Renal nerve ablation

Where are we today? Discussed by Giuseppe Mancia from Italy

Few other cardiovascular research areas have suffered from ups and downs more than the use of renal denervation for antihypertensive treatment. The starting step was the recognition that, as far as the blood pressure (BP) lowering potential is concerned, renal denervation has a convincing rationale because:

(1) renal nerves modulate a substantial fraction of systemic vascular resistance,
(2) sympathetic nerve activity is increased in hypertension, and more so when this condition is resistant to multiple drug therapy, and
(3) afferent nerve signals from the kidney may contribute to the hypertensive status.1

Then there were studies which confirmed the above premise in the clinical setting by showing that removal of the hypertensive influences of the renal nerves by radiofrequency destruction from the renal artery lumen led to a substantial BP reduction in patients with resistant hypertension, the effect being long-lasting and free from major inconveniences or threats to therapeutic safety.2,3

The third step, however, was an unexpected shocking disappointment because in a trial which compared renal denervation with a sham denervation procedure, the Simplicity-HTN-3 trial, the effect on office and ambulatory BP did not differ significantly between the two groups.4

Although affected by important limitations, such as the failure to measure adherence to treatment, the frequent unchecked changes in drug therapy and the inexperience of the interventional centres involved, the trial was taken as providing conclusive evidence that renal denervation is ineffective and should thus be excluded from therapeutic measures to consider in conditions in which antihypertensive drugs do not achieve BP control.

From this dip, however, renal denervation has taken a slow but steady resurrection path.

First, a greater BP lowering effect has been observed in studies on resistant hypertensive patients, in which renal denervation was compared with optimal drug treatment, and confounders left unchecked by the Simplicity-HTN-3 trial (adherence to treatment and drug changes) were controlled.5

Second, evidence has been obtained that achieving complete renal denervation is difficult and thus greater procedural efforts (e.g., radio-frequency applications to both the main renal artery and its branches) are needed to achieve this goal.1

Finally, another trial (Spyral-HTN-OFF MED) in which the design included sham denervation has obtained results different from the Simplicity-HTN-3 trial. Namely, it has shown that in patients with hypertension of a variable severity in whom treatment was withdrawn to eliminate a major potential confounder of the Simplicity-HTN-3 trial, i.e., a possible between-group difference in drug assumption, renal denervation lowered office and ambulatory BP significantly more than sham denervation.6

This has recently been reinforced by two trials, both designed to compare renal denervation with a sham denervation group. In one trial, Spyral-HTN-ON MED7 recruitment was extended to patients with hypertension of variable severity in whom however, background drug treatment was maintained. Medication adherence was measured by drug surveillance and found to be variable between patients but overall similar between groups. This was not the case for the BP reductions which, after 6 months, were significantly greater in the renal denervation than in the sham denervation group, the systo-diastolic BP difference being 6.8/3.5 mmHg for office and 7.4/4.1 mmHg for 24 h mean BP.

Similar results have been reported in the second trial which was published simultaneously with the previous one and focused on hypertensive patients with 24 h mean BP values between 135/85 mmHg and <170/105 mmHg. Rather than by radiofrequency the kidneys were denervated by an endovascular ultrasound approach, and the observation period after the renal denervation or sham procedure was restricted to 2 months to allow the trial to be conducted off drug treatment. The results showed that day-time mean BP underwent a significantly greater reduction in the renal than in the sham denervation group, the baseline adjusted difference being 6.3 mmHg for systolic and 3.1 mmHg for diastolic BP.8

In both trials and in neither group no major adverse event was recorded.

The message that can be extracted from the studies made available after the Simplicity-HTN-3 trial seems to me clear. Renal denervation has a BP lowering effect which is not limited to patients with severe but extends to patients with a wide range of BP elevations above the cut-off value dividing hypertension from normotension.

The BP reduction:

(1) is visible in both office and daily life BP;
(2) extends to either untreated patients and to patients taking antihypertensive drug treatment; and
(3) can be obtained with no serious inconveniences or major side effects.

This supports the conclusion that studies aiming at further clarifying the clinical aspects of this device-based antihypertensive treatment are clinically relevant and that in the meantime its use may be considered whenever ineffectiveness or poor adherence make antihypertensive drug treatment an unquestionable failure.

Research efforts should be directed to technological improvements as well as to clarification of which drugs may be more effective when combined with the reduction of sympathetic drive induced by renal denervation. A treatment strategy based on a drug-device association appears to be necessary because the latest trials that have scored in favour of the BP lowering effectiveness of renal denervation have consistently shown the office systolic BP reduction to be around 10 mmHg. Except when treatment involves patients with a high normal BP (130–139 mmHg systolic and/or 85–89 mmHg diastolic BP), in all other hypertensives this does not make renal denervation alone capable to lower BP to <130/80 mmHg which is the target value for treatment recommended by both the European and the US guidelines.9,10
Conflict of interest: G.M. has received honoraria for participation in national and international meetings as speaker/chairman from: Boehringer Ingelheim, CVRx, Daiichi Sankyo, Ferrer, Medtronic, Menarini, Merck, Novartis, Recordati, Sanofi and Servier.

References
References are available as supplementary material at European Heart Journal online.