Renal denervation—implications for chronic kidney disease

Roland Veelken and Roland. E. Schmieder

Abstract | Catheter-based renal denervation to treat patients with resistant hypertension and chronic kidney disease (CKD) has generated considerable interest. Data from the majority of, but not all, observational studies and randomized controlled trials suggest that the procedure does not impair renal function and can effectively reduce office and ambulatory blood pressure in patients with primary hypertension. The putative beneficial effects of renal denervation seem to result from the interruption of renal efferent and afferent nerves. In patients with resistant hypertension and CKD, interruption of afferent reflexes might lead to a reduction in global sympathetic tone. The subsequent sustained reduction in blood pressure is expected to slow the progression of renal disease. However, renal denervation might also improve glucose metabolism, increase insulin sensitivity and reduce renal inflammation, with renoprotective effects in patients with CKD. Additional large randomized controlled trials of renal denervation in hypertensive and normotensive patients with CKD are required to precisely define the clinical value of the procedure in this population.

Veelken, R. & Schmieder, R. E. *Nat. Rev. Nephrol*. advance online publication 15 April 2014; doi:10.1038/nrneph.2014.59

Introduction

The number of patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) is increasingly dramatically worldwide.[1,2] The vast majority of these patients also have hypertension,[3] which has a key role in the progression of renal dysfunction as well as in the increased morbidity and mortality of this population.[4,5] In patients with kidney disease, blood pressure is often difficult to control using conventional drug therapy.[6,7] Interest in the use of catheter-based renal denervation (Figure 1) to treat resistant hypertension in patients with or without CKD has increased since the first proof-of-principle cohort study in patients with normal renal function was published in 2009.[8] The majority of the available data from observational studies and randomized (but not placebo-controlled) clinical trials suggest that renal denervation is effective in lowering blood pressure in patients with resistant hypertension. However, the Simplicity HTN-3 trial, in which 535 patients with treatment-resistant hypertension were randomly assigned to renal denervation or sham-control groups, failed to meet its primary efficacy endpoint[9]—a finding that requires careful analysis.

Increased sympathetic nerve traffic has been almost unequivocally described as detrimental in the setting of hypertension with established end-organ damage and progression of renal disease.[10–14] Thus, the putative benefits of renal nerve ablation in patients with ESRD might be a focus of further research. In this Review, we discuss the evidence for increased sympathetic tone in patients with kidney disease, the physiology of renal nerves and the potential role of renal denervation as a treatment strategy to attenuate or inhibit the progression of CKD.

Sympathetic tone, hypertension and CKD

The first indirect evidence for enhanced sympathetic activation in patients with ESRD and hypertension was reported by Kim *et al.*[15] in 1972. These researchers found that, among patients with uraemia, peripheral vascular resistance was higher in those with hypertension ($n = 52$) than in those who were normotensive ($n = 23$). Furthermore, bilateral nephrectomy resulted in a significant reduction in blood pressure and peripheral vascular resistance in 12 patients with hypertension and uraemia on maintenance haemodialysis.[15] A subsequent study showed that acute total autonomic blockade with atropine, prazosin and propranolol resulted in a significant decrease in blood pressure and peripheral resistance in 20 patients with hypertension on haemodialysis.[16] Hypertensive patients with moderate to severe renal failure ($n = 14$) also showed a pronounced decrease in blood pressure and peripheral resistance in response to acute (6 weeks) or chronic (6 months) treatment with oral clonidine, an

Competing Interests
R.E.S. is a member of the speakers' bureau or has received honoraria from AstraZeneca, Berlin Chemie AG, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Novartis, Servier, Takeda Pharmaceuticals and Terumo. He has acted as a consultant for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Novartis and Servier, and has received grant or research support (awarded to the University Hospital, University Erlangen/Nürnberg) from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Bundesminesterium für Bildung und Forschung, Daiichi Sankyo, Novartis and Medtronic. R.V. declares that he has received grant or research support from Medtronic (awarded to the University Hospital, University Erlangen/Nürnberg).

Department of Nephrology and Hypertension, University Hospital, University Erlangen/Nürnberg, Ulmenweg 18, 91054 Erlangen, Germany (**R.V.**, **R.E.S.**)

Correspondence to: R.E.S. roland.schmieder@uk-erlangen.de

Key points

- Sympathetic tone and blood pressure are increased in patients with resistant hypertension and chronic kidney disease (CKD); the kidneys are a source of this increased sympathetic tone
- Renal denervation reduces renal inflammation and injury in experimental animals and might have similar effects in patients with CKD
- The majority of the available data suggest that renal denervation causes sustained reductions in office and ambulatory blood pressure in patients with resistant hypertension
- No adverse effects of renal denervation on long-term renal function have been reported
- Renal denervation seems to improve glucose metabolism and insulin sensitivity; these effects might be renoprotective in patients with CKD

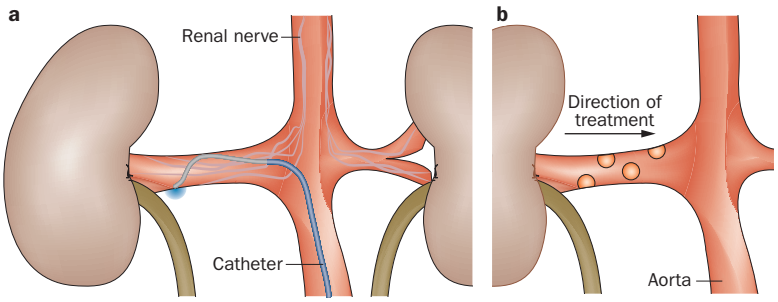

Figure 1 | Renal sympathetic denervation. **a** | The catheter is passed up the descending aorta and into the renal artery. **b** | Denervation (using radiofrequency energy or ultrasound) is performed around the renal artery at ≥5 mm intervals in a distal-to-proximal direction. Permission obtained from Nature Publishing Group © Bakris, G. L. *Nat. Rev. Cardiol.* **10**, 434–436 (2013).

agent which acts on the central nervous system to reduce sympathetic tone.[17]

In 1992, a study in which microneurography was used to measure muscle sympathetic nerve activity (MSNA) in patients with ESRD undergoing haemodialysis, provided the first direct evidence of elevated sympathetic nerve traffic in these patients.[18] Importantly, bilaterally nephrectomized patients on haemodialysis ($n = 5$) had comparable sympathetic drive to control participants who did not have renal failure ($n = 11$) and had lower blood pressure than patients with ESRD on haemodialysis who had not undergone nephrectomy ($n = 18$). A subsequent study showed that despite correction of uraemia by renal transplantation, patients with diseased native kidneys ($n = 32$) had elevated MSNA similar to that observed in patients on long-term haemodialysis ($n = 13$).[19] Normal peripheral sympathetic neurograms were observed only in patients who had undergone bilateral nephrectomy as well as transplantation, confirming that the diseased kidneys were responsible for the increased sympathetic nerve traffic.

Further evidence for a crucial involvement of the sympathetic nervous system in the pathogenesis of hypertension in patients with impaired kidney function came from a study in which MSNA was recorded in hypertensive patients with moderate chronic renal failure ($n = 42$) or normal renal function ($n = 31$).[20] The researchers found that MSNA was higher in the patients with impaired renal function. Furthermore, an inverse correlation between estimated glomerular filtration rate (eGFR) and MSNA was observed, suggesting that increased sympathetic activation is an early event in the pathogenesis of CKD.

Physiology of renal nerves

Renal efferent nerves

The use of catheter-based renal denervation as a treatment for patients with CKD and/or hypertension requires an understanding of how the activation of efferent and afferent renal nerves contributes to the development of these diseases. Increased efferent sympathetic nerve activity mediates changes in renal function through innervation of all essential renal structures, including the renal vasculature, tubules and juxtaglomerular apparatus.[21,22] Consequently, renal sympathetic activation results in water retention, sodium reabsorption, a reduction in blood flow and activation of the renin–angiotensin–aldosterone system (RAAS; Figure 2).[21,22]

As the juxtaglomerular and tubular cells are more sensitive to changes in sympathetic activity than are other renal structures, tubular sodium and water reabsorption and renin release can be observed in response to mild sympathetic activation without causing vasoconstriction or a reduction in GFR.[21] Reduced excretion of salt and water and increased renin release as a result of increased renal sympathetic tone might lead to a sustained increase in blood pressure in patients with kidney disease.[21,22] Careful review of the available evidence also suggests that sympathetic innervation is closely linked to salt-conserving mechanisms[23,24] involved in pressure diuresis.[22] Although, the various aspects of sodium metabolism might not be of uniform importance in hypertension, afferent renal innervation might be beneficial in slowing the development of salt-sensitive hypertension.[25,26] One could speculate that renal denervation might, therefore, be detrimental in patients with salt-sensitive hypertension, but no evidence currently supports this hypothesis.

Renal afferent nerves

In addition to efferent nerves, the kidney has an extensive network of afferent nerves that transmit sensory information to the central nervous system.[21,22] Afferent fibres from the kidney enter the dorsal root ganglia and project to neurons at both spinal and supraspinal levels. Renal afferent nerves are thought to relay information to the central nervous system from chemoreceptors and mechanoreceptors in the kidneys (Figure 2). Several substances (including nitric oxide, hydrogen ions, adenosine, calcitonin gene-related peptide [CGRP], substance P, bradykinin, neurokinin A, prostaglandins and vanilloids) have been postulated or proven to stimulate renal afferents under various conditions.[21,22,27–30]

Activation of several well-characterized renal afferent nerves is sympathoinhibitory in normal animals.[18,20,22] In healthy kidneys, tonic activation of renal afferent nerve fibres might have a role as a compensatory mechanism to prevent increases in blood pressure. Thus, the possibility exists that increased efferent sympathetic activity in hypertension and related cardiovascular diseases is associated with decreased renal sympathoinhibitory afferent activity. However, this interpretation seems to be counterintuitive in light of studies that suggest the existence of sympathoexcitatory renal afferent nerve fibers.[24,25] Furthermore, a putative sympathoinhibitory function of renal afferents

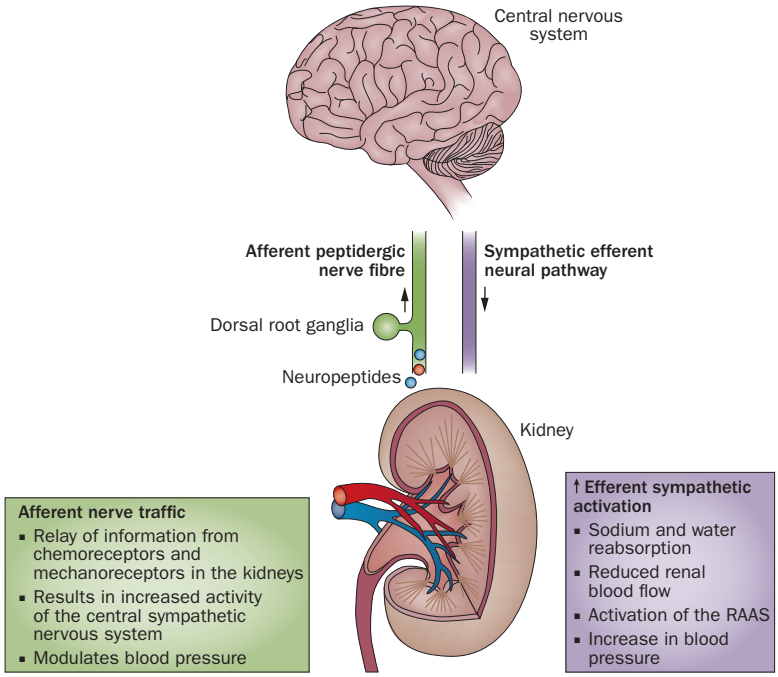

Figure 2 | Sympathomodulation of the efferent sympathetic nervous system. Intensive crosstalk occurs between the central sympathetic nervous system and the kidneys via afferent peptidergic and sympathetic efferent neural pathways. Afferent nerve fibres respond to mechanical and chemical stimuli and modulate centrally efferent sympathetic activity. The first neurons of these fibres are found in the dorsal root ganglia.

cannot explain why the interruption of renal afferent nerves by renal denervation reduces increased sympathetic tone in patients with hypertension.[31]

To our knowledge, the presence of sympathoexcitatory renal afferent nerve fibres has not yet been shown using direct nerve recordings in animal models. However, indirect evidence suggests that interruption of renal afferents reduces sympathetic tone and blood pressure regardless of the underlying mechanism. For example, in a rat model of hypertension induced by renal ischaemia (that is, renal artery stenosis plus unilateral nephrectomy), selective afferent denervation using bilateral dorsal rhizotomy resulted in a significant reduction in blood pressure, whereas unilateral rhizotomy on the side of the nephrectomy had no effect.[32] Two additional studies in rats suggest that sympathoexcitatory afferent nerve activity occurs after renal injury. In normal rats, injury induced by injection of 10% by volume aqueous phenol (50 µl) into the lower pole of one kidney resulted in a sustained increase in renal afferent nervous activity and a reflex increase in sympathetic tone and blood pressure.[33] Similarly, renal failure in 5/6 nephrectomized rats caused renal afferent activation and a reflex increase in sympathetic tone and blood pressure that was eliminated by bilateral dorsal rhizotomy.[11] Rats subjected to dorsal rhizotomy had less severe renal dysfunction (lower serum creatinine levels) and glomerulosclerosis than those that underwent sham rhizotomy. In contrast to the effects of renal afferent denervation in rats with renal ischaemia or injury, dorsal rhizotomy did not prevent the development of genetic hypertension or hypertension induced by deoxycortisone acetate plus salt loading in rats without overt renal dysfunction.[34] Based on these findings,[11,32–34] we suggest that pathological conditions in the kidneys (that is, renal ischaemia or dysfunction) might modulate afferent fibres such that sympathetic tone is increased.

Interestingly, a marked decrease in single-unit and multiunit MSNA 3 months after renal denervation was reported in 25 patients with resistant hypertension and normal renal function (eGFR >45 ml/min/1.73 m²).[31] However, a similar trial that included 12 patients with 'difficult-to-control' hypertension showed no decrease in MSNA 3–6 months after renal nerve ablation.[35] Not all participants in this study had resistant hypertension (blood pressure was <140 mmHg in some patients) and the investigators did not measure single-unit MSNA, which best reflects vasoconstrictive nervous fibre activity.[36,37] Moreover, another measure of central sympathetic activity, total noradrenaline spillover, decreased by approximately 20% after renal denervation.[38] The results of these studies suggest that a decrease in sympathetic activity to the periphery—in particular to the small resistance arteries—might occur as a consequence of the interruption of sympathoexcitatory renal afferent nerve fibres. A sympathoexcitatory signal transmitted by renal afferents might occur even in patients with resistant and long-standing hypertension who have normal renal function (eGFR >45 ml/min/1.73 m²) as a result of subclinical renal damage.[39] Additional studies are warranted to investigate the mechanism of renal afferent activation and the role of these nerves in altering sympathetic tone and blood pressure in hypertensive patients with or without concomitant CKD.

Renal nerves and inflammation

Evidence from experimental animals suggests that renal nerves might also have an important role in renal inflammation and injury. In rats, bilateral surgical renal denervation performed 2 days before induction of anti-Thy1.1 glomerulonephritis (by injection of the monoclonal antibody OX7) significantly reduced the levels of albuminuria (Figure 3a), mesangiolysis, microaneurysm formation, deposition of glomerular collagen IV and expression of transforming growth factor β (TGF-β) that were observed 6 days after induction of the disease.[13] Furthermore, the reduction in renal injury in the rats that had undergone renal denervation was not accompanied by changes in blood pressure. Renal inflammation, identified by accumulation of interstitial macrophages (Figure 3b), expression of tumour necrosis factor (TNF; Figure 3c) and proliferation of mesangial cells, was significantly reduced in the renal-denervation group compared with sham-operated animals. These results are consistent with data from an earlier study, which showed that administration of the centrally acting sympatholytic agent moxonidine led to amelioration of vascular and glomerular injury in subtotally nephrectomized rats despite unchanged systemic blood pressure.[40]

Although the precise mechanisms by which renal nerves mediate inflammation and injury are unknown, several possibilities exist. In the kidneys, catecholamines have direct effects on tubular cell proliferation that are

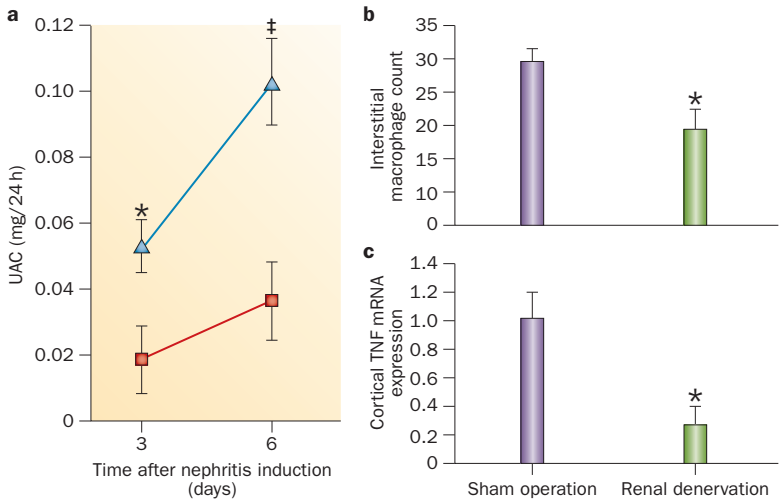

Figure 3 | Effects of bilateral surgical renal denervation on albuminuria and inflammation in rats with anti-Thy1.1 nephritis. **a** | Albuminuria detected 3 days and 6 days after antibody challenge was attenuated in rats with bilateral surgical renal denervation. Data are means ± SEM. **b** | Renal macrophage counts and **c** | cortical TNF mRNA expression was reduced in the renal denervation group versus sham-operated controls. Renal denervation was performed 2 days before injection of anti-Thy1.1 monoclonal antibody. *$P \leq 0.05$ versus sham-operated rats. ‡$P \leq 0.01$ versus sham-operated rats. Abbreviations: TNF, tumour necrosis factor; UAC, urinary albumin excretion. Republished with permission of American Society of Nephrology, from Veelken, R. *et al. J. Am. Soc. Nephrol.* **19**, 1371–1378 (2008); permission conveyed through Copyright Clearance Center, Inc.

mediated by β-adrenergic receptors.[41] Excessive β-receptor activation might, therefore, cause renal injury. In addition, catecholamines might influence the function of podocytes, which are considered to be key target cells in the genesis of glomerular injury.[42] Sympathetic activation might cause hypercontraction of podocyte foot processes or podocyte injury, resulting in disruption of the glomerular filtration barrier and leakage of large molecules, such as albumin.[42]

In addition to noradrenaline, renal nerves contain a variety of neuropeptides that include neuropetide Y, vasoactive intestinal polypeptide, CGRP, somatostatin and substance P.[43] Some of these peptides are localized in afferent nerves and have a role in sensory neurotransmission.[21,28,29] The release of neuropeptides and catecholamines might contribute to neuroimmune interactions within the kidney. Together with β-adrenergic simulation by noradrenaline,[44] neuropeptide Y,[45] somatostatin[46] and vasoactive intestinal peptide[47] seem to at least partly downregulate inflammatory responses. By contrast, stimulation of α-adrenergic receptors by substance P and noradrenaline are proinflammatory.[44,48] The role of CGRP in inflammation remains somewhat controversial as anti-inflammatory and pro-inflammatory effects of this peptide have been reported.[49,50] As CGRP is a strong vasodilator, the net effects of its release might depend on the specific inflammatory process. Furthermore, efferent sympathetic activation can lead to the release of renin from juxtaglomerular cells, resulting in increased plasma levels of angiotensin II,[21] which can cause overexpression of TGF-β in immune cells.[51] Pro-inflammatory cytokines (such as TNF and IL-1β) released from immune cells via α-adrenergic activation, or substance P released from afferent nerves, can directly reach the central nervous system via the circulation or alternatively stimulate renal afferent nerve fibres, thereby causing a further increase in sympathetic tone.[52] As increased renal sympathetic activation could result in further release of cytokines and activation of afferent or efferent renal nerves, a positive-feedback cycle that augments local inflammation and injury in the kidneys might exist (Figure 4). Additional human and animal studies are needed to further elucidate the role of these pathways in renal inflammation and injury as well as the potential effects of renal denervation on these processes.

Efficacy of renal denervation

The data discussed above provide a rationale for the hypothesis that renal denervation might be effective in reducing blood pressure in patients with resistant hypertension and also suggest that the procedure might have renoprotective effects beyond lowering blood pressure. The efficacy of renal denervation in hypertensive patients with or without kidney disease has now been investigated in prospective studies.

Patients with preserved renal function

Blood pressure

Data from the Symplicity HTN-1[8,53] and HTN-2[54,55] trials suggest that catheter-based renal denervation has a favourable safety profile and results in sustained reductions of blood pressure in patients with resistant hypertension and preserved renal function (eGFR ≥45 ml/min/1.73 m^2). In these studies, which included a total of 239 patients, treatment-resistant hypertension was defined as office systolic blood pressure ≥160 mmHg (or ≥150 mmHg in patients with type 2 diabetes mellitus) and failure to achieve target blood pressure despite use of at least three antihypertensive drugs, including a diuretic. In addition to a reduction in office blood pressure, a reduction in 24 h ambulatory blood pressure following renal denervation was reported in a subgroup of the Symplicity HTN-2 participants ($n = 20$).[54] These observations have since been confirmed in larger patient cohorts.[56,57] However, a number of studies with small sample sizes and open designs[58,59] have reported either failure of renal denervation to ameliorate resistant hypertension or lower decreases in blood pressure after the procedure than those observed in the Symplicity HTN-1[8,53] and HTN-2 trials.[54,55] Similarly, the large, double-blind Symplicity HTN-3 prospective randomized clinical trial, which investigated the blood-pressure-lowering effects of renal denervation versus a sham procedure, reported failure of renal denervation to decrease office blood pressure by >10 mmHg from baseline at 6 months.[9] The reasons for these conflicting findings are not yet clear and data on 24 h ambulatory blood pressure are not yet available.

Data showing greater lowering of office blood pressure than ambulatory blood pressure after renal denervation[54,57] have also led to concerns regarding the efficacy of the procedure.[60] However, even in large prospective trials of antihypertensive drugs[61] (which led to the recommendation that a reduction in blood pressure reduces cardiovascular morbidity and mortality[62]) office blood

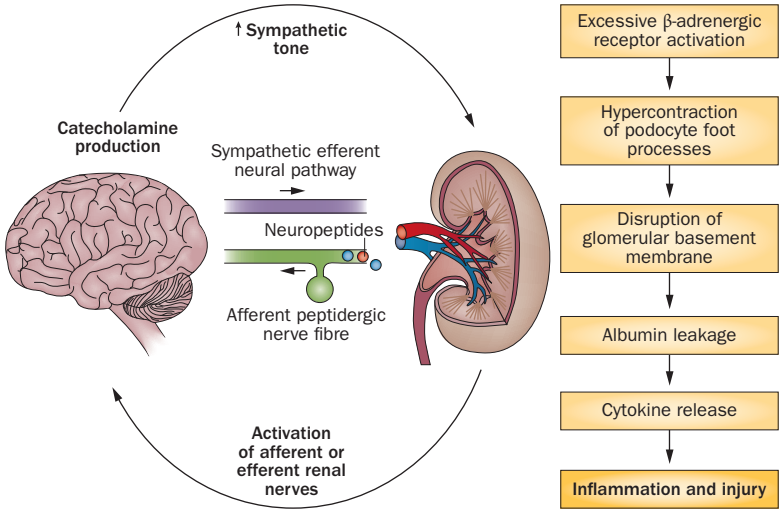

Figure 4 | Potential role of renal nerves in renal inflammation and injury. In the kidneys, catecholamines might cause excessive β-receptor activation and hypercontraction of podocyte foot processes, leading to renal inflammation and injury. Moreover, in addition to their neurogenic function, afferent petidergic nerve fibres secrete vasoactive proinflammatory substances, such as substance P and calcitonin gene related peptide, which are likely to have effects in the kidney (this concept has not yet been unequivocally proven). Proinflammatory cytokines released from immune cells in the kidney via α-adrenergic activation, or substance P released from afferent nerves, can reach the central nervous system via the circulation or directly stimulate renal afferent nerve fibres, resulting in a further increase in sympathetic tone. As increased renal sympathetic activation could result in further release of cytokines and activation of afferent or efferent renal nerves, a positive-feedback cycle that augments local inflammation and injury in the kidneys might exist.

pressure measurements (and not ambulatory blood pressure) were applied to the study protocols.[61] A meta-analysis that included 44 studies of antihypertensive drugs reported a greater blood-pressure-lowering effect of these agents on office blood pressure than on ambulatory blood pressure.[63] These discrepancies and their implications for patients should be addressed on a broad scale with respect to all therapeutic approaches in hypertension, including renal denervation.

Renal function

The potential beneficial and adverse effects of renal denervation on normal renal function have been investigated in patients with hypertension. Firstly, insight into the effects of renal denervation on renal perfusion and renal vascular resistance in hypertensive patients with normal renal function was obtained using MRI with arterial spin labelling.[64] In 19 patients with resistant hypertension and preserved renal function, renal perfusion and renal vascular resistance were measured 1 day before, 1 day after and 3 months after renal denervation. Although a significant drop in arterial blood pressure occurred, renal vascular resistance decreased and renal perfusion remained constant 1 day and 3 months after the procedure. These findings suggest that reducing blood pressure by renal denervation does not lead to renal injury as a result of a decrease in renal perfusion.

In the Symplicity HTN-2 trial, no difference in eGFR, serum creatinine or serum cystatin C levels in the renal denervation ($n = 49$) and control groups ($n = 35$) was reported at 6 months and 12 months of follow-up monitoring.[54,55] Similarly, other analyses with 1 year of follow-up data showed that renal function (assessed using levels of cystatin C, serum creatinine and eGFR) was not adversely affected by renal denervation.[57,65] Long-term follow-up data from Symplicity HTN-2 showed no change in eGFR from baseline at 3 years among patients who underwent renal denervation at enrolment (eGFR 76.7 ± 18.8 ml/min/1.73 m² versus 77.1 ± 18 ml/min/1.73 m²) or among those who received renal denervation after 6 months (88.6 ml/min/1.73 m² versus 87.8 ml/min/1.73 m²).[66] However, in Symplicity HTN-1, a decrease in mean eGFR after renal denervation of 2–3 ml/min/1.73 m² per year was reported in the 88 participants who had complete follow-up data at 3 years.[67] These conflicting findings might reflect the heterogeneity of the patient populations, continued injury as a result of long-standing uncontrolled hypertension (a legacy effect) or changes in use of diuretic or RAAS blockade during the follow-up period. Unfortunately, these potential mechanisms were not adequately analysed in the studies.[66,67] In Symplicity HTN-3, the prespecified primary safety end point (incidence of major adverse events at 1 month and incidence of renal artery stenosis at 6 months after randomization) was met and no safety concerns were detected. To date, only two cases of renal artery stenosis after renal denervation have been reported.[68,69]

The effects of renal denervation on renal function and urinary albumin excretion were investigated in 88 patients with resistant hypertension and preserved renal function.[70] In this study, a significant reduction in the renal resistive index and office blood pressure was reported at 3 months and 6 months after the procedure. Furthermore, at 3 months and at 6 months after renal denervation, the proportion of patients with normal urinary albumin excretion increased by 5% and 12%, whereas the proportion of patients with microalbuminuria and macroalbuminuria decreased by 10% and 23%, respectively. Importantly, eGFR (determined using cystatin C levels) was unchanged 6 months after renal denervation. Similarly, in our unpublished study that included 59 patients with resistant hypertension, levels of albuminuria were significantly decreased 6 months after renal denervation in those who had microalbuminuria and macroproteinuria at baseline. As changes in albuminuria are indicative of renal and cardiovascular progression in patients with high cardiovascular risk,[71] a reduction in albuminuria after renal denervation suggests improved prognosis.

Metabolic profile and insulin resistance

Activation of the sympathetic nervous system is thought to be an important contributor to insulin resistance, metabolic syndrome associated with central obesity and the risk of type 2 diabetes mellitus.[72,73] The effect of renal denervation on glucose control was assessed in a pilot study that included 50 patients with resistant hypertension.[74] In addition to significant reductions in blood pressure from baseline at 1 month and 3 months after renal denervation, fasting blood glucose and insulin levels were

significantly reduced at 3 months in the renal denervation group ($n = 37$). Moreover, insulin resistance (quantified using the homeostasis model assessment) and mean 2 h glucose levels (during oral glucose tolerance testing) were also significantly reduced from baseline 3 months after the procedure. No changes in these parameters were reported in the control group. A study that investigated the effects of renal denervation in 10 patients with resistant hypertension and obstructive sleep apnoea reported similar findings.[75] In addition to a decrease in the severity of obstructive sleep apnoea, significant decreases in 2 h glucose concentrations during oral glucose tolerance testing and in haemoglobin A_{1c} (HbA_{1c}) levels at 6 months after renal denervation were reported.

The mechanisms that lead to lower blood glucose levels and improved insulin sensitivity after renal denervation are not clear. However, a reduction in sympathetic tone is thought to move blood away from less-insulin-sensitive visceral tissue to more-sensitive skeletal muscle and to reduce glucagon secretion.[76] The effect of renal denervation on these metabolic parameters is potentially important for long-term kidney function, as insulin resistance in the absence of overt diabetes or hypertension is an important risk factor for CKD.[77,78] Thus, an improvement in metabolic profile after renal denervation might have beneficial effects on long-term renal function that are independent of reduced blood pressure.

Patients with impaired renal function

A pilot study that investigated the safety and efficacy of renal denervation in 15 patients with stage 3–4 CKD (eGFR ≤45 ml/min/1.73 m²) and resistant hypertension (mean baseline office blood pressure 174/91 mmHg despite use of a mean of 5.6 antihypertensive drugs), showed a significant decrease in office systolic and diastolic blood pressure following the procedure (decreases of 34/14 mmHg at 1 month, 25/11 mmHg at 3 months, 32/15 mmHg at 6 months and 33/10 mmHg at 12 months).[79] Another important finding was that the patients did not experience deterioration of renal function assessed using eGFR (based on levels of serum creatinine or cystatin C). Trends toward increased haemoglobin concentration and gradual decreases in plasma brain natriuretic peptide levels, the urinary albumin to creatinine ratio, proteinuria and plasma HbA_{1c} levels in patients with CKD after renal denervation were also reported. These effects might be a consequence of blood-pressure lowering alone, but could also reflect an effect of renal denervation on the progression of renal disease independent of its effect on blood pressure. In an observational study that included 24 patients with CKD and treatment-resistant hypertension, renal denervation resulted in improved blood pressure control accompanied by a reduction in blood pressure without any decrease in renal function.[80]

Preliminary data on the safety and efficacy of renal denervation in patients with ESRD and uncontrolled hypertension have also been reported. In 12 patients with treatment-resistant hypertension (mean office blood pressure 171/89 mmHg despite use of a mean of 3.8 antihypertensive drugs) on chronic haemodialysis, office systolic blood pressure was reduced by a mean of 18 mmHg, 16 mmHg and 28 mmHg at 3 months, 6 months and 12 months after renal denervation, respectively.[81] Moreover, sympathetic nerve activity and noradrenaline levels were substantially elevated at baseline in the five patients who had these measurements, and were reduced at 12 months in the two patients who underwent repeat assessment.

The effect of renal denervation on renal function was investigated in a prospective pilot study.[82] In this study, which included 15 patients with treatment-resistant hypertension, renal function was determined retrospectively for the 3 years prior to renal denervation and prospectively for 1 year after the procedure. The change in eGFR over time was calculated individually for each patient using the regression slope. Before renal denervation, the mean blood pressure of the participants was 162/78 mmHg; 1 year after the procedure, the systolic office and 24 h ambulatory blood pressures had decreased by 26 mmHg and 13 mmHg, respectively. Most strikingly, the mean decline in eGFR before renal denervation was 5.6 ml/min/1.73 m² per year but eGFR remained stable after renal denervation, with a significant improvement in annual change in eGFR before and after the procedure (-5.6 ± 4.4 ml/min/1.73 m² per year versus 2.2 ± 8.0 ml/min/1.73 m² per year, $P = 0.021$).[82] These preliminary data support a potential renoprotective effect of renal denervation, either as a result of blood-pressure lowering alone or of blood pressure reduction in conjunction with decreased global and/or renal sympathetic activity.

Potential limitations

Patients with CKD require more medical attention during the renal denervation procedure than do patients with normal renal function; the renal arteries in these patients have smaller diameters and application of contrast medium should be minimized. The available data suggest that renal denervation does not adversely affect kidney function. However, in patients with impaired renal function, appropriate prehydration and the use of iso-osmolar contrast agents during the procedure are advisable to prevent contrast-induced nephropathy.[83–85] In addition, use of carbon dioxide angiography during renal denervation might help to reduce the volume of contrast agent required.[79] On the basis of the currently available data, eGFR >45 ml/min/1.73 m² is recommended as an eligibility criterion for renal denervation.[83,85,86] Long-term monitoring of renal function and blood pressure control following renal denervation is mandatory in patients with CKD.[83,85,86]

Future directions

Initial clinical data on the effects of renal denervation in patients with hypertension and CKD are promising. In these patients, blood pressure is reported to be substantially decreased and eGFR remains stable 3–6 months after the procedure.[80–82] Although renal sympathoexcitatory activity is increased in the settings of hypertension and renal ischaemia and/or dysfunction, renal afferent activity also seems to mediate increased sympathetic tone in

patients with resistant hypertension and preserved renal function.[11,33,39] However, the mechanisms responsible for this increased sympathetic tone are not yet clear, and further studies are necessary.

Data from animal models suggest that renal denervation might protect against inflammation and renal injury,[13] and the early clinical data on renal function after renal denervation in patients with CKD and hypertension are in accordance with this concept.[80–82] Renal denervation might directly protect the kidney and reduce renal injury by lowering blood pressure and improving blood glucose levels. However, additional studies are needed to clarify the independent effects of each of these mechanisms on renal function.

No clinical data on the effects of renal denervation on renal dysfunction or structural damage in normotensive patients are currently available. The possibility exists that renal denervation might have a therapeutic role in patients with CKD who do not have hypertension, but randomized controlled clinical trials are required to investigate this hypothesis. To date, the primary goal of renal denervation in patients with resistant hypertension has been to control blood pressure. Future studies are needed to determine if renal denervation also reduces damage to target organs (kidneys, heart and brain) and the risk of cardiovascular events.

Conclusions

The majority of the available data suggest that, if properly conducted, renal denervation might reduce office and ambulatory blood pressure in patients with resistant hypertension and either normal or impaired renal function. However, large randomized controlled trials are needed to investigate the putative beneficial effects of renal denervation in patients with CKD. Identification of factors that predict blood pressure reduction after renal denervation might aid the design of future studies. Initial safety data are promising; although more than 5,000 procedures have been performed, and several hundred patients have been followed-up for 3 years,[67,66] only two cases of renal artery stenosis after renal denervation have been reported.[68,69] Moreover, initial studies indicate that the procedure does not have a detrimental effect on renal function in patients with hypertension.[64,66]

The beneficial effects of renal denervation seem to result from the interruption of renal afferent and efferent nerve traffic. In patients with resistant hypertension and CKD, sympathoexcitatory reflexes are dominant and the interruption of these afferent reflexes leads to a reduction in global sympathetic tone. Preliminary data from animal and clinical studies suggest that, in addition to sustained lowering of blood pressure, renal denervation might result in improvements in pathogenetic factors that include elevated blood glucose levels and inflammation, which might have beneficial effects on renal function. Some small studies[58,59] and the Symplicity HTN-3 trial[9] have reported failure of renal denervation to substantially ameliorate resistant hypertension. However, these data were obtained in patients with primary hypertension and eGFR >45 ml/min/1.73 m^2. Initial results from pilot studies of renal denervation in hypertensive patients with lower levels of eGFR are encouraging as they indicate preservation of renal function combined with a reduction in proteinuria. A better understanding of the pathophysiology of resistant hypertension, further stringent standardization of the ablation technique, larger cohorts and a greater number of randomized controlled clinical trials in primary and secondary hypertension together with an increasing amount of registry data on the long-term outcomes of renal nerve ablation will help to explain these apparently contradictory results and clarify whether and to what extent renal denervation might exert renoprotective effects.

Review criteria

A search for original articles published between 1950 and 2013 was performed using the PubMed database. The search terms used were "antihypertensive therapy", "resistant hypertension", "renal denervation", "renal nerve ablation", "sympathetic innervation", "renal inflammation", "chronic kidney disease" and "neuroimmunology", alone and in combination. All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers.

1. Mailloux, L. U. & Haley, W. E. Hypertension in the ESRD patient: pathophysiology, therapy, outcomes, and future directions. *Am. J. Kidney Dis.* **32**, 705–719 (1998).
2. Ritz, E., Rychlik, I., Locatelli, F. & Halimi, S. End-stage renal failure in type 2 diabetes: a medical catastrophe of worldwide dimensions. *Am. J. Kidney Dis.* **34**, 795–808 (1999).
3. Klag, M. J. *et al.* Blood pressure and end-stage renal disease in men. *N. Engl. J. Med.* **334**, 13–18 (1996).
4. Rostand, S. G., Brunzell, J. D., Cannon, R. O. 3rd & Victor, R. G. Cardiovascular complications in renal failure. *J. Am. Soc. Nephrol.* **2**, 1053–1062 (1991).
5. Herzog, C. A., Ma, J. Z. & Collins, A. J. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N. Engl. J. Med.* **339**, 799–805 (1998).
6. Coresh, J. *et al.* Prevalence of high blood pressure and elevated serum creatinine level in the United States: findings from the third National Health and Nutrition Examination Survey (1988–1994). *Arch. Intern. Med.* **161**, 1207–1216 (2001).
7. Tonelli, M. *et al.* Cardiac risk factors and the use of cardioprotective medications in patients with chronic renal insufficiency. *Am. J. Kidney Dis.* **37**, 484–489 (2001).
8. Krum, H. *et al.* Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* **373**, 1275–1281 (2009).
9. Medtronic Inc. Press release: Medtronic announces US renal denervation pivotal trial fails to meet primary efficacy endpoint while meeting primary safety endpoint. *Medtronic* [online] http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=1889335&highlight=&utm_source=MDT_com_Symplifybptrial_Home_Page&utm_medium=Impt_Info_ReadPR_Link&utm_campaign=Renal_Denervation_RDN_Press_Release_010914 (2014).
10. Campese, V. M. & Kogosov, E. Renal afferent denervation prevents hypertension in rats with chronic renal failure. *Hypertension* **25**, 878–882 (1995).
11. Campese, V. M., Kogosov, E. & Koss, M. Renal afferent denervation prevents the progression of renal disease in the renal ablation model of chronic renal failure in the rat. *Am. J. Kidney Dis.* **26**, 861–865 (1995).
12. Amann, K. *et al.* Effects of low dose sympathetic inhibition on glomerulosclerosis and albuminuria in subtotally nephrectomized rats. *J. Am. Soc. Nephrol.* **11**, 1469–1478 (2000).
13. Veelken, R. *et al.* Autonomic renal denervation ameliorates experimental glomerulonephritis. *J. Am. Soc. Nephrol.* **19**, 1371–1378 (2008).
14. Strojek, K., Grzeszczak, W., Gorska, J., Leschinger, M. I. & Ritz, E. Lowering of microalbuminuria in diabetic patients by a

sympathicoplegic agent: novel approach to prevent progression of diabetic nephropathy? *J. Am. Soc. Nephrol.* **12**, 602–605 (2001).
15. Kim, K. E., Onesti, G., Schwartz, A. B., Chinitz, J. L. & Swartz, C. Hemodynamics of hypertension in chronic end-stage renal disease. *Circulation* **46**, 456–464 (1972).
16. McGrath, B. P. *et al.* Autonomic blockade and the Valsalva maneuver in patients on maintenance hemodialysis: a hemodynamic study. *Kidney Int.* **12**, 294–302 (1977).
17. Levitan, D., Massry, S. G., Romoff, M. & Campese, V. M. Plasma catecholamines and autonomic nervous system function in patients with early renal insufficiency and hypertension: effect of clonidine. *Nephron* **36**, 24–29 (1984).
18. Converse, R. L. Jr *et al.* Sympathetic overactivity in patients with chronic renal failure. *N. Engl. J. Med.* **327**, 1912–1918 (1992).
19. Hausberg, M. *et al.* Sympathetic nerve activity in end-stage renal disease. *Circulation* **106**, 1974–1979 (2002).
20. Grassi, G. *et al.* Early sympathetic activation in the initial clinical stages of chronic renal failure. *Hypertension* **57**, 846–851 (2011).
21. DiBona, G. F. & Kopp, U. C. Neural control of renal function. *Physiol. Rev.* **77**, 75–197 (1997).
22. DiBona, G. F. & Esler, M. Translational medicine: the antihypertensive effect of renal denervation. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **298**, R245–R253 (2010).
23. DiBona, G. F. & Sawin, L. L. Renal nerves in renal adaption to dietary sodium restriction. *Am. J. Physiol.* **245**, F322–F328 (1983).
24. Friberg, P. *et al.* Evidence for increased renal norepinephrine overflow during sodium restriction in humans. *Hypertension* **16**, 121–130 (1990).
25. Kopp, U. C., Cicha, M. Z. & Smith, L. A. Dietary sodium loading increases arterial pressure in afferent renal-denervated rats. *Hypertension* **42**, 968–973 (2003).
26. Xie, C. & Wang, D. H. Effects of a high-salt diet on TRPV-1-dependent renal nerve activity in Dahl salt-sensitive rats. *Am. J. Nephrol.* **32**, 194–200 (2010).
27. Stella, A. & Zanchetti, A. Functional role of renal afferents. *Physiol. Rev.* **71**, 659–682 (1991).
28. Kopp, U. C., Farley, D. M., Cicha, M. Z. & Smith, L. A. Activation of renal mechanosensitive neurons involves bradykinin, protein kinase C, PGE_2, and substance P. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **278**, R937–R946 (2000).
29. Xie, C., Sachs, J. R. & Wang, D. H. Interdependent regulation of afferent renal nerve activity and renal function: role of transient receptor potential vanilloid type 1, neurokinin 1, and calcitonin gene-related peptide receptors. *J. Pharmacol. Exp. Ther.* **325**, 751–757 (2008).
30. Ditting, T. *et al.* Tonic postganglionic sympathetic inhibition induced by afferent renal nerves? *Hypertension* **59**, 467–476 (2012).
31. Hering, D. *et al.* Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. *Hypertension* **61**, 457–464 (2013).
32. Wyss, J. M., Aboukarsh, N. & Oparil, S. Sensory denervation of the kidney attenuates renovascular hypertension in the rat. *Am. J. Physiol.* **250**, H82–H86 (1986).
33. Ye, S., Zhong, H., Yanamadala, V. & Campese, V. M. Renal injury caused by intrarenal injection of phenol increases afferent and efferent renal sympathetic nerve activity. *Am. J. Hypertens.* **15**, 717–724 (2002).
34. Wyss, J. M., Oparil, S. & Sripairojthikoon, W. Neuronal control of the kidney: contribution to hypertension. *Can. J. Physiol. Pharmacol.* **70**, 759–770 (1992).
35. Brinkmann, J. *et al.* Catheter-based renal nerve ablation and centrally generated sympathetic activity in difficult-to-control hypertensive patients: prospective case series. *Hypertension* **60**, 1485–1490 (2012).
36. Macefield, V. G., Wallin, B. G. & Vallbo, A. B. The discharge behaviour of single vasoconstrictor motoneurones in human muscle nerves. *J. Physiol.* **481** (Pt 3), 799–809 (1994).
37. Greenwood, J. P., Stoker, J. B. & Mary, D. A. Single-unit sympathetic discharge: quantitative assessment in human hypertensive disease. *Circulation* **100**, 1305–1310 (1999).
38. Schlaich, M. P. *et al.* Effects of transcatheter renal nerve ablation on sympathetic and neurohormonal activity in patients with resistant hypertension [abstract]. *J. Hypertens.* **30** (e-Suppl. 1), a787 (2012).
39. Oliveras, A. *et al.* Urinary albumin excretion is associated with true resistant hypertension. *J. Hum. Hypertens.* **24**, 27–33 (2010).
40. Amann, K. *et al.* Effects of low dose sympathetic inhibition on glomerulosclerosis and albuminuria in subtotally nephrectomized rats. *J. Am. Soc. Nephrol.* **11**, 1469–1478 (2000).
41. Wolf, G., Helmchen, U. & Stahl, R. A. Isoproterenol stimulates tubular DNA replication in mice. *Nephrol. Dial. Transplant.* **11**, 2288–2292 (1996).
42. Pavenstadt, H. Roles of the podocyte in glomerular function. *Am. J. Physiol. Renal. Physiol.* **278**, F173–F179 (2000).
43. Reinecke, M. & Forssmann, W. G. Neuropeptide (neuropeptide Y, neurotensin, vasoactive intestinal polypeptide, substance P, calcitonin gene-related peptide, somatostatin) immunohistochemistry and ultrastructure of renal nerves. *Histochemistry* **89**, 1–9 (1988).
44. Elenkov, I. J., Wilder, R. L., Chrousos, G. P. & Vizi, E. S. The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system. *Pharmacol. Rev.* **52**, 595–638 (2000).
45. Nave, H. *et al.* Reduced tissue immigration of monocytes by neuropeptide Y during endotoxemia is associated with Y2 receptor activation. *J. Neuroimmunol.* **155**, 1–12 (2004).
46. ten Bokum, A. M., Hofland, L. J. & van Hagen, P. M. Somatostatin and somatostatin receptors in the immune system: a review. *Eur. Cytokine Netw.* **11**, 161–176 (2000).
47. Delgado, M., Pozo, D. & Ganea, D. The significance of vasoactive intestinal peptide in immunomodulation. *Pharmacol. Rev.* **56**, 249–290 (2004).
48. Kezuka, T. *et al.* Peritoneal exudate cells treated with calcitonin gene-related peptide suppress murine experimental autoimmune uveoretinitis via IL-10. *J. Immunol.* **173**, 1454–1462 (2004).
49. O'Connor, T. M. *et al.* The role of substance P in inflammatory disease. *J. Cell Physiol.* **201**, 167–180 (2004).
50. Bowler, K. E. *et al.* Evidence for anti-inflammatory and putative analgesic effects of a monoclonal antibody to calcitonin gene-related peptide. *Neuroscience* **228**, 271–282 (2013).
51. Peters, H. *et al.* Angiotensin-converting enzyme inhibition but not β-adrenergic blockade limits transforming growth factor-β overexpression in acute normotensive anti-thy1 glomerulonephritis. *J. Hypertens.* **21**, 771–780 (2003).
52. Ditting, T., Tiegs, G. & Veelken, R. Autonomous innervation in renal inflammatory disease-innocent bystander or active modulator? *J. Mol. Med. (Berl.)* **87**, 865–870 (2009).
53. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* **57**, 911–917 (2011).
54. Symplicity HTN-2 Investigators *et al.* Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* **376**, 1903–1909 (2010).
55. Esler, M. D. *et al.* Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the Symplicity HTN-2 randomized, controlled trial. *Circulation* **126**, 2976–2982 (2012).
56. Worthley, S. G. *et al.* Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial. *Eur. Heart J.* **34**, 2132–2140 (2013).
57. Mahfoud, F. *et al.* Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. *Circulation* **128**, 132–140 (2013).
58. Persu, A. *et al.* Blood pressure changes after renal denervation at 10 European expert centers. *J. Hum. Hypertens.* **28**, 150–156 (2013).
59. Fadl Elmula, F. E. *et al.* Renal sympathetic denervation in patients with treatment-resistant hypertension after witnessed intake of medication before qualifying ambulatory blood pressure. *Hypertension* **62**, 526–532 (2013).
60. Schmieder, R. E., Ruilope, L. M., Ott, C., Mahfoud, F. & Bohm, M. Interpreting treatment-induced blood pressure reductions measured by ambulatory blood pressure monitoring. *J. Hum. Hypertens.* **27**, 715–720 (2013).
61. Jackson, R., Lawes, C. M., Bennett, D. A., Milne, R. J. & Rodgers, A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. *Lancet* **365**, 434–441 (2005).
62. Mancia, G. *et al.* 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J. Hypertens.* **31**, 1281–1357 (2013).
63. Mancia, G. & Parati, G. Office compared with ambulatory blood pressure in assessing response to antihypertensive treatment: a meta-analysis. *J. Hypertens.* **22**, 435–445 (2004).
64. Ott, C. *et al.* Vascular and renal hemodynamic changes after renal denervation. *Clin. J. Am. Soc. Nephrol.* **8**, 1195–1201 (2013).
65. Krum, H. *et al.* Renal artery denervation via catheter-based delivery of low-power radiofrequency energy provides safe and durable blood pressure reduction: complete 3 year results from SYMPLICITY HTN-1 [abstract]. *Eur. Heart J.* **34** (Suppl. 1), 3787 (2013).
66. Esler, M. D., Krum, H., Schlaich, M., Schmieder, R. E. & Boehm, M. TCT-58 persistent and safe blood pressure lowering effects of renal artery denervation: three year follow-up from the Symplicity HTN-2 Trial. *J. Am. Coll. Cardiol.* **62** (Suppl. 1), B19 (2013).
67. Krum, H. *et al.* Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet* **383**, 622–629 (2014).
68. Kaltenbach, B. *et al.* Renal artery stenosis after renal sympathetic denervation. *J. Am. Coll. Cardiol.* **60**, 2694–2695 (2012).
69. Vonend, O., Antoch, G., Rump, L. C. & Blondin, D. Secondary rise in blood pressure after renal denervation. *Lancet* **380**, 778 (2012).

70. Mahfoud, F. *et al.* Renal hemodynamics and renal function after catheter-based renal sympathetic denervation in patients with resistant hypertension. *Hypertension* **60**, 419–424 (2012).
71. Schmieder, R. E. *et al.* Changes in albuminuria predict mortality and morbidity in patients with vascular disease. *J. Am. Soc. Nephrol.* **22**, 1353–1364 (2011).
72. Grassi, G. *et al.* Neuroadrenergic and reflex abnormalities in patients with metabolic syndrome. *Diabetologia* **48**, 1359–1365 (2005).
73. Huggett, R. J. *et al.* Impact of type 2 diabetes mellitus on sympathetic neural mechanisms in hypertension. *Circulation* **108**, 3097–3101 (2003).
74. Mahfoud, F. *et al.* Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation* **123**, 1940–1946 (2011).
75. Witkowski, A. *et al.* Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. *Hypertension* **58**, 559–565 (2011).
76. DiBona, G. F. Sympathetic nervous system and hypertension. *Hypertension* **61**, 556–560 (2013).
77. Kurella, M., Lo, J. C. & Chertow, G. M. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J. Am. Soc. Nephrol.* **16**, 2134–2140 (2005).
78. Ryu, S. *et al.* Time-dependent association between metabolic syndrome and risk of CKD in Korean men without hypertension or diabetes. *Am. J. Kidney Dis.* **53**, 59–69 (2009).
79. Hering, D. *et al.* Renal denervation in moderate to severe CKD. *J. Am. Soc. Nephrol.* **23**, 1250–1257 (2012).
80. Kiuchi, M. G. *et al.* Effects of renal denervation with a standard irrigated cardiac ablation catheter on blood pressure and renal function in patients with chronic kidney disease and resistant hypertension. *Eur. Heart J.* **34**, 2114–2121 (2013).
81. Schlaich, M. P. *et al.* Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease. *Int. J. Cardiol.* **168**, 2214–2220 (2013).
82. Schmieder, R. E. *et al.* Does renal denervation stop renal function decline in treatment resistant hypertension: results of a pilot study [abstract]. *Circulation* **128**, A17557 (2013).
83. Mahfoud, F. *et al.* Expert consensus document from the European Society of Cardiology on catheter-based renal denervation. *Eur. Heart J.* **34**, 2149–2157 (2013).
84. Tsioufis, C. *et al.* What the interventionalist should know about renal denervation in hypertensive patients: a position paper by the ESH WG on the interventional treatment of hypertension. *EuroIntervention* **9**, 1027–1035 (2014).
85. Schmieder, R. E. *et al.* Updated ESH position paper on interventional therapy of resistant hypertension. *EuroIntervention* **9** (Suppl. R), R58–R66 (2013).
86. Schlaich, M. P. *et al.* International expert consensus statement: percutaneous transluminal renal denervation for the treatment of resistant hypertension. *J. Am. Coll. Cardiol.* **62**, 2031–2045 (2013).

Author contributions

R.V. and R.E.S. researched the data for the article, wrote the manuscript, provided substantial contributions to discussions of the content, and reviewed and/or edited the manuscript before submission.