

# Renal Denervation: Where We Stand After the FDA Panels

Experts' thoughts on what defines a clinically meaningful reduction in blood pressure, roles of office-based and ambulatory blood pressure monitoring, ideal candidates for renal denervation and patient preference as a driver for the procedure, options that could meet the FDA's request for more data, and applying a team-based approach to screening and treatment.

With Ajay J. Kirtane, MD, SM; Eric A. Secemsky, MD, MSc, RPVI, FACC, FSCAI, FSVM; and Taisei Kobayashi, MD



**First, what do each of you consider to be a clinically meaningful reduction in blood pressure (BP) in patients with uncontrolled hypertension, whether on multiple medications or not?**

**Dr. Kobayashi:** Previous meta-analyses of large population-based studies have shown that a small decrease of 5 mm Hg has a large projected impact on cardiovascular mortality. Further decreases in BP (ie, 10 mm Hg) have a proportional larger decrease in projected cardiovascular mortality.

**Dr. Secemsky:** I think every persistent point reduction in BP counts. It is on a continuum—we always strive for the greatest reduction we can achieve, but even a 5 mm Hg reduction in systolic BP translates into a half less pill and a meaningful reduction in cardiovascular events.

**Dr. Kirtane:** Remember that a summary estimate of a BP reduction is a “mean of a distribution,” with some patients with more and others with less; this is probably why a 5-mm Hg average reduction in ambulatory BP is likely clinically meaningful.



**What are the current roles of office-based and ambulatory BP monitoring (ABPM), both in and outside of the trial**

**setting? What are your impressions on their best applications?**

**Dr. Kobayashi:** The primary outcome for most renal denervation (RDN) trials has been 24-hour ABPM reduction; however, lowering office systolic BP can be thought of as blunting of the adrenaline response and likely have impact in the long term, although this concept is not yet proven. Thus, I would rely on 24-hour ABPM to assess for efficacy given the trials.

**Dr. Kirtane:** ABPM—while ideal in reducing within-patient variability—is very difficult for patients to do, especially several times. That’s why I personally think the future lies in serial assessments of home BP with Bluetooth/Wi-Fi cuffs. This also potentially allows circumvention of the white coat effect.

**Dr. Secemsky:** I personally think office BP is a more clinically relevant endpoint than ABPM. It is imperative that we confirm true BP control outside the office, but ABPMs are not practical for routine clinical practice currently, as they can be costly with no reimbursement and take resources. I think corroborating an office-based BP using appropriate technique with a home-based BP should be used to meet the clinical demands of practice today.

**? One question the panel considered highly important to the future of RDN is how to precisely determine which patients are most likely to benefit from RDN. Based on the data collected so far, who most likely comprises this population? How can this best be explored and demonstrated via subsequent trials or data collection?**

**Dr. Kirtane:** This is very difficult to assess at present because there don't appear to be clear markers. However, medications also don't have anything close to 100% effectiveness, plus they require adherence.

**Dr. Secemsky:** Very challenging question. Much work has gone into this without a clear answer. Nerve-based interrogation to identify autonomic depressors and pressors did not help create a practical approach, and at best, a heart rate > 70 bpm has shown some signs that patients may be greater responders. I think more critical is first targeting those who need this therapy the most. Patients with previous cardiovascular events, diabetes, and higher baseline BPs all have a lot to gain with this therapy and, with the safety profile, should be highly prioritized for RDN treatment.

**Dr. Kobayashi:** It is currently unknown which factors will mitigate a hyperresponder versus a nonresponder to RDN in a pre hoc fashion. It would be interesting to find an intraprocedural marker that would signify that you've done enough treatments to the area to confer a response; however, no marker has been studied to be stable or utilizable in real time in humans. There are some nuclear markers that may have potential that are being studied; however, these would be analyzed in a post hoc setting and would likely not be able to affect intraprocedural behaviors of the operators.

**? Although considerable work went into the patient preference studies, some members of the panel did not regard them highly. With patient preference likely a key driver for RDN if it is approved in the United States, what are your impressions of the data and of patient preferences regarding an interventional option for their uncontrolled hypertension?**

**Dr. Kobayashi:** Many Americans continue to struggle with control of their BP. I would suspect that RDN may follow similar patterns to other medications or technologies that are being used for weight loss in that there are many other methods for weight loss outside of sur-

gery or GLP1 agonists. However, many Americans prefer and will take a medication to hasten their desired effect. This may ultimately drive many patients to seek out RDN operators when this becomes commercialized.

**Dr. Secemsky:** I think the issue is patient preference studies are hard to design and execute and also challenging to interpret. Patient preference is key. Although these studies shed light on the possible pool of RDN candidates, in reality, we really just need validated shared decision-making tools that are designed to provide all the education on the risks and benefits of RDN therapy that can help the patient make an informed decision.

**Dr. Kirtane:** Patient preference is important when considering a shared decision-making approach. Some patients absolutely don't want to have a procedure; for those patients, RDN likely wouldn't be the best approach. RDN might be better suited for patients who are more interested in device-based therapies.

**? Following up on the previous question, will acceptance in the larger hypertension community take evidence showing reduction in medication, or will reductions in cardiovascular events (while clearly a longer endpoint to track) be viable in your opinion?**

**Dr. Kirtane:** I do think that ultimately outcomes-based studies are necessary. But for now, if RDN can achieve BP reductions in patients who remain hypertensive despite best efforts to control them with conventional means, it should gain acceptance.

**Dr. Secemsky:** Data on hard endpoints will always help a therapy, in particular a device-based treatment, but I also think the general community of clinicians managing hypertension understand the challenge of getting patients to take medications, change their lifestyle, and meet guideline-recommended thresholds. It's not like we are meeting our goals in the management of hypertension; in fact, we're failing quite miserably. So, I think the acceptance of this device will come with some real-world experience. I see it as an adjunct to help make medical therapy more effective and tolerable. Although it would be great to see cardiovascular event reduction, this would take a very large trial and a very long time, and as the FDA noted, BP is a well-validated surrogate endpoint.

**Dr. Kobayashi:** It would be safe to assume that this will be scrutinously studied with hard endpoints given

that all primary outcomes for trials look at reductions in BP alone and projected cardiovascular mortality. However, these other hard outcomes have not been directly measured. It would be interesting to see how RDN changes major adverse cardiovascular or major adverse cardiac and cerebrovascular event rates in the future.



**As a group with unique proximity to the panel proceedings, what are some of the details you feel may have been missed by the general public or those not “in the room,” so to speak?**

**Dr. Kobayashi:** It was a fairly balanced panel and while I disagree with the ultimate decision for the Spyral device (Medtronic), most points were made in a balanced fashion.

**Dr. Secemsky:** My general take is that everyone believed these RDN devices were safe. That was very clear from both panel days. I think the conversations about the trial designs and statistical considerations got nuanced and challenged the flow of the conversation. The bottom line was that there were certainly patients who are going to benefit from this therapy. A large proportion had a 5 mm Hg or greater reduction in BP on either ABPM or office-based BP. I think this got missed a little, especially with the vote. Furthermore, many of those voting had concerns about the label but not the effectiveness of the therapy. This was confusing for everyone.

**Dr. Kirtane:** RDN has flown somewhat under the radar since the publication of SYMPPLICITY HTN-3. I think that many in the public will be surprised to realize that RDN has shown BP reductions in multiple sham-controlled studies. But, that is a good thing because a sham-controlled randomized trial is the highest level of evidence that one can provide from a data standpoint.



**At FDA’s request, the panel deliberated on how best to design a potential post-approval study in this population, but consensus was elusive given the challenges inherent in resistant hypertension as demonstrated in trial experiences to date. What are your thoughts on creative options to meet the demand for subsequent data, possibly postapproval, in a practical fashion?**

**Dr. Secemsky:** This is a major challenge if the goal is to continue to evaluate efficacy after approval. Safety is much easier to assess in postmarket registries and studies. But this field has been so dependent on sham-

controlled trials that it is hard to imagine any nonrandomized trial confirming efficacy. I think that the market will help determine the efficacy of RDN. If patients are not getting BP reductions in practice, no one is going to refer or want to perform the procedure. So, we need to get comfortable with single-arm registry studies, like those proposed to the FDA, that diversify the patient population and follow longitudinal outcomes.

**Dr. Kirtane:** I think that more data are always a good thing. It would be very useful to generate longer-term longitudinal data across a broad group of patients to demonstrate further efficacy of this technology.

**Dr. Kobayashi:** Once the Centers for Medicare & Medicaid Services has designated a CPT code for the procedure, larger national databases can be used to look into reductions of various different downstream deleterious effects of hypertension, including myocardial infarction, stroke, and aortic dissections. Furthermore, the national inpatient database can be interrogated to look at reductions in hospital admissions for hypertension urgency/emergency in “high-risk” patients or “frequent utilizers.”



**Looking ahead, if the FDA approves RDN, what will be the hallmarks of facilities and teams best suited to providing this procedure?**

**Dr. Kirtane:** I hope that multidisciplinary hypertension teams and centers will lead the way in this endeavor. It’s very important to apply this technology to the right patients.

**Dr. Kobayashi:** Most RDN centers will mimic the setup for transcatheter aortic valve repair in that there will be a multidisciplinary team that approaches the patient, provides the appropriate workup and screening, and then, when ready, perform RDN. Furthermore, the same team will need to provide post-RDN care as well.

**Dr. Secemsky:** I feel strongly that no one person can run an RDN program. An interventionalist needs a noninvasive partner and vice versa. I think centers that were in the trials or those with functioning hypertension centers and dedicated endovascular specialists will be most positioned to adopt this technology first.

The composition of this team, including the operator, will vary based on the availability of physician specialties, including a noninvasive hypertension lead, an RDN operator, and support staff. ■

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