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# Cardio Catch-Up: Medtronic Still Has Work To Do On RDN After FDA Advisory Panel

by Reed Miller

FDA's circulatory system advisory panel narrowly voted against Medtronic's Symplicity Spyral, because one of the pivotal trials of the radiofrequency renal denervation system missed its primary endpoint and the patient population evaluated in the trial does not match the requested indication.

*Medtronic*'s long struggle to launch its Symplicity Spyral renal denervation (RDN) technology on the US market is not going to get any easier following a mixed review by the US Food and Drug Administration's circulatory system devices advisory panel.

The panel considered the company's premarket approval application (PMA) for Symplicity Spyral on 23 August, one day after it considered a similar application from *ReCor Medical* for its Paradise ultrasound RDN system. (Also see "*Cardio Catch-Up: Advisory Panel Gives Recor Momentum Toward US Launch Of RDN System*" - Medtech Insight, 30 Aug, 2023.)

While the panel's final votes largely favored ReCor's submission, its final votes on Medtronic's technology were mixed and leaned toward unfavorable. [See Box: "Final Advisory Panel Votes"]

After the votes, panel chair Richard Lange, from Texas Tech University Health Sciences Center in El Paso, emphasized that FDA advisory panels' votes do not decide if the FDA will approve a PMA. The votes just summarize the panel's overall conclusions, which the agency can chose to follow, or not, depending on its own analysis.

"The panel is voting on the questions that

### *Final Advisory Panel Votes*

After reviewing a PMA, FDA's circulatory system devices advisory panel votes on three questions: Does the available evidence show the device is safe? Does the available evidence show the device is effective? Do you think the

were posed to us by the FDA, the FDA takes those votes [along with] the very rich, candid and thoughtful discussion we had," he explained. "The FDA will work with the sponsor and make a decision about what will transpire in the future."

Medtronic began developing the Symplicity technology when it acquired Ardian for $800m in 2010. Symplicity Spyral has a CE mark, but the company has invested heavily in clinical trials to secure FDA approval for the system for about a decade. (Also see "*With Trial Approval, Medtronic Aims For Symplicity RF Catheter Launch In 2014*" - Medtech Insight, 18 Jul, 2011.)

The company completed its PMA for the system in November 2022. Medtronic is *asking the FDA* to approve the Symplicity Spyral System for the reduction of blood pressure in patients who have uncontrolled hypertension that persists despite the use of anti-hypertensive medications, or in patients who respond poorly to anti-hypertension therapies.

benefits of the device outweigh its risk?

On 23 August, the panel unanimously agreed (voting 13-0) that that Medtronic's Symplicity Spyral radiofrequency renal denervation (RDN) system is safe for the treatment of hypertension.

However, the panel voted 7 to 6 on the question of Symplicity Spyral's efficacy. On the critical question of risk-vs-benefit, the panel voted 6 to 6 with one abstention.

To break the tie, panel chair Richard Lange voted "no," so technically the panel concluded that the available evidence does not confirm that the risks of the Symplicity Spyral therapy outweigh its risks.

"For the indications proposed, I don't think [Symplicity Spyral] was proved to be effective," Lange said. "I can't honestly look patients in the eye and tell them that I believe the benefit outweighs the risk to the patient population at large."

## What's Next For Symplicity Spyral? Everyone Has A Guess!

The FDA is not obligated to follow an advisory panel's recommendations, regardless of the vote, but some Wall Street analysts believe this panel meeting represents the end of the road for Medtronic's RDN technology. (Also see "*Medtronic Bets On Blockbuster Hypertension Market With Ardian Acquisition*" - Medtech Insight, 29 Nov, 2010.)

"Given the vote, we think that the FDA is unlikely to approve Symplicity Spyral," Needham analyst Mike Matson wrote on 24 August. "And given Medtronic's long and costly RDN program, combined with multiple disappointments along the way … we expect Medtronic to abandon RDN if it fails to obtain an FDA approval this time around."

While the advisory panel did not go Medtronic's way, several analysts pointed out that

Symplicity Spyral has FDA's breakthrough device status and suggested that the agency is motivated to help bring it to market.

Jayson Blair of Raymond James predicted that FDA will probably approve Symplicity Spyral for a more limited indication and that commercial payers may be reluctant to cover it unless the company can define the subpopulation that is most likely to benefit.

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"Medtronic will receive FDA approval for the device, but we anticipate that the label may be narrower than originally thought, which may limit the addressable [total addressable market]," Blair wrote in a 23 August note.

Barclays analyst Matt Miksic agreed. "Despite the extensive debate and roughly split recommendations on efficacy and risk/benefit, we expect Medtronic to continue to work with the FDA to obtain approval for this breakthrough-designated device," he wrote on 23 August.

During the company's fiscal 2024 first-quarter earnings call on 22 August – prior to the advisory panel meeting – Sean Salmon, the president of Medtronic's cardiovascular business, predicted that the FDA could approve Symplicity Spiral in the second half of fiscal 2024, which ends in April 2024.

### *FDA May Approve RDN, But Who Will Pay For It?*

Because Symplicity Spyral has FDA's breakthrough status, it could be eligible for automatic Medicare coverage under the Center for Medicare and Medicaid's (CMS)

proposed Transitional Coverage of Emerging Technologies (TCET). (Also see "*Industry Proposes TCET Timeline, CED Changes During CMS Stakeholder Call*" - Medtech Insight, 2 Aug, 2023.)

But private payers may be reluctant to cover RDN until they see convincing evidence that it offers significant clinical benefits to a defined patient population.

“We see a greater than 50% chance of [FDA] approval,” Wells Fargo analyst Larry Biegelsen wrote on 23 August. “[But,] Panel comments on the limited efficacy of Symplicity increase the risk around reimbursement. Medtronic could pursue the proposed TCET pathway which could help secure reimbursement if the proposal is finalized.”

Wells Fargo projects of it could yield $14m for Medtronic in fiscal 2024 and $371m annually within five years, “but given today's panel vote, we see potential downside to those numbers,” Biegelsen explained.

Medtronic has previously projected that the RDN market to be worth $500m by 2026 and up to $3bn by 2030, but analysts are not counting on revenue from RDN in their models of Medtronic’s future revenue and earnings.

CL King & Associates’ Kristen Stewart believes RDN could eventually be the $1bn market opportunity that Medtronic hopes it will be, but it will take many years to get

## One Missed Endpoint Made The Difference

Medtronic's PMA for Symplicity Spyral is based primarily results from two separate sham-controlled trials: *SPYRAL HTN OFF MED* and *SPYRAL HTN ON MED*. Both trials showed that the procedure is extremely safe with almost no adverse events. (Also see "*Medtronic Completes PMA Application For Symplicity Spyral Hypertension Device*" - Medtech Insight, 8 Nov, 2022.)

there.

"At this point, we model *de minimis* revenues for RDN, given the mixed clinical data outcomes and uncertainty around approval," she wrote on 21 August. "Even if FDA approves the Symplicity Spyral, Medtronic will face a long road ahead with reimbursement hurdles."

Medtronic reported $1.44bn in fiscal 2023 revenue and expects total revenue to grow 4.5% in fiscal 2024.

Medtronic agreed to run a trial of Symplicity Spyral in patients not taking antihypertensive drugs because the disappointing results from the *SYMPLICITY HTN 3* trial in 2014 suggested that variation in patients' medication regimens obfuscates the results of a controlled trial of renal denervation. (Also see "*Work With Patients To Design Trials For Anti-Hypertensive Devices, FDA Advisors Suggest*" - Medtech Insight, 6 Dec, 2018.)

*Three-month results* from 331 patients in the SPYRAL HTN OFF MED showed renal denervation significantly lowers blood pressure in patients not taking antihypertensive drugs. Blood pressure in the patients treated with Symplicity Spyral dropped by an average of 9.6mmHg, while the average improvement in the sham-control group was 3.5mmHg. The 6.6mmHg difference was statistically significant.

The panel agreed that the SPYRAL HTN OFF MED results show that RDN provided a small benefit to hypertensive patients not taking medications.

Long-time panel member, John Somberg from Rush University in Chicago, suggested these results show that the procedure should be offered as an adjunct therapy in patients in patients that cannot tolerate or be compliant with medication. "But it's a modest effect, approximately equal to [adding] one drug."

The final module for the PMA also included the full six-month results from 337 patients in the *SPYRAL HTN ON MED*, which compared RDN to a sham control procedure in patients with uncontrolled hypertension taking up to three antihypertensive medications.

The study easily met its primary safety endpoint with a low incidence of procedure-related and

clinical adverse events at six months.

However, several panelists pointed out that SPYRAL HTN ON MED did not meet its primary efficacy endpoint because the relative improvement in 24-hour systolic ambulatory blood pressure was not statistically significant. The average improvement in this measure was 6.5mmHg in the RDN group and 4.5mmHg in the control group.

About half the panelists concluded that missing the endpoint means the trial is "negative" and does not support RDN with Symplicity Spyral. Some of them also pointed out that the trial did not show that the benefit of the therapy is durable, but the trial was not designed to show durability.

Julia Lewis, a nephrologist at Vanderbilt University in Nashville, said. "You can come up with all kinds of reasons that [SPYRAL HTN ON MED] might be negative, but it might be negative because *the null hypothesis* is correct. And there's no way of getting around that."

According to the trial's investigators – led by David Kandzari from the Piedmont Heart Institute in Atlanta – the trial may have missed its endpoint because of protocol violations in the sham-control group which led to better-than-expected outcomes in those patients. About 22% of the patients in the sham-control group changed the dosage or the number of medications they were taking prior to the six-month follow up, while only 2% of the RDN group changed their medication regimen.

About 80% of the patients enrolled in the second stage of the trial entered the trial during the COVID-19 pandemic, which may have skewed the outcomes of the trial in favor of the control group.

While the trial missed its primary endpoint, a Bayesian analysis of the results found a 51% probability that RDN was superior to sham control for the reduction in 24-hr systolic ambulatory blood pressure.

Also, the trial's pre-specified secondary endpoint was the improvement in systolic blood pressure measured in a doctor's office from baseline to the six-month follow-up visit. On this measure, RDN looked a lot better. The average blood-pressure reduction in the RDN group was on 9.9 mmHg versus a 4.9 mmHg reduction in the sham control group.

The study also measured "Win Ratio," an endpoint that combines the reduction in blood pressure with the reduction in medication burden to assess the overall benefit of RDN. The Win Ratio was significantly better in the RDN group than the sham-control group at six months.

Benjamin Saville, a statistician with Berry Consultants in Austin, said "My interpretation of

[SPYRAL HTN ON MED] is that you really have two correlated endpoints – systolic blood pressure and you have a number of medications [and] it's hard to interpret one while ignoring the other. … You're maybe not benefiting the blood pressure, but you're certainly benefiting the number of meds that are required to get there."

But all the secondary analyses of SPYRAL HTN ON MED were not enough to persuade some panelists to support Medtronic's PMA. Lange concluded, at the end, it's a negative study – regardless of whether that's due to the confounding factor or the fact that it just doesn't do what they'd hoped for it to do."

## What Should The Indication Be?

Several panelists argued that the two pivotal trials of Symplicity Spyral did not study the population described by Medtronic's suggested indications for use (IFU).

"There's a huge disconnect between the current IFU [as suggested] and what was studied," Keith Allen of St. Luke's Hospital in Kansas City said. "What was studied was: 'How does RDN work in a patient who has mild or moderate blood pressure?' And that effect is quite small at three months and goes away at six months [in patients taking] medications."

Lewis said, "They didn't document intolerance The [patients in the trials] are not necessarily drug- resistant."

Somberg suggested that FDA should consider approving Symplicity Spyral for a different indication than the one Medtronic requested. "If it was approved, the indication would have to suggest that it's for mild to moderate hypertension, and that it offers the same benefits as, possibly, one pharmacologic therapy that is appropriately escalated."

Matthew Corriere, a cardiovascular surgeon at the University of Michigan in Ann Arbor, abstained from voting on the question of risk vs benefit because, "We don't know which patients are most likely to have a benefit that outweighs the risk."

"More selective labeling and indicating the product for more severe instances of hypertension – not things like 'one-drug hypertension – would potentially tip that balance more in favor of the benefit outweighing the risk."

Patrick Nachman, a nephrologist at the University of Minnesota, also argued for further research to define a more specific patient population that could benefit from RDN.

"I am convinced that there is a subgroup of patients who would benefit from this, but I worry that that subgroup is a not defined and could possibly be a minority of patients," he said. "I worry about opening the gates to do a lot of procedure to only benefit a minority of patients."

Several panelists offered suggestions for possible post-market trial designs to precisely identify the "drug-resistant" patients who are most likely to benefit from RDN.

"Why not run a trial with patients that serving as their own control? And the way you would do that would be to enroll a patient that has to meet goal-directed hypertension management," Allen explained. "And after he gets on the drugs, you make sure he's taking his drugs through urine testing. And if he's resistant you know he's risk but if he has good control, he could still then get the therapy. .. And if they still don't meet their goal, then you know [then] by definition, that they're drug-resistant."

Saville suggested a post-market registry with both patients treated with RDN and patients treated with drugs only, including complex analysis with propensity-score matching to compare the outcomes between the two groups.

"That may be [the] best chance to really look long-term at more real-world benefits," he said. "Because it is really hard to figure how this works in the real world with the data we have right now from these randomized trials."

Robert Yeh, a cardiologist and outcomes researcher at Harvard University, argued that the totality of the evidence presented by Medtronic shows there is a patient population that can benefit from RDN and that a postmarket study would be the best way identify those patients. "Making the device available will help the community figure out who those patients are and accelerate treatment of patients in need," he said.