Justin Davies

Lessons learned from HTN-3: pharmacological non-adherence in hypertension and the potential of Spyral™

Renal denervation has recently been in the spotlight following the failure of the HTN-3 trial to meet its primary endpoint. *Confluence* spoke to Dr Justin Davies, Senior Research Fellow and Consultant Cardiologist, Imperial College London, to discuss some of the lessons learned from HTN-3, including the role of pharmacological non-adherence in hypertension. We also spoke about how future trials may be conducted and the potential of the new Spyral™ catheter.

How do we define non-adherence?

Dr Justin Davies (JD): I suppose that the clearest definition of non-adherence is patients being prescribed tablets or drugs, which they do not take for one reason or another. All of us are culpable of this and, for most of us, it is probably in the form of antibiotics. To take some drugs just for a few days is obviously quite an easy thing to do, yet we still struggle. So when you are asking patients to take multiple antihypertensive drugs for 20 or 30 years, it is very easy to see and understand if they become less adherent than would be desirable.

What factors can impact adherence?

JD: Larger numbers of drugs or increasing frequency of administration are two key factors. Furthermore, if people have significant comorbidity and other conditions that exist simultaneously, then they may often have side effects from those conditions, which they may put down to their drugs, and which, in turn, can often diminish the likelihood that they will continue to take their medication.

Side effects are also a problem. Ultimately no one likes taking drugs – especially if patients consider that they make them feel worse. With regard to antihypertensives, two of the main classes of drugs are beta-blockers and diuretics. People actually avoid taking diuretics before going out, to avoid unexpectedly needing the bathroom, whereas beta-blockers often make them feel lethargic and slow, and can also negatively affect libido.

Do you think that patients find it hard to see direct benefits from their treatment? Do you think that they feel they are taking the tablets for no good reason?

JD: This is entirely correct. One of the clearest illustrations you can see is in people with heart failure, who are prescribed and take many of the same tablets. However, in heart failure, if you stop taking the tablets, you become very breathless and very sick. Therefore the likelihood of patients taking medication with heart failure is much higher. I stress these are many of the same drugs that would be prescribed in hypertension, albeit at different doses. However, due to symptomatic improvement, the heart failure patients are much 'keener' to adhere to therapy.

Angina is another case, again managed with many of the same drugs. If people have definite chest-pain symptoms and breathlessness, they will have a higher likelihood of taking the drugs. As you say correctly, in both of these scenarios one of the main reasons for increased compliance is that patients feel the benefit from the drugs whereas they cannot see an immediate advantage in blood pressure reduction. It really takes quite an in-depth analysis to understand the long-term risks and potential benefits in cardio- and neurovascular adverse events that a fall in blood pressure has. These may only affect you in 10 or 15 years' time, reducing the chance of a stroke, but actually taking that on board when you are younger is often quite difficult.

What impact does non-adherence have? For example, is it more impactful in patients with already high blood pressure; are patients with low blood pressure less at risk of suffering ill effects from non-adherence?

JD: The higher the blood pressure, the worse the impact of non-adherence, as higher blood pressures are associated with a marked risk of stroke, cardiovascular disease, coronary disease, renal disease and eye disease. Moreover, the longer you leave patient with high blood pressure, the worse these complications can be. For instance, consider a patient who is early-middle-aged and has moderate hypertension, even though their blood pressure may not be as bad as that of somebody who is 70 or 80 with higher blood pressure. If you leave those levels of more moderate hypertension for many years then potentially that patient may actually do worse in the long run. We know that untreated hypertension is a very bad thing to have with regard to multiple systems being affected. Of course, we also know the advantageous effect of treating blood pressure well. You can see, in blood pressure trials, that if you can effectively manage blood pressure, it is possible to markedly reduce the chances of stroke and cardiovascular disease.

What is the estimated prevalence of non-adherence?

JD: It is very common. To date, most studies that have looked at those people who are said to be truly resistant hypertensive patients for whom the drugs do not work. However, when you actually give them the tablets and you observe the blood pressure, it actually turns out that only about 15% of the people are truly drug-resistant, while many others are resistant to taking their medication more than anything else! While you can certainly sympathize, this is certainly a major problem that is being increasingly recognized. Essentially, we leave a portion of our population with less adequately well-controlled blood pressure than is desirable.

Does that link in to your 2-year patient blood pressure diary (recently presented at TCT, 2014)? What do those results demonstrate for us?

JD: Blood pressure diaries are important because, frequently, patients are managed by their primary care physicians or a specialist in the clinic in hospital and subsequently have a period of time when their blood pressure is well-controlled. However, with the pressures of the modern healthcare system, we know that often these patients are discharged back into the community, where often their blood pressure relapses. Diaries provide a longer-term snapshot of pressures at home. This provides a really good idea of what the patient's blood pressure is doing over a prolonged period of time.

Often when you see longer-term trends of blood pressure elevation over many years with troughs where patients seek additional medical care, where perhaps they are referred to specialist clinics. However, over time, as they are outside of routine healthcare review, their blood pressure slowly starts to rise and goes back to the baseline value of where it was before.

Constant reinforcement is therefore needed for patients to get them to take their medication. I can sympathize with them, because taking four or five pills a day for the rest of your life – however much of an advantage it may or may not have for you with regard to your cardiovascular risk in 15 or 20 years' time – it is still a big commitment to ask of anyone. You can understand why patients find it is easy to slip out of the habit of taking their medication.

How can we use such long-term data in clinical practice to help patients to understand the benefits of taking their medicine?

JD: Education plays a crucial part in encouraging patients to take their medications, training patients in terms of particular thresholds to look at regarding their blood pressure. However, a more dynamic and interactive process with primary care physicians, to try to gain better blood pressure control, is also essential. Healthcare professionals

are reliant on the willingness of patient to engage in their own healthcare. However, often, due to work and social commitments, it can be very difficult.

If we were to use the same policy [of inadequate control] with immunization, I am sure that infectious disease would be rife around the world. This is because if you rely on people to self-administer, even though they know these diseases are potentially extremely dangerous, they just don't do it. That is why drugs such as vaccines are so highly effective, because essentially they go into the system and then you forget about them and your body takes care of the rest: essentially, after you have been successfully vaccinated as a child the effects are still working throughout the course of your life.

Renal denervation has the potential to offer a long-term solution to hypertension. While earlier trials appeared to show good efficacy, the recent results from the HTN-3 study were not as strong as expected. Do you think non-adherence had an impact on the results of HTN-3?

JD: We know that the basic science suggests that renal denervation works. However, designing a study is very complex and HTN-3 has exposed huge layers of complexity in study design. For example, factors such as drug adherence or changes to blood pressure following during the course of the study can make a huge difference to the overall results. Moreover, you have psychosocial factors coming into play in terms of whether patients are receiving medication for the first time, or have been on long-term medication. Many of these disparities have been overcome in big blockbuster drug trials by having tens of thousands of patients in each arm, which irons out such irregularities and powers for an increased variability. However, carrying out that kind of study in a device-based therapy is very challenging, because you cannot physically enrol that many patients due to excessive costs and time.

What HTN-3 has done is to make us realise that we need to step back and see what is working and what is not. We need to try to address the problems that can be addressed – whether they are technical, or population based, or patient adherence, or whether it is other drugs patients have been on. It has drawn a line in the sand, and we need to look very carefully before moving on to the next step in terms of designing a study that is likely to show the efficacy, which has been demonstrated in the animal models.

Do you think that ambulatory blood pressure monitoring might have had an impact on adherence and possibly accounted for some of the differences in results between HTN-2 and HTN-3? How do you think we can overcome adherence issues in future renal denervation trial?

JD: The big difference in those studies is really one of study design. HTN-3 was performed with much more rigour and we should certainly give Medtronic a great deal of credit for the design. The big difference, of course, is the fact that there was a sham control arm and that, more than anything else, was the big differentiator here. Some subsequent studies have shown a more obvious reduction in blood pressure. However, this is due, in part, to some of the factors we have discussed earlier with regard to psychosocial factors and pharmacological adherence, and other factors such as an increasing understanding of the technology and better delivery of the technology.

We have done the first part of a pilot study (the follow-up will take place very soon), which uses a unique model to overcome confounding adherence data. By having a fellow administering the drugs to the patients over 2 days and then making measurements, it is possible to standardize the effects of drug therapy. This means it is possible to assess a better reflection of the effects of renal denervation. An alternative would be stop all the medication, attain stable baseline, perform denervation, and then repeat the baseline measurements after a follow-up period, with all patients off medication.

Under both of these conditions, therefore, both before and after denervation, again with and without the sham arm here, we would have controlled conditions – either with drug, or without drug. This means that the variability of compliance amongst these patients would be removed from these studies as a potential confounder. Essentially, this would mean that the study could then be powered better with a smaller number of patients.

The anatomies of patients has recently been highlighted as playing an important role in the efficacy of renal denervation. What data are there out there?

JD: Again, there is a great deal of very exciting animal data which has come out in the last 6 to 9 months. There was a study presented by Bob Melder from Medtronic at TCT 2014. This used a denervation applied more liberally in both distal branches and the main branch, in both kidneys. This was done using a next-generation multi-array, Spyral™ (Medtronic, Inc., Minnesota, USA) electro-catheter, which has four electrodes and a far shorter denervation time than the original Flex catheter.

The Spyral device is essentially it is a pre-shaped catheter, delivered over a guidewire. When you pull the wire back, the catheter takes on the shape of a corkscrew. The corkscrew expands out to take the shape of the vessel and the electrode makes contact with the vessel wall. It is simple to use: there is a simple graphic user-interface, which shows you the contact between the electrode and the vessel wall, and it enables each of the electrodes to work independently from one another at each of the individual sites.

One of the advantages that this kind of technology gives, is the ability to deliver a great deal of therapy very rapidly. This may be increasingly important if it is possible to demonstrate benefits from distal denervation of branches and the distal main trunk. The calibre of the device is small and it is not bulky, so it can easily fit into these branches and it can be used essentially to go ahead and do the job.

The potential advantage of denervation in more distal renal arteries has been highlighted in recent human cadaver studies. These show that the nerves move more distally along the vessel toward the kidneys, they move closer to the wall. Therefore, the amount of energy needed, and the distance to the nerve is less, and so although the number of nerves is roughly the same (perhaps slightly less distally than proximally), this means that the probability of you breaking this nerve junction is higher.

If you combine such distal denervation with an increased frequency of ablation points, you increase the probability that you will disrupt nerve traffic. The animal data are pretty convincing in that they show that you have a much more reproducible ablation in all of the animals if you denervate distally with a high number of denervations.

To some extent, we can see similar data from the HTN-3 study, but we must caution against this small non pre-specified subanalysis. Here, there was a trend towards having a bigger reduction in blood pressure, when more denervation ablations were performed, and also in patients who had more of the quadrants targeted. This was a secondary subanalysis, for which the study was underpowered, and these data should be treated as a hypothesis-generating exercise. I am encouraged by the animal data which could be used to plan for another study. However, it is too early to make any clear conclusions from the HTN-3 findings with regard to these findings.

Are there any negative or adverse events associated with going to the more distal branches of the kidney?

JD: Not that we have seen. We have done more distal ablations in a series of patients, which, we plan to present next year. To date we have had no acute or early problems at all. Clearly, as with using a guidewire in any vessel – whether it is the heart or the kidney – you need to be respectful of the guidewire position at all times, and ensure that denervation is being performed in vessels with an appropriate diameter. If you follow these rules, and you work respectfully with the kidney anatomy then, to date, the procedure should be very safe to perform.

Looking to future studies, could you give us an overview of what you see as being critical factors that will play a vital role in ensuring that the next trials are as fair and well-balanced as possible?

JD: There are three things:

Firstly, we absolutely need to have the blinded sham control arm. Everyone agrees on that and I suspect it would be a requirement of the FDA.

Secondly, we need to control for drug therapies as effectively as possible. This could be done by

stopping all drugs for a period of time before and after measurements, both before and after denervation. An alternative would be giving directly observed tablets therapy before and after measurements.

Thirdly, it is important to increase the likelihood of gaining the biggest fall in blood pressure but also, most importantly, achieving the smallest variability between patients and reducing the standard deviation. We hope that this new denervation strategy – distal branch denervation and main trunk denervation, bilaterally using a multi-array catheter, such as the Spyral™ catheter – will help us to achieve that.

How much more evidence do you think is required for physicians to be confident in using renal denervation to manage their patients effectively?

JD: There is no doubt about it: the HTN-3 study has shaken the whole field. People who have done a great deal of animal work know that this technique works, and there are many people who have used it widely around the world, who feel that the technique works in their hands. It will take at least one, well-constructed and large successful clinical trial with a sham control arm to empower physicians to want to start using the technique again. If this can be done, then the technique will take off and will fly. Such data can explain the underlying problems in HTN-3 and how they have been resolved. That then opens the door to the next chapter, with the more widespread adoption of denervation.

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