	7.4	0.005
24-hour diastolic ambulatory BP*	6.0	1.9	4.1	0.03
Office systolic BP	9.4	2.6	6.8	0.02
Office diastolic BP	5.2	1.7	3.5	0.05
Daytime systolic BP	8.8	3.2	5.7	0.04
Daytime diastolic BP	6.3	2.8	3.5	0.07
Nighttime systolic BP	9.8	Increase of 2.1	11.9	0.0003
Nighttime diastolic BP	5.9	0.3	5.6	0.02

**Primary endpoints. Source: EuroPCR presentation.*

On Med will indeed continue: its primary endpoint is 24-hour ambulatory systolic blood pressure at three years post-procedure. By then, though, a far more important trial might have yielded data. Medtronic has begun a pivotal US study of Spyral, which should report in 2020 (*Medtronic tries again with renal denervation, April 18, 2018*).

Underdog

Since Boston Scientific canned the trial of its renal denervation system Vessix, after an analysis showed continuing would be futile, Recor Medical has been the only company squaring up to Medtronic in this space.

Like Spyral, Recor's Paradise has been CE marked and available in Europe for many years. Also like Spyral – and half a dozen other CE-marked devices – its sales will have been poor since the catastrophic failure of the pivotal US trial of Medtronic's earlier-generation Symplicity device, back in 2014.

The Solo cohort of the Radiance-HTN study of Paradise, data from which were presented immediately following the On Med data, met its primary endpoint and many of its secondary measures. Paradise-treated patients had an 8.5mmHg decline in their daytime systolic ambulatory blood pressure, compared with 2.2mmHg for the sham group, a statistically significant difference.

At two months, two thirds of those treated with renal denervation had a reduction in daytime ambulatory systolic blood pressure of 5mmHg or more, compared with one third in the sham group. No major adverse events were seen.

The 146 patients in the trial were not receiving antihypertensive drugs, necessitating a shorter trial period so the sham group were not endangered.

Radiance-HTN (NCT02649426) Solo cohort data

	Sham-controlled reduction (mmHg)	P value
Daytime systolic ambulatory BP*	6.3	0.005
Daytime diastolic ambulatory BP	2.6	0.012
24-hour systolic ambulatory BP	4.1	0.006
24-hour diastolic ambulatory BP	1.8	0.07
Office systolic BP	6.5	0.007
Office diastolic BP	4.1	0.005
Nighttime systolic ambulatory BP	2.5	0.15
Nighttime diastolic ambulatory BP	1.4	0.25
Home systolic BP	7.1	<0.001
Home diastolic BP	3.6	<0.001

**Primary endpoint - decline in BP was 8.5mmHg with Paradise vs 2.2mmHg with sham. Source: EuroPCR presentation.*

Readers should remember that these two trials are not comparable – Medtronic's assessed denervation in patients taking blood pressure drugs, whereas the patients in Recor's were off medication.

Instead the Solo study is roughly analogous to Medtronic's Spyral Off Med. But Recor is working on an equivalent to On Med – Trio, the other cohort of Radiance-HTN, in which patients will take at least three blood pressure drugs, is currently enrolling.

Recor has applied to the US FDA for leave to begin a pivotal US study of Paradise. It is possible that this will report before Medtronic's ongoing pivotal trial, depending on the timing of its endpoints, but it is probably safe to assume that the FDA will request similar data from both, putting Medtronic ahead.

As for success on the market, that will depend on the effect sizes seen in the pivotal studies. The On Med investigators insist that the magnitude of blood pressure decline in that trial is "clinically significant, associated with lower rates of both cardiovascular events and mortality in prior studies", but whether doctors will accept this contention is as yet unclear.

Commenting on the Solo data in the *Lancet*, Professors Sverre Kjeldsen of the University of Oslo and Murray Esler of the Baker Heart and Diabetes Institute in Melbourne said the 6.3mmHg reduction in daytime

ambulatory systolic blood pressure would roughly correspond to the benefit of one effective antihypertensive drug. But they warn that there might be responders and non-responders, and some subgroups might benefit more than others; identification of these patients will be crucial.

Developers must also confirm long-term safety and whether there is a sustained blood pressure-lowering effect, they write, since this could render the procedure cost-effective.

Perhaps, as is not uncommon in medtech or pharma, it will come down to marketing – and one of these groups has a definite edge there. If this ends up being a David-and-Goliath battle, the smart money is on Goliath.

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