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ACC 2021 – Otsuka’s denervation system hits in mid-stage trial

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But does it hit hard enough?

The Paradise renal denervation system developed by Recor Medical, now a subsidiary of Otsuka, reduced blood pressure in patients whose hypertension did not respond to drug treatment, data presented at the virtual ACC meeting show. Renal denervation is essentially a two-horse race, and yesterday’s results suggest that Otsuka’s system is comparable to Medtronic’s Symplicity Spyral device.

Unfortunately there is a broader question: whether the reduction seen with the technique is large enough to translate into a benefit on cardiovascular events, thereby justifying patients undergoing the procedure.

Renal denervation is a technique in which a catheter-mounted probe is inserted through the vasculature and used to burn the nerves in the renal arteries. This process causes a reduction in sympathetic nerve activity, which decreases blood pressure.

The new data come from the Trio cohort of the Radiance-HTN study, consisting of patients on a three-drug combination antihypertensive therapy. Patients treated with the Paradise system had a median daytime ambulatory blood pressure reduction – the primary efficacy endpoint – of 8.0mmHg at two months. Compared with the control group, who underwent a sham procedure, the median between-group difference was a statistically significant 4.5mmHg.

Radiance-HTN (NCT02649426) data				
	Solo cohort (without drugs)		**Trio cohort (with drugs)**	
	Sham-controlled reduction (mmHg)	**P value**	**Sham-controlled reduction (mmHg)**	**P value**
Daytime systolic ambulatory BP	6.3	0.005	4.5	0.022
Daytime diastolic ambulatory BP	2.6	0.012	1.8	0.18
24-hour systolic ambulatory BP	4.1	0.006	4.2	0.016
24-hour diastolic ambulatory BP	1.8	0.07	2.0	0.12
Office systolic BP	6.5	0.007	7.0	0.037
Office diastolic BP	4.1	0.005	4.0	0.16
Nighttime systolic ambulatory BP	2.5	0.15	3.9	0.044
Nighttime diastolic ambulatory BP	1.4	0.25	2.8	0.053
Home systolic BP	7.1	<0.001	4.0	0.052
Home diastolic BP	3.6	<0.001	3.0	0.053
Before randomisation subjects were hypertensive in the absence of hypertension medication (Solo) or despite treatment with a fixed-dose combination of amlodipine, valsartan/olmesartan and hydrochlorothiazide (Trio). Source: EuroPCR 2018, ACC 2021 & the Lancet.				

Results from Radiance-HTN-Trio were generally not as impressive as those from the Solo cohort, consisting of patients who were hypertensive without having received drug therapy. In Solo, data from which were reported three years ago, patients treated with Paradise had a median two-month blood pressure reduction 6.3mmHg greater than those who underwent the sham.

Putting this in context, Medtronic's Spyral HTN-On Med trial, which is roughly analogous to the Trio cohort in Otsuka's trial, showed a sham-adjusted reduction of 5.7mmHg in daytime systolic pressure. Those results were an interim cut from the trial concerning six-month data from the first 80 patients. Full data from On Med are expected towards the end of this year.

Beyond the usual concerns of comparing data from different trials, there is another major difference between Medtronic's and Otsuka's systems: Paradise uses ultrasound to ablate the renal nerves, whereas Spyral uses radiofrequency energy.

Relevance

In an editorial in the Lancet accompanying publication of the Trio results, Professor Michael Böhm and Dr Lucas Lauder of Saarland University Hospital in Homburg, Germany wrote that though a blood pressure reduction of 4.5mmHg seemed small it could be clinically relevant, since in hypertensive drug trials a decline of this magnitude translates into a 15-20% reduction in major cardiovascular events.

The researchers wrote that more data were needed to make a definitive link between blood pressure reduction and clinical outcomes.

It is unlikely that this could come from the pivotal trial of Paradise. Radiance II has two co-primary endpoints: change in daytime ambulatory systolic blood pressure at two months and the incidence of major adverse events within 30 days of the procedure. The time frame of the last means it is likely a way to assess the safety of the denervation procedure rather than the effect of denervation on outcomes, since the latter would require a longer-term look.

Still, Radiance II's endpoints have been agreed with the US FDA, so when the trial reports next year a hit would presumably be sufficient for US approval. But cardiologists will have to be convinced that renal denervation can improve patients' lives if the technique is to truly take off.

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