

● Hypertension

Renal denervation: the need for more analysis



Scientific method has overcome fiscal hype over a catheter which could ablate the sympathetic nerves in the renal arteries, thereby reportedly reducing blood pressure where treatment with drugs had failed, writes **Prof Eoin O'Brien**

A remarkable story of the battle between financial forces and scientific reasoning began in January 2011 when Medtronic Inc acquired a privately-held company Ardian Inc for \$800 million (€585 million), with additional cash payments to be related to profit over four years.

The ring in the bracket was the Symplicity Catheter System developed by Ardian. This catheter could ablate the sympathetic nerves in the renal arteries – renal denervation – and thereby (it was claimed) reduce blood pressure that was resistant to treatment with drugs.

The hype

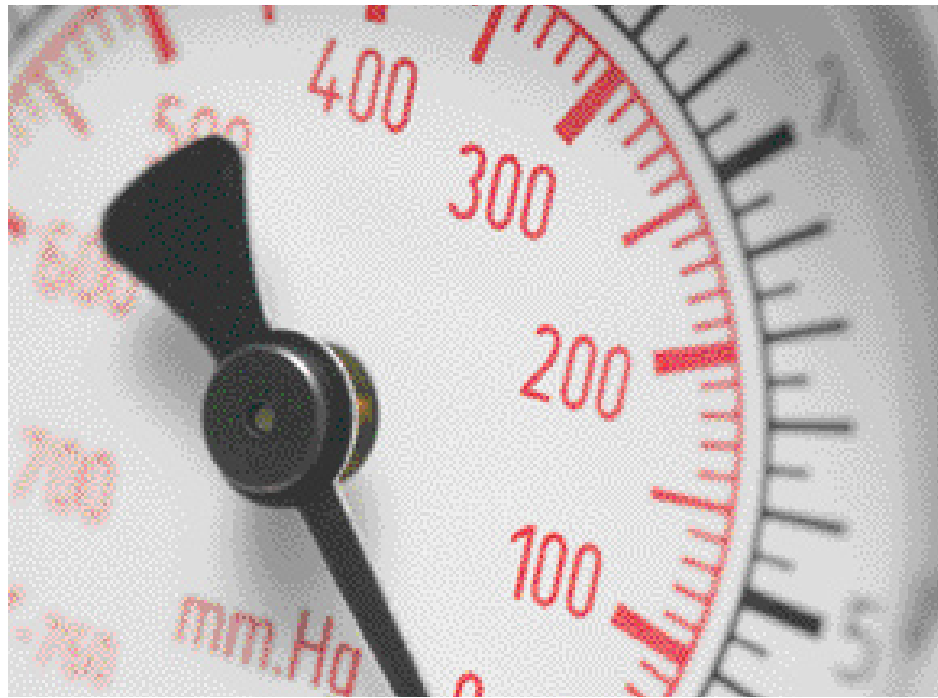
Medtronic immediately embarked on a number of trials. The results of the Symplicity 1 and 2 studies gave what were hailed by many as results so promising that the technique could be applied not only to patients with resistant hypertension, but also even to those with moderate blood pressure elevation.

Renal denervation would not only cure hypertension, it would also improve cardiovascular outcome in other co-morbid conditions such as heart failure, diabetes mellitus, sleep apnea and arrhythmias.

It was anticipated that studies would soon show that the procedure would allow patients to throw away their tablets and be permanently cured of hypertension. And this in spite of the fact that patients who had undergone renal denervation still required medication to control their blood pressure!

With 1.2 billion people suffering from hypertension worldwide, the market potential was so staggering (Medtronic estimated \$3 billion [€2.2 billion] in annual sales) that irritating scientific facts could be easily ignored. It was not long before other manufacturers were producing catheters claiming to have qualities that were superior to the Medtronic Ardian catheter.

These included Boston Scientific (which reportedly acquired the Vessix V2 Renal Denervation System for \$125 million (€91.5 million), plus an additional \$300 million (€219 million) to be paid between 2013 and 2017), St Jude Medical, Dublin-based Covidien, Terumo (Europe) and ReCor Medical. Meanwhile, the pharmaceuti-



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cal industry watched these developments with some degree of anxiety.

The science

But there were scientists who questioned the impetus for a treatment that was based on economic rather than scientific considerations.^{1,2} We wrote: "In our opinion, one cannot countenance a move towards using these techniques in 'mild-to-moderate, non-resistant hypertension' until they have been shown unequivocally to be effective in resistant hypertension."²

Guidelines were drawn up for the procedure and largely ignored as the medical profession became beneficiaries to the largesse accruing from the procedure.^{3,4} Cardiologists, whose income had been declining due to the reduction in coronary artery stenting, suddenly became interested in hypertension and the 'prevalence' of resistant hypertension rose alarmingly in some quarters.

Importantly, the guidelines stipulated that before resistant hypertension could be diagnosed, white coat hypertension had to be excluded using ambulatory blood pressure monitoring (ABPM).

This very logical stipulation was conveniently overlooked by the investigators of most trials, who chose office rather than ABPM as the primary endpoint. Indeed, when data from ABPM were available, they were seldom reported

and, when analysed, did not show significant blood pressure reduction.

The guidelines pointed out that resistant hypertension was difficult to diagnose because compliance to treatment had to be proven (not always easy to do). Moreover, secondary hypertension had to be excluded (for which a rigorous investigational protocol is required).

The guidelines also stipulated that patients for renal denervation should be referred for the procedure by a hypertension specialist, and not be selected for the procedure by the operator.

Finally, and by no means least, cautious scientists warned that the procedure, although apparently safe in the short term, might induce changes in the future due to the more general effects of renal sympathetic denervation and possibly vascular damage to the renal arteries.

Reality and sense

Nonetheless, renal denervation moved on at an alarming pace. It is estimated that some 5,000 renal denervation procedures have been performed worldwide and the procedure is reimbursed in several European countries but not in the US.

Then bad news started to emerge. Firstly, in December 2013 St Jude announced that its pivotal trial, which planned to recruit 590 patients with resistant hypertension, was being stopped after enrolling

fewer than 10 patients, allegedly because of anticipated recruitment difficulties.

However worrisome this might have been, few could have anticipated the bombshell that landed on the news waves with a press release on January 9, 2014, stating that Medtronic's trial on renal denervation for treatment-resistant hypertension, Symplicity HTN-3, had failed to meet its primary efficacy endpoint, which was a reduction of 10mmHg in systolic blood pressure.

This phase 3 study sponsored by Medtronic, which had commenced in September 2011, randomised 535 treatment-resistant hypertension (office systolic blood pressure

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>160mmHg) to intervention with renal denervation and continuance of baseline antihypertensive medications, or to a control non-intervention group, who underwent renal angiography alone and were similarly maintained on baseline antihypertensive medications.

On a positive note, the press release announced that the trial's data safety monitoring board had concluded that the trial met its primary safety endpoint. However, this assurance can be given only for the short period of follow-up, and longer assessment of patients in the study will be required before the procedure can be declared free of adverse effects. In this regard, it is encouraging that follow-up for all patients randomised in the trial will continue as planned out to five years.

Medtronic also announced that enrolment in Symplicity 4, a US study to be conducted for regulatory approval, and in trials being conducted in Japan and India would be suspended.

Without access to the data from Symplicity HTN-3 (they will be presented at a scientific conference in the next few months and published in the peer-reviewed literature in due course) it is only possible to speculate on the results.

The primary endpoint of the study was the change in office systolic blood pressure at six months, while the six-month change in the average 24-hour systolic blood pressure assessed by ABPM was a secondary endpoint.

It may well be that the ABPM results, which were either ignored or badly analysed in previous studies, showed what a number of scientists had been warning, namely that renal denervation would not reduce blood pressure in patients assessed with this technique.^{1,2}

The future of renal denervation

These events are good news for science, although disappointing for patients and their doctors who had hoped for an alternative treatment to drugs for hypertension.

There is, however, a moral to the tale, namely that the outcome of Symplicity HTN-3 was predictable and if hyperbole had not been allowed to overcome sound scientific reasoning, properly designed studies would have prevented the enormous wastage of money, time and effort.

In this regard, the relative ease with which interventional treatments can be brought to the market in some regulatory jurisdictions needs to be aligned with the procedures required for a drug to be approved by regulatory bodies. Not for the first time the FDA has shown that evidence is required before a procedure is approved, and it is unlikely that renal denervation will become an accepted technique in the US in the foreseeable future.

And what of renal denerva-

tion? Is the technique doomed? Not at all. First, we need to see the full results and look forward to the presentation of what was a well-designed and well-conducted trial, and especially to the results of ABPM.

The Symplicity HTN-3 study should be seen as the first scientific step to explore further an interesting and promising technique, to evaluate the different catheters, to examine different procedures, and to analyse not only the blood pressure-lowering effects of renal denervation, but also to assess the other potentially beneficial (and adverse) consequences of sympathetic manipulation.

This will call for carefully designed studies, such as has been proposed by the European Network COordinating research on Renal Denervation (ENCOREd),⁵ and it is to be hoped that the financial might of the renal denervation industry will now be directed towards supporting such endeavours.

Finally, in the light of the Symplicity HTN-3 results, should renal denervation be offered to patients as a therapeutic option? It would be difficult, in my view, to recommend a procedure that has been shown to be ineffective, and it is unlikely that patients would agree to undergo renal denervation if the Symplicity HTN-3 results were presented to them.

However, the full results of the study will need to be evaluated, and no doubt the bodies responsible for guidelines on the technique will make recommendations in due course.

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