
*Michael Böhm*

# Is renal denervation dead or alive?

Hypertension is a medical problem that, for many people, is difficult to control with medication and lifestyle measures. Renal denervation (RDN), the process of disrupting the nerves surrounding the renal artery (for example, by applying radiofrequency energy), has been approved for the treatment of uncontrolled hypertension and offers another treatment strategy for patients. However, in the SYMPLICITY HTN-3 trial, although a reduction in blood pressure was seen following RDN, and the primary safety endpoint was met, a significant efficacy benefit for RDN over a sham procedure was not observed.

*Confluence* spoke with Professor Michael Böhm, Director of the Clinic for Internal Medicine and Chief of Cardiology at the University of the Saarland, Homburg/Saar, Germany, to discuss the limitations of the trial, what the trial has taught us about the uncontrolled hypertension population, and how this has informed the design of the next generation of RDN trials that are now underway.

## What treatment options are available to patients with medication-resistant hypertension?

**Professor Michael Böhm (MB):** Even before any medication is prescribed, the first steps that are usually taken for hypertensive patients are general lifestyle modifications, like increased exercise, reduction in alcohol and salt consumption, as well as adjustment of the other risk factors, and this usually brings blood pressure down a little, assuming the patient is willing to comply. However, in patients whose hypertension is poorly controlled on medication, these measures have usually already been tried. Patients with medication-resistant hypertension have usually also tried several drugs or combinations of drugs to control their high blood pressure. This lack of treatment options for these patients led to the development of interventional techniques. Among them is renal denervation (RDN), where the largest investigation of this technique in the world is currently taking place.

## Can you outline some of the research into RDN that has been carried out to date?

**MB:** The first attempt at RDN for medication-resistant hypertension was the SYMPLICITY programme with the HTN-1[1] and HTN-2[2] trials, followed by the more recent HTN-3.[3] HTN-3 was not successful for a number of reasons: there were concerns over the impact of changes made to blood pressure medication during the follow-up period of the study, and potentially suboptimal procedures. Moreover, these patients were also very late in their medical journey, so they were very truly resistant hypertension patients that may not have been the most amenable to RDN therapy.

The problem in the SYMPLICITY HTN-3 trial was not that blood pressure did not go down – it went down – but there was also a very strong effect in the sham procedure control group, which meant the difference in effect between the treatment groups was not significant. There was, however, a wide variation in blood pressure among patients who had the sham procedure. Our current thinking is that these patients were initially controlled on very high doses of medication, but eventually became non-adherent after the procedure. This resulted in a small difference in the initial study but could explain the limited long-term blood pressure reduction in the sham group. The data from the follow-up study was presented at the 2014 European Society of Cardiology congress. Patients who had RDN maintained low blood pressure values, while in those going out of the trial and maybe off medication, because their adherence is so poor, their blood pressure started to increase again.

## Is there anything that you can do in future trials to improve medication adherence?

**MB:** Yes, there is a new trial design that is being used for the new RDN clinical trials, referred to as the SPYRAL HTN Global Clinical programme. There will be two initial trials in the SYPRAL programme. In one study, patients will be taken off all of their current medication, so adherence will not be an issue (SPYRAL HTN OFF-MED). In the second study, patients will stop all pre-trial medication and instead receive three drug classes; a thiazide diuretic, a calcium antagonist, and an ACE inhibitor or angiotensin receptor antagonist (SPYRAL HTN ON-MED). These drug classes can either be in the form of a single combination pill, or separate medications. Having these two trials with different medication regimens will help us to better understand the impact of RDN on blood pressure, by ensuring that the pharmaceutical management of all patients is clearly defined.

An added benefit of using the single combination pill therapy is that we think we can achieve optimal adherence. Furthermore, all patients will undergo urinary screening to test for treatment adherence or to check if there are decreases in medication, which is another potential challenge in the on-medication arm. Patients are told that we are going to monitor whether they take their medication or not, so this may also help to improve adherence.

These treatment adherence data will help us to figure out what happens to those patients who are not compliant. However, as we use an intention-to-treat design, these patients will remain in the primary endpoint analysis. We hope that the measures we have taken – having a very simplified treatment strategy, and also telling patients that we will test whether they are taking their medication – will result in much better adherence than in the previous trials.

## What lessons were learned from the SYMPLICITY HTN trials, and how have these influenced the design of the SPYRAL trials?

**MB:** After HTN-3, we reinvestigated the technical and physiological aspects of the technology, and conducted several new animal studies to answer some of the questions generated by the HTN-3 results. We found that in the proximal renal artery (close to the aorta), the nerves are quite far away from the lumen and are therefore less susceptible to radiofrequency ablation, with perhaps only

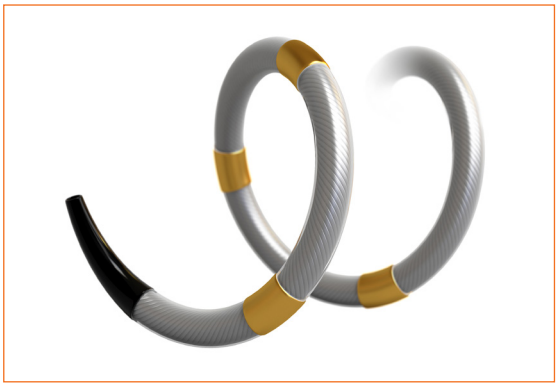

fig. 1
Symplicity Spyral™ catheter

10–20% of nerves affected. Animal research identified that by ablating in the distal portion of the main stem of the renal artery, and also the renal artery branches lying beyond the main vessel, there was a greater reduction in norepinephrine in study animals, and also the scatter and the deviation of the individual norepinephrine reduction was reduced.

In HTN-3 we employed a mono-electrode device, the Symplicity Flex™ catheter system, which is positioned by sight in order to achieve the circumferential ablation. It turned out that only a small proportion of patients in HTN-3 had four-quadrant ablation.[4] We also found a differential blood pressure response between those with and without an evenly-distributed four-quadrant ablation, with a greater reduction in systolic blood pressure in the former. In the SPYRAL HTN programme, we will be using a new technology, the Symplicity Spyral™ catheter (figure 1), which takes on a helical conformation within the artery, and has four electrodes that automatically position evenly around the lumen of the artery, providing a greater potential to achieve full circumferential ablation.

There was also some evidence of severe under-treatment in HTN-3, and a *post hoc* analysis found that blood pressure response was greater after six to eight ablations per vessel, compared to two or three ablations.[4] The approach we are now investigating is to perform more intensive ablation, beyond the main artery, and in some patients we can now do this with the Symplicity Spyral™ device in the branches, achieving up to 40 ablation points per patient, so this is really a strong difference.

In the new trial, the combination of the Symplicity Spyral™ device improving circumferential ablation and including treatment of the periphery may help reduce sympathetic activity further than was achieved in HTN-3.

Another difference is that we are moving a little bit away from the most severe forms of hypertension and towards forms of hypertension that might be easier to treat. According to the literature, patients with resistant hypertension who are not controlled on three or more drugs, including a diuretic at appropriate doses, represent 9–15% of all cases. By contrast, patients who are not controlled on one to three drugs represent the vast majority, maybe 80%, of uncontrolled patients, so these are the patients you are more likely to see in the clinic. There is also one arm in these trial programmes looking at off-medication patients, and I think the study of the possibility of treating patients with RDN as an alternative to medical treatments is the direction in which the new data may direct us.

The last point I would like to make is that operator experience is important. In HTN-3, 31% of operators carried out one procedure during the trial, and over half carried out no more than two.[4] In the SPYRAL HTN programme we will use more experienced global investigators. This is one reason for expanding the trial to other countries, where more procedures have been done before.

## Are there any differences between the SYMPLICITY and SYPRAL clinical trial programmes in terms of the endpoints that you are using?

**MB:** I think we have had to rethink our endpoints in hypertension trials in general. Office blood pressure has been used historically due to the fact that for endpoint reduction, you need huge numbers to see differences in stroke, myocardial infarction or cardiovascular death. In SPYRAL HTN, we use the gold standard of ambulatory blood pressure monitoring (ABPM), in addition to office blood pressure, which was used to assess outcomes in HTN-3. As ABPM is measured over a 24-hour period, it is not as susceptible to regression to the mean or placebo effects as office blood pressure. As mentioned above, the patients in this trial have slightly lower blood pressure than in those in HTN-3, so we are expecting maybe a little bit less of a reduction in blood pressure. Although we will have smaller reductions, we can be more precise and therefore better able to reliably detect true changes in blood pressure, so the use of ABPM is a major difference.

## Do you think that these trials will answer the question as to whether RDN is a clinically viable option?

**MB:** SPYRAL HTN is not the final step, but it is the penultimate step we have to take. On the basis of these two trials, ON and OFF medication, we will perform the power calculation for the pivotal trial, which is expected to be larger and require more patients. If one of these initial trials fails unexpectedly, prior to the pivotal trial, of course we will have to analyse what went wrong, but hopefully that situation will not arise. We have implemented many changes and adaptations to the protocol that we hope will lead to greater efficacy in blood pressure reduction with RDN, but we will have to wait to see the results.

## What levels of blood pressure reduction should we be aiming for and how much clinical impact do smaller blood pressure reductions have?

**MB:** The numbers do not mean anything, because when you look at clinical practice and clinical trials for drug treatments there is only a 4–5 mmHg reduction, but in practice this is higher due to individual variation in technique, the white coat effect and other factors; so in practice everything is greater than in clinical trials.

I would not extrapolate reduction – whether it is 8, 10 or 15 mmHg – to the situation in the clinic. Epidemiologically, a 2 mmHg decrease in systolic blood pressure equates to a 10% reduction in stroke mortality and a 7% reduction in deaths from ischaemic heart disease.[5] Therefore, every mmHg counts, particularly in those patients who are unwilling to take, or non-compliant with medication. These adherence problems do not affect the interventional procedure; once that is done, it is done, and therefore, over time, we hope that there will be a much greater reduction than with any drug therapy we have had before.

## How do you think the results of something like the SPRINT trial are going to impact thinking in terms of treating and managing hypertension?

**MB:** SPRINT is most interesting, and there are two different points to make.[6] Patients with a systolic blood pressure of ≥130 mmHg were randomised to a target systolic blood pressure of <120 mmHg (intensive) or <140 mmHg (standard), and rates of clinical events, including myocardial infarction,

other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes were compared between the two groups. Intensive treatment reduced the risk of experiencing the composite endpoint of cardiovascular outcomes (listed above) by 25%, which is interesting, and I think there will be a discussion on whether we change the target values in the published guidelines. If the target value is reduced to 120 mmHg, this obviously creates a much larger population that requires strict blood pressure control. This probably equates to somewhere between four to six times as many patients as those that are classified as uncontrolled under current guidelines.

Therefore, patients who start with a blood pressure of 180 mmHg and manage to reduce this to 140 mmHg with drug treatment before side effects lead to discontinuation of drugs, could represent a population in whom interventional techniques are of particular interest. We are moving away from the very late stage patients, towards patients who are really present in the clinic; patients who take three drugs and when they require more than this, they do not take them because they have so many side effects. This is the real-life population, who are present in our society of millions of people, who will suffer from stroke after a couple of years.

## What role do you see RDN playing in hypertension management? Do you see it becoming a mainstay, or is it going to be for selected patients only?

**MB:** First of all, we have to verify that the therapy is effective. If it is effective, we have to figure out which patients are benefiting the most from a blood pressure effect. If it is effective and we understand which patients to use it for, it will become a mainstay in reducing blood pressure.

The next step, which in my view is even more interesting, is to look at high-risk patients with maybe borderline blood pressure or uncontrolled blood pressure who have already had an event. These patients are at particularly high risk of another event. If we can obtain experimental data showing that we can prevent heart failure or atherosclerosis or atrial fibrillation, or even that we might be able to address some forms of ventricular arrhythmias, then we have a mainstay treatment, not only for hypertension but in cardiovascular therapies in general.

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REFERENCES:

1. Wang Y. *Lancet* 2014;383(9932):1885.
2. Esler MD, et al. *Eur Heart J* 2014;35(26):1752–9.
3. Bhatt DL, et al. *N Engl J Med* 2014;370(15):1393–401.
4. Kandzari DE, et al. *Eur Heart J* 2015;36(4): 219–27.
5. Lewington S, et al. *Lancet* 2002;360(9349):1903–13.
6. Wright JT Jr, et al. *N Engl J Med* 2015;373(22):2103–16.

DISCLOSURES: MB has a consulting relationship with Medtronic, Bayer, Novartis and SERVIER, and is a Global Principal Investigator of the SPYRAL HTN Global Clinical Trial Programme.