David Kandzari

Perspectives on the latest SYMPLICITY data: HTN-3 trial results

At the American College of Cardiology (ACC) 2014 Scientific Sessions (29–31 March, Washington, DC, USA), it was reported that the SYMPLICITY Hypertension-3 (HTN-3) renal denervation trial had failed to achieve its primary efficacy endpoint. However, the trial also demonstrated the excellent safety profile of this therapy. *Confluence* spoke with Dr David Kandzari, Chief Scientific Officer and Director of Interventional Cardiology at Piedmont Heart Institute, Atlanta, GA, USA, and one of the Primary Investigators on HTN-3 about the trial, its results and the future of renal denervation.

Could you give us some background on the SYMPLICITY HTN-3 study?

The SYMPLICITY HTN-3 study is not only the largest, but also the first, controlled clinical trial in renal denervation therapy to be both randomized and blinded. This study falls against the background of numerous single-arm studies, as well as one randomized but unblinded clinical trial of smaller size, which have consistently demonstrated significant reductions in both systolic blood pressure measured in the clinic – so-called "office" blood pressure – as well as ambulatory blood pressure between pre-treatment and 6-month values, if not longer. Those previous studies have also demonstrated the durability of renal denervation therapy now through 3 years of follow-up and beyond for selected patients.[1–5]

There remains, however, a need to study more carefully the role of renal denervation therapy against a background of maximized or optimal medical therapy for patients who are identified with treatment-resistant hypertension. To that purpose, the SYMPLICITY HTN-3 study randomized 535 patients in a 2:1 fashion to either renal denervation therapy or control therapy. Patients were deemed eligible for enrollment by having an office systolic blood pressure of at least 160 mm/Hg on at least two separate clinic visits. In addition, their 24-hour ambulatory blood pressure must have been at least 135 mm/Hg. Finally, patients must have been on at least three maximally dosed or maximally tolerated medications according to hypertension guidelines and one of these therapies must have been a diuretic agent.

Patients were blinded through a masked blinding process or sham controlled process such that, following enrollment and determination of eligibility for randomization, randomization occurred only after the patients were blinded to their treatment status following renal angiography. All randomized patients (treatment and control groups) were managed identically following renal angiography to maintain blinding.

Of the 535 patients enrolled, a total of 364 patients underwent renal denervation, while 171 patients were randomized to the sham control group. At the 6-month follow-up, 350 patients (96%) were available for follow-up in the renal denervation group and 169 patients (99%) were available for follow-up in the control group. Importantly, in both groups, patients were instructed per protocol to maintain their same medications, with the allowance of medication changes only for certain exceptions. The role of this was to maintain the background of medical therapy so that we could more truly discern the treatment effect of renal denervation.

Is it fair to say that all the patients were treatment resistant?

That is right. By 'treatment resistance', we mean that they are taking medical therapy and yet we cannot get their blood pressure down to achievable goals. While patients may have been on multiple medications, if we were to withdraw those medications perhaps their blood pressure would go even higher and their risk of stroke would accordingly be even greater, along with other complications of hypertension.

This study truly identified a treatment-resistant patient population but unlike the Hypertension-2 study, it required patients not only to have a blood pressure greater than 160 mm/Hg, but it also an ambulatory blood pressure over 24 hours of at least 135 mm/Hg.

When we look at the patient demographics, the average office blood pressure for the total study population was approximately 180 mm/Hg and the 24-hour mean ambulatory blood pressure was approximately 160 mm/Hg. This represented quite a treatment-resistant, hypertensive patient population.

Can you describe the demographics for this patient population?

Yes, this is important to consider especially in the context of previous studies. Some of the important issues were that, unlike previous studies, this study was performed in the United States in approximately 80 centres and about 25% of the patient population were African-American in ethnic origin. There was also a very high prevalence of diabetes – about 45%. Consistent with previous studies, the average number of anti-hypertensive medications was quite high, with the average number being about five medications per patient. Again, along with the blood pressure values that I shared, that represents a very treatment-resistant patient population.

Could you give us an overview of the results from the trial?

The study had two primary endpoints. One was a safety endpoint, which was a composite of major adverse events that included bleeding and vascular complications. The major adverse event rate in the study was compared against a performance goal, which was an estimate derived from previous studies involving the treatment of renal artery stenosis with stenting. It also had a factor within it of the likelihood for patients coming back with hypertensive urgencies or emergencies. The major adverse event rate not only represented procedural complications, but also the possibility that patients could have hypertensive emergencies during the follow-up period as well. However, this event rate, for which the estimated goal was 9.8%, was in fact much lower at only 1.4%. This really underscores the consistency across previous clinical trials of the safety of this procedure.

The second component of the primary endpoint was one of efficacy. It is important to note that, in contrast to previous studies of renal denervation typically reporting the difference and relative significance between baseline blood pressure and 6-month follow-up blood pressure, HTN-3 instead compared the difference in blood pressure at 6 months between the renal denervation group and the sham control group. The pre-specified definition for superiority was that the difference must have exceeded roughly 5 mm/Hg. When we incorporate some statistical modelling into that and assumptions around confidence intervals, put simply, the difference required between the two groups was probably required to be about 10 mm/Hg.

In HTN-3, among patients receiving renal denervation therapy, the reduction in systolic office blood pressure at 6 months was about 14 mm/Hg, while in the sham control group it was 12 mm/Hg: specifically, 14.1 mm/Hg in the renal denervation group and 11.7 mm/Hg in the sham group. Therefore, the difference was less than expected – it was a difference of only 2.4 mm/Hg and therefore the study did not achieve its statistical significance in its pre-specified primary endpoint.

It should be noted, however, that the pharmaceutical industry spends billions of dollars each year to devise pharmaceutical agents that are intended to reduce the blood pressure by 3–5 mm/Hg. In this context, the reductions observed in this trial in both groups may be clinically significant; however, the renal denervation aspect of the procedure did not show a significant difference from the control group itself.

An important secondary endpoint of the trial was 24-hour ambulatory blood pressure at 6 months. These differences are generally expected to be less than the office systolic blood pressure measurements and indeed, in this trial, the renal denervation group reduction in ambulatory blood pressure at 6 months was 6.8 mm/Hg. It was 4.8 mm/Hg in the sham group. This difference also did not achieve its intended superiority margin and therefore was also not significant.

What explanations might there be for these results?

Since the announcement of the overall results of this trial, there has been expectedly great speculation regarding why the results of this study

might be discordant with previous trial results and a large body of clinical experience, as exemplified by the Global SYMPLICITY Registry (GSR), which was also presented at ACC 2014.

Some of these reasons for differences have been suspected to be related to the trial design; to the study population; to opportunities for observer and patient biases; to the Hawthorne effect (whereby participants alter their behaviour as a result of being part of a study); and also to perhaps the procedure itself.

This study, in contrast to previous studies, was not only the largest but it was the only randomized, sham-controlled, blinded clinical trial. Furthermore, HTN-3 also enrolled a more esoteric group of patients with treatment-resistant hypertension than previous trials. The protocol mandated that doses of medications must be maximally adjusted, creating an artificial scenario not commonly found in clinical practice. In addition, patients were enrolled on the basis of ambulatory blood pressure, rather than office blood pressure alone. Furthermore, the study enrolled a high prevalence of patients with African-American ethnicity. It is interesting to note that in a subgroup analysis, while both African-American and non-African-American patients responded similarly to renal denervation; African-American patients derived a considerably greater benefit in the control arm.

It is important to recognize, however, that among the non-African-American patients, although the reduction in systolic blood pressure with renal denervation was significant, the overall reduction in blood pressure was still less than 10 mm/Hg. While we may see some signals in sub-group analyses with regard to younger patients, non-African-American patients, or patients with preserved renal function deriving a potential significant reduction in blood pressure, the relative blood pressure reductions remain modest. It is important to note that these remain exploratory analyses in the context of an overall negative study.

In addition to differences in study population, it has also been supposed that perhaps patients may have an opportunity to behave differently in clinical trials, the so-called Hawthorne effect. While the observation of simply a blood pressure reduction in the control group was not surprising (as such effects occur in many trials across multiple therapeutic areas), the degree to which this occurred was.

As an example, the recent CORAL study[6], which randomized patients to either renal stenting or medical therapy, was not blinded and it was not therefore sham-controlled but, interestingly, once patients were enrolled in the study in both cohorts, the blood pressure was significantly reduced by roughly 13 mm/Hg. That reduction was sustained in both cohorts during 3 years of follow-up. This highlights the potential impact of the Hawthorne effect; that patients may somehow behave differently in the context of participating in a clinical trial than they might otherwise. In particular, this may be related to changes in dietary or lifestyle habits, but it may also reflect a greater compliance with medications, too. While we assessed the medical compliance in the HTN-3 trial, we only assessed it in the early phase of enrollment and towards the later phase of the 6-months primary endpoint ascertainment. We assayed it according to patient reports, rather than with other more sophisticated methods, such as drug monitoring, pill counts or even urinary samples for drugs as well.

I think that in future, trials will have to reconsider how to mitigate the occurrence of a placebo or Hawthorne effect. Part of this may be related to medical compliance and there has been a great deal of discussion for future designs of clinical trials about how we may more carefully monitor medical adherence. Perhaps having a longer run-in period, in which we allow many of these differences to settle, so to speak, prior to active randomization to control or renal denervation might be an option.

A great deal of speculation has also been raised regarding potential differences in the procedure, or even in the catheter itself. Earlier studies in renal denervation had used a slightly different version of the catheter compared with that used in the HTN-3 study. However, subsequent analyses have probably dismissed that specific issue as a significant contributor.

Another confounding factor might be differences in how the procedure is performed – this is an area of ongoing interest and study. In SYMPLICITY HTN-3, 86 of 88 sites had no prior experience with renal denervation procedure, despite being experienced cardiologists. However, in the SYMPLICITY Hypertension-2 (HTN-2) trial, a study which demonstrated a significant reduction in blood pressure, 50% of centres had prior

experience with renal denervation. At first glance, there appears to be a high prevalence in both studies of operators who are unfamiliar with the procedure. However, in the HTN-3 study, there were a far greater number of operators who performed two or fewer procedures, and so therefore their total experience in performing renal denervation was more limited than operators in previous studies. There is currently investigation into whether more ablations in the vessel was associated with a greater reduction in blood pressure in the HTN-3 study. We need to truly revisit the basic science of this therapy to better understand the translation of the device therapy to the pathophysiology, to understand whether a difference in technique or method might somehow have influenced the results. Again, this remains very much speculative and by no means could be considered to be the singular issue that led to the decline and failure to meet the primary efficacy endpoint.

How will patients enrolled in HTN-3 be followed up?

Patients in HTN-3 will be followed for 5 years. At the moment we still have quite limited follow-up, even at 1 year in the trial.

I believe it is essential to follow these patients very carefully over the long term. Such long-term follow-up of these patients will allow us to investigate whether there is any difference in outcome once patients are unblinded to their treatment. One might expect that after patients have been made aware of their treatment status at the 6-month follow-up visit that those patients who were assigned to the control group and did not receive renal denervation may begin to return to their more normal or more usual lifestyle habits. This may also include differences in medical compliance. One might expect if these patients were to relapse to bad habits that their blood pressure would perhaps return upwards towards higher levels, whereas, if renal denervation therapy is effective, these patients may have a sustained reduction in blood pressure. Importantly, however, this remains to be seen.

What further studies are being carried out to investigate the factors that may have led to the failure of the trial?

We are more intensively examining the procedure itself, in the context of the SYMPLICITY HTN-3 trial results. We will also make some comparisons with the Global SYMPLICITY Registry. In addition, pre-clinical studies will more carefully examine the dose/response relationship to renal denervation and reductions in, for example, norepinephrine levels as well.

Our view is that, with regard to the need to revisit the basic science of this therapy, we should be reminded that, to date, there is no consistent predictor of a treatment response to renal denervation in human patients, other than having simply a very high blood pressure at baseline. Secondly, this is a procedure for which, unlike most if not all other device therapies, we have no procedural biomarker or surrogate of procedural efficacy. This means that we do not know when we perform renal denervation, whether we are effectively achieving complete or perhaps incomplete denervation of the renal efferent and afferent nodes. Further investigation of these factors will be valuable.

The HTN-3 trial was carried out in the United States alone, whereas the previous trials (HTN-1 and HTN-2) had international patient populations. Could this have had an impact on the outcomes seen in the HTN-3 trial?

While the issue of geographical differences has been raised, it is unlikely that these differences contributed to the disparate results of this trial versus others, except that in the sense that this trial involved a higher prevalence of African-American patients who seemed to derive a differential non-response to non-African-American patients. I don't believe that any geographical differences in where the studies were conducted played a role – particularly when we realise that this study, by the criteria we discussed, addressed a very treatment-resistant, high-risk, patient population.

One difference, however, is that in the United States, most of the patients came from cardiovascular programmes that were not necessarily specialist hypertension centres, unlike in the European, Australia and New Zealand experiences.

How do you reconcile these HTN-3 data with that 'real-world' experience from the Global SYMPLICITY Registry?

To begin with, the GSR once again highlights the safety of this procedure. In the first 1,000 patients treated with this technology, included in the

registry, the event rate of adverse safety events is extremely low and consistent with the HTN-3 study. First of all, that is a very reassuring and consistent message.

Despite the limitations of comparing the GSR, a single-arm, non-randomized experience, with the randomized, blinded controlled HTN-3 study, the reduction in blood pressure is slightly larger at 6 months than in the GSR. However, it is important to note that this represents a much broader, less selective patient population than those patients included in clinical trials with more rigorous enrollment criteria. For example, only approximately one-third of the patients in the GSR had the blood pressure measurements that were required of the HTN-3 study. Nevertheless, when we look at the GSR for patients who would have fulfilled similar blood pressure criteria as the HTN-3 study, these patients achieved quite remarkable reductions in office blood pressure at 6 months. Their reductions were about 20 mm/Hg and, again, keep that in mind in the context of the 14 mm/Hg for patients who received renal denervation in the HTN-3 study.

Due to the registry nature of the study it is, however, difficult to account for the potential for a placebo effect, or what the placebo effect might contribute to it. It is also important to note the differences in the population and we have talked about African-Americans, who were enrolled very infrequent in the GSR. There were also differences in the intensity of anti-hypertensive therapy.

What message do you have for the physicians using renal denervation in their clinical practice?

We recognise that there is still a great deal of enthusiasm for renal denervation globally, given that these patients often represent what might be considered a 'no alternative' patient population. That said, I think there will be greater caution and reservation in patient selection for renal denervation in those regions where the therapy is commercially available. However, when it is performed I think we can clearly reassure patients regarding the safety of the procedure itself.

Perhaps the most important point is that, when renal denervation is to be performed in clinical practice, these patients are subject to careful and continued follow-up with regard to the safety and efficacy of this treatment.

Address for correspondence
David E. Kandzari, MD, FACC, FSCAI
Director, Interventional Cardiology and Chief Scientific Officer,
Piedmont Heart Institute,
Atlanta, GA 30309

Tel: +404 605 5526

david.kandzari@piedmont.org

REFERENCES:

1. Krum H, et al. *Lancet* 2009;373:1275-81.
2. Symplicity HTN-2 Investigators, et al. *Lancet* 2010;376:1903-9.
3. Symplicity HTN-1 Investigators. *Hypertension* 2011;57:911-7.
4. Krum H, et al. *J Am Coll Cardiol* 2012;60(17_S).
5. Mahfoud F. Early results following renal denervation for treatment of hypertension in a real world population: the global SYMPLICITY registry. Presentation at EuroPCR Scientific Meeting 2013.
6. Cooper CJ, et al. *New Engl J Med* 2014;370:13-22.

DISCLOSURES: DK has received research and grant support, and consulting honoraria from Medtronic, Inc., and Boston Scientific.