

# Proceedings from the European clinical consensus conference for renal denervation: considerations on future clinical trial design

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## Introduction

Approximately 8–18% of all patients with high blood pressure (BP) are apparently resistant to drug treatment.<sup>1,2</sup> In this situation, new strategies to help reduce BP are urgently needed but the complex pathophysiology of resistant hypertension makes this search difficult. Not surprisingly in this context, the latest non-drug treatment which triggered controversy is catheter-based renal denervation (RDN).<sup>3,4</sup> The method uses radiofrequency energy, or alternatively ultrasound or chemical denervation, to disrupt renal nerves within the renal artery wall, thereby reducing sympathetic efferent and sensory afferent signalling to and from the kidneys.<sup>5,6</sup> Various experimental models of hypertension strongly support this concept<sup>7,8</sup> and available evidence also suggests that sympathetic nervous system activation

contributes to the development and progression of hypertension and subsequently to target organ damage.<sup>7–11</sup> Historical observations have shown that surgical sympathectomy can reduce BP as well as morbidity and mortality in patients with uncontrolled hypertension.<sup>12,13</sup> However, the clinical evidence in support of RDN as an effective interventional technique in patients with resistant hypertension is conflicting. A number of observational studies and three randomized, controlled trials (Symplicity HTN-2, Prague-15, and DENERHTN) support both safety and efficacy of this new therapy<sup>14–22</sup> but some smaller studies and the large, single-blind, randomized, sham-controlled symplicity HTN-3 trial failed to show superiority of RDN when compared with medical therapy alone.<sup>23–25</sup>

Whatever the shortcomings of individual trials may be, the possibility remains that the observed BP responses were due to placebo

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response, the Hawthorne effect, regression to the mean, unknown co-interventions or other bias.<sup>26</sup> The design, conduct, and interpretation of the trials in RDN have been discussed extensively elsewhere.<sup>27–30</sup> Accordingly, since the publication of the Symplicity HTN-3 results, some health care providers have been unwilling to endorse RDN in the absence of incontrovertible efficacy data. However, current evidence also seems equally insufficient to declare the technology a proven failure. Whenever doubts arise around the effectiveness of new treatment approaches, an assessment by rigorously designed studies is necessary to furnish conclusive evidence. With this controversy in mind, a multidisciplinary European Expert Group has convened on 9 December 2014 to assess the current gaps in our knowledge about RDN, unmet needs and where clinical trials may best be focused in the future. The current document represents a summary of the main conclusions of this clinical consensus conference. The topics are divided into three sections: procedural aspects, patient populations, and design considerations for future clinical trials.

## Procedural aspects

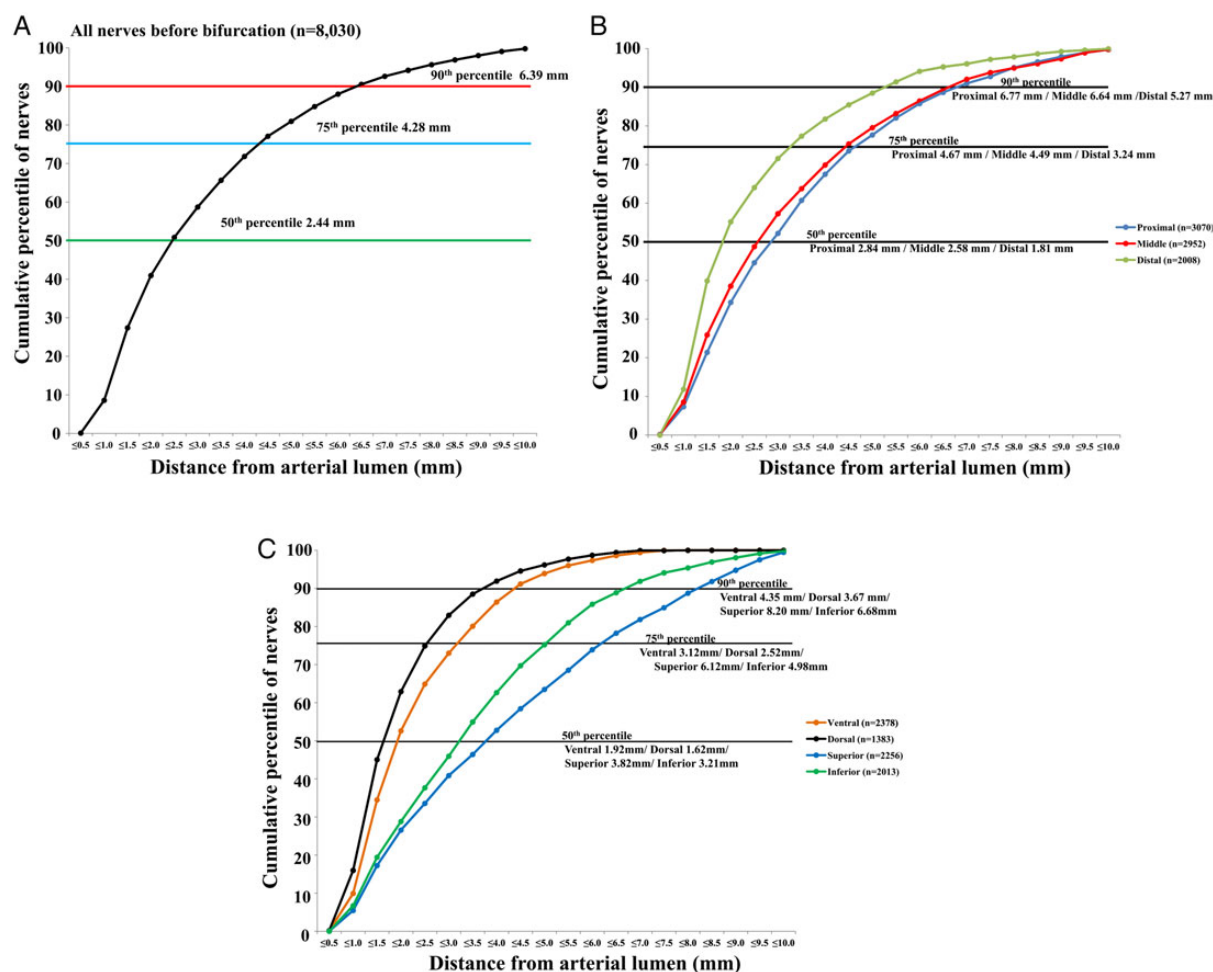
In the years, since the first studies on RDN, our view of the technique has significantly evolved.<sup>31–34</sup> Far from being a simple procedure that could be performed with little training by any interventionist regardless of their subspecialty, it is now recognized as a complex, specialized therapy whose primary and secondary success depends on a large number of influencing factors and uncertainties that may not be filled by our current knowledge. Moreover, there are a number of different systems, methods, and strategies currently employed in RDN (using uni- or bipolar radiofrequency energy, high-energy ultrasound and chemical ablation), which make it difficult to standardize treatment recommendations and compare different treatment modalities in patients.

The European Expert Group agreed that several procedural aspects need to be considered for future clinical trials, as they would help to improve reliability and thereby efficacy of the denervation technique:

- (i) Preclinical studies to assess the safety and efficacy of any RDN system are currently performed in healthy, normotensive animals. Our knowledge of peri-arterial renal nerve distribution in chronically hypertensive patients is very limited and it is unclear how far preclinical results can be applied to vessels subject to atherosclerosis. A suitable, hypertensive animal model would greatly help to answer open questions and to compare the different available catheters in terms of both surrogate markers (e.g. histological renal nerve ablation, renal norepinephrine content) and BP effects.
- (ii) The optimal degree of contact against the renal artery wall and the depth, location, duration, and intensity of energy delivery to provide the best procedural results are still being investigated. An extensive human autopsy study has shown the large variation in distribution and density of the renal sympathetic nervous system in the adventitia of renal arteries (Figure 1)<sup>33</sup>: the highest average number of nerves was observed in the proximal and middle segments of the renal artery and the lowest in the distal segments. Additionally, the mean distance from the

lumen to the nerve was much longer in proximal than in distal segments. These human and other preclinical observations suggest that asymmetric and most probably distal renal artery targeting is required to achieve effective ablation of renal sympathetic nerves.<sup>34,35</sup> However, in many of the clinical trials there was no specific advice on how to apply energy and thus interventionists did not specifically treat in this area, potentially thereby reducing the efficacy of the procedure.<sup>28</sup>

- (iii) The degree of RDN has been documented by norepinephrine spillover before and 30 days after the procedure in a small subgroup of 17 patients.<sup>36</sup> The response to RDN was 40% on average, but was highly variable, ranging from 0 to 80%. Such a variability of treatment effects has also been documented in preclinical studies in pigs, when four radiofrequency ablations were applied in the main renal artery.<sup>28</sup> The application of radiofrequency energy post-bifurcation has been shown to reduce variability in treatment effects in pigs. It should be kept in mind that, if distal ablation may improve the effectiveness of RDN, it should also not increase the risk of the procedure. However, the occurrence of distal RDN-induced renal artery stenosis (RAS), if any, may be more challenging to revascularize by angioplasty, stenting or surgery. Further, the proximity to the ureter and other soft tissue need be considered.
- (iv) Maximum procedural efficacy would also mean the achievement of ablation in all four quadrants, the whole circumference, of both renal arteries. In Symplicity, this was achieved in only a small proportion of patients (<30%). A *post hoc* analysis indicated that per-protocol bilateral 4-quadrant RDN was associated with the greatest reductions in office, home and ambulatory systolic BP.<sup>29</sup> Low-pressure balloon catheters designed for RDN<sup>20,37</sup> may achieve a more complete and reproducible circumferential ablation with less between-interventionists procedural variability, but head-to-head comparisons of available catheters are lacking.
- (v) There appears to be a 'dose–response' dependency between the number of ablation attempts and the efficacy of renal nerve ablation in both *post hoc* clinical and prospective preclinical investigations.<sup>29</sup> However, the minimum and maximum 'effective dose' of energy delivery and ablation attempts at the individual level remains to be determined precisely, although there is no simple way to assess it in humans.
- (vi) The feasibility, need and consequences of treating small renal arteries (<4 mm), accessory, polar or segment arteries remains to be clarified. Indeed, some of these small arteries cannot be treated by the available catheters. The new emerging systems may need modification of their profile to enable better and safer access to renal arteries of different calibre. Furthermore, induction of a *de novo* RAS or progression of pre-existing RAS after RDN and long-term vascular safety need to be carefully investigated.<sup>38,39</sup>
- (vii) The lack of reliable markers of procedural success to immediately establish on time whether denervation has been completely achieved in a specific patient remains the major unmet need. As a result, it is uncertain if the negative trials arise from sub-optimal application of the technology or if the technique, even when optimally applied, does not work. A number of efficacy markers have been explored but there is no consensus on



**Figure 1** Cumulative distribution of nerves at distance from lumen before the bifurcation (A), divided into proximal, middle, and distal segments (B), and divided into ventral, dorsal, superior, and inferior regions (C). With permission from Sakakura et al.<sup>33</sup>

their usefulness, even when indices of sympathetic control, such as baroreflex function, has been taken into account.<sup>40</sup> Some early studies indicated that noradrenaline levels or electrical stimulation of the renal artery may correlate with ablation efficacy,<sup>41,42</sup> but this would need confirmation in larger studies and besides the latter is associated with pain and substantial discomfort to patients.

## Patient population

Catheter-based RDN has been investigated and used primarily as a last resort in patients with resistant hypertension (defined as systolic BP  $\geq 160$  mmHg,  $\geq 150$  mmHg in diabetes mellitus while on a regimen of  $\geq 3$  anti-hypertensive drugs of different classes, including a diuretic, at maximal or highest tolerated dose).<sup>1,3</sup> The rationale was the great need to lower BP and thereby cardiovascular events in high-risk patients lacking suitable alternative treatments, as these patients are per definition resistant to standard drug treatment.<sup>1</sup> Renal denervation was not developed to replace the ongoing anti-hypertensive treatment. Standardized evaluation of patients referred

to specialized hypertension clinics because of apparent resistant hypertension, has shown that this patient group is characterized by a variable mix of conditions not necessarily likely to exhibit the greatest response to RDN therapy.<sup>18,43</sup> Indeed, the high prevalence of target organ damage, including renal fibrosis and vascular stiffness, which are difficult to reverse, renders BP control difficult to achieve whatever methods are used. Moreover, in these patients, the ongoing oral anti-hypertensive treatment prescribed by the physicians in a variable and non-reproducible manner and taken by the patients in a variable and non-reproducible manner remains a major confounding factor to analyse precisely the true BP effect of any procedure. There was an extensive and controversial discussion within the European Expert Group, which patients will have the highest likelihood to benefit from RDN.

## Identification of the appropriate patient population

To improve the efficacy of RDN, the procedure needs to be targeted upon a population with high probability of BP response. This is complicated by (i) the complex pathophysiology of hypertension,

especially resistant hypertension, (ii) the lack of clinically applicable, reliable, easy, and reproducible measures of 'increased sympathetic activity' that could be used to guide treatment decisions, and (iii) the absence of pre-procedural useful predictors of the long-term BP response following RDN. Although the importance of renal nerve signalling in hypertension has been shown by a number of studies in humans,<sup>8,10</sup> there are many factors besides sympathetic nervous system activation that can drive increases in BP. To date, there is no clearly established link between sympathetic nervous system activity and response to RDN<sup>44,45</sup>; however, this does not necessarily mean that the concept is mistaken. Rather an appropriate investigative method to quantify precisely and reliably the central sympathetic activity in humans with such a precision to delineate predictive parameters in each individual patient is missing. Clearly, there is a need for more research on this topic. A caveat with the above discussion is therefore that there is currently insufficient evidence to conclude that reducing sympathetic activity to the kidneys would inevitably reduce BP in patients with increased sympathetic nervous system activity.

Isolated systolic hypertension (ISH), defined as office systolic BP  $\geq 140$  mmHg and diastolic BP  $< 90$  mmHg is the pre-dominant hypertensive subtype in elderly patients.<sup>46,47</sup> ISH is characterized by an increased aortic stiffness, increased pressure wave reflections, and low pulse pressure amplification.<sup>48</sup> Data indicate that ISH is associated with limited response to RDN,<sup>49,50</sup> as it could be expected from drug trials. Accordingly, increased central pulse pressure indicate of aortic stiffness is related to worse BP response after RDN.<sup>50</sup> Furthermore, patients who failed to respond to RDN exhibited striking BP lowering in the ROX Coupler Study,<sup>51</sup> suggesting that targeting arterial stiffness rather than sympathomodulation would be a superior approach in such patients.

## Methodology and clinical trials

Any new trial in RDN needs to undoubtedly demonstrate that the technology is actually effective, i.e. that catheter-based RDN reduces the generally accepted surrogate marker BP. The European Expert Group did not attempt to design a comprehensive clinical trial protocol in detail. The discussion did focus on a number of salient methodological points that need to be taken into consideration and identified open questions as follows.

### What is the most suitable patient population?

Patients with resistant hypertension currently considered eligible for RDN therapy may not be the population most likely to respond with the greatest decrease in BP. Also, it is challenging to find a sufficient number of proven, treatment-resistant severely hypertensive patients for an adequately powered trial.<sup>22</sup> An alternative may be to run a trial in younger patients with milder forms of hypertension. This would have several advantages. First and foremost, younger patients tend to have greater sympathetic nervous system activation than older patients.<sup>52,53</sup> Secondly, the arterial wall in younger, less severely hypertensive patients might be more responsive to RDN-induced changes in sympathetic tone since vascular remodelling is still in a reversible state. Reducing pill burden might be of particular

benefit in this young population. However, it is deemed necessary to consider potential concerns when treating patients with mild stages of hypertension (e.g. to take the risk-benefit ratio into account). Indeed, a new trial in severe resistant hypertension would not pose ethical concerns, since there are only limited other therapeutic alternatives.<sup>51,54</sup> In contrast, patients with mild to moderate hypertension have safe and well-established alternatives to an invasive procedure and may respond well to such conservative treatment. A way to ensure an ethical conduct would be to include the option of patient's preference in the study design. The European Expert group favoured the inclusion of patients with moderate rather than resistant hypertension as preferred population to be studied next. Whichever the degree of hypertension is chosen, there is widespread consensus among the Expert group that patients with ISH or severe grade III chronic kidney disease (CKD) (defined as  $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ ) should be excluded from the proof of concept (phase II) and phase III efficacy trials. Impaired renal function is also currently considered a contraindication for RDN, due to safety issues.<sup>3</sup> Nephrologists within the Experts Group argued for applying RDN in CKD based on a very strong pathophysiologic rationale<sup>55</sup> and preliminary clinical data.<sup>56–59</sup>

### Should there be a washout period?

A medication washout period is often recommended in the design of clinical trials to allow the BP to return to pre-treatment levels.<sup>60</sup> However, the European Expert Group considered this to be unacceptable for further studies of RDN in resistant hypertensive patients. In general, patients with high BP on multiple drugs should not be subjected to washout as this is well known to be associated with increased risk for events, in particular stroke.<sup>61,62</sup> Conceptually, a washout period may be acceptable in patients treated with one or two drugs provided strict regimens for escape algorithms would be applied in order to assess the 'pure' effect of RDN on BP. There was wide agreement within the Expert group that washout should only be performed, if at all, by highly experienced investigators and research centres familiar with drug withdrawal algorithms.<sup>22</sup>

### Should ambulatory blood pressure be the primary end point instead of office blood pressure?

Twenty-four hour ambulatory BP monitoring (ABPM) provides more precise BP profiles when compared with office BP, since it provides the average of a large number of readings performed during normal conditions of life but also during nocturnal rest.<sup>63–65</sup> Several studies documented better prognostic value of ambulatory over office BP in different populations.<sup>66–70</sup> In patients with resistant hypertension, the use of ABPM is considered mandatory for exclusion of pseudo-resistance due to 'white-coat' effect.<sup>1,3,4</sup> The BP reduction induced by any anti-hypertensive treatment largely differs when the measurement are performed by office or ABPM and the extent of the discrepancies depends on the BP values at baseline and the degree of white-coat reaction.<sup>67,71</sup> The absence of ABPM as the efficacy measure has been noted as a weakness of many trials in RDN,<sup>26,72</sup> except for the DENERHTN study which successfully used change in daytime mean ambulatory systolic BP as the primary endpoint.<sup>22</sup> The Expert group was strongly in favour of



ambulatory BP as the primary measure of response to RDN but also as inclusion criterion for a number of reasons. Ambulatory BP monitoring is less susceptible to bias and placebo effect than office-based measurements,<sup>64,73</sup> can be easily analysed blind to the allocation of treatment, and allows improved selection of patients for the procedure, as patients with white-coat hypertension will unlikely show any effect on 24-h BP.<sup>17</sup> Importantly, ambulatory BP is an independent predictor of outcome<sup>70,74</sup> and hence a valid end point. The only weakness is the lack of evidence-based recommendations for target BP based on ambulatory values, although the ESH has provided threshold for normal ambulatory BP levels,<sup>64</sup> but this is of minor importance since the magnitude of decrease in ambulatory BP is the primary study objective. The Expert group considered a reduction of 5 mmHg in daytime systolic BP as a clinical meaningful reduction, which might be used for sample size calculations. In order to reduce between-patients variability and thus the standard deviation around the expected difference, ABPM should be standardized (validated devices, appropriate cuff, timing with regards of the last intake of anti-hypertensive drugs, number of BP measurements, etc.) according to international guidelines<sup>64</sup> and optimally analysed by a blinded core lab.

## How should adherence with anti-hypertensive therapies be measured and ensured?

Non-adherence to treatment is frequent in 'resistant' hypertensive patients.<sup>75,76</sup> It has been speculated that lack of standardized treatment and sub-optimal adherence before as well as after denervation may have confounded the results of earlier studies.<sup>26</sup> In any further trial, it will be essential to standardize the concomitant therapies and to at least evaluate or even optimize adherence. Given the doubts around the efficacy of RDN,<sup>23</sup> adherence criteria in patients receiving multiple anti-hypertensive drugs may well need to be stricter than in a pharmacological trial, although it is very difficult to ensure and assess adherence properly.<sup>77</sup> Furthermore, there are no strategies to improve medication adherence that have been demonstrated to be of long-term benefit. Directly observed therapy where patients take their drugs in the presence of a healthcare professional,<sup>78</sup> has been successfully used in smaller RDN studies but may be difficult to implement in a large-scale multicentre trial.<sup>24,28</sup> Today, there are multiple ways of assessing drug adherence in patients but only few of them are really accurate and the most accurate one are difficult to implement in clinical practise.<sup>79,80</sup> However, the option to include adherence-promoting programmes and compliance assessment in a trial design seems worth exploring. Electronic pill dispensers record each opening of a pill container over weeks or months and thus may provide an account of the regularity of drug intake and represent an attractive tool for future studies in the field, but this method does not guarantee that the patient has indeed taken the treatment.<sup>81</sup> Consensus has been reached that at least meticulous monitoring of adherence is required in future trials. This would at least allow adjusting the results for this major confounder.

## Is a sham procedure necessary?

The use of a sham procedure and the associated unmasking of a placebo effect has been suggested as the reason for the lack of

observed benefits from RDN in symplicity HTN-3.<sup>82</sup> Sham procedures can reduce possible placebo and Hawthorne effects; however, their use does not eliminate other sources of bias such as variations in treatment score and dosages prescribed by the physicians and adherence to treatment by the patients. The Expert group questions and expressed serious concerns, whether a sham procedure would be necessary in a trial of resistant hypertensive on standardized treatment and if adherence variability can be minimized with ambulatory BP as the primary end point. In addition, the risk to patients from the sham procedure should be taken into consideration. In the case of RDN, this risk is not negligible and the use of invasive sham is possibly unethical in mild to moderate hypertensive patients, although probably most adequate to be implemented in this patient population. A sham procedure might be acceptable if it consists only of general anaesthesia and puncture of the groin with no use of renal angiography (which would expose patients to radiation, contrast dye unnecessarily and the risk of selective renal arteriography).

## Handling of concomitant medication

The European Expert Group had a clear opinion on standardization of concomitant therapy. A longer stable run-in period with unchanged adequate combination of anti-hypertensive drugs, including a maximal dose of diuretic and at best a renin-angiotensin system blocker and a calcium channel blocker of at least 4–8 weeks appeared to be appropriate. There was contention about whether all patients need to be switched onto the same treatment regimen prior to RDN to reduce between-subject variability, as done in the DENERHTN trial.<sup>22</sup> It remains to be disputed whether all patients should be on mineralocorticoid antagonist or at least should have been exposed to this drug class before RDN is considered. The prescription of a 4th line of anti-hypertensive treatment, such as spironolactone, may decrease BP but would make the recruitment still more difficult. Moreover, the addition of one more pill on top of many others before entry into the trial may influence compliance to treatment. Unanimously, strict standardization of the anti-hypertensive treatment appeared to be the key.

## Health economics issues: impact on the clinical pathway

There have been several publications on the economic evaluation of RDN for the treatment of resistant hypertension.<sup>83–85</sup> These publications rely on Markov models applied on the very positive results of Symplicity HTN-2,<sup>15</sup> which allow the extrapolation of systolic BP changes on reduction in cardiovascular endpoints. The models used are very similar and yield consistent results in terms of gain in quality adjusted life years of ~1-year gain over patient's lifetime. The economic studies use extrapolation models, which all assume that the reduction in systolic BP obtained by RDN are (i) sustainable and (ii) associated with the same decrease in events as reduction induced by drug treatment in the course of randomized trials. Both assumptions can be challenged by the fact that effectiveness of a drug investigated in a trial is higher compared with real life situations.<sup>86,87</sup> In addition, these models ignore the costs of setting-up an outpatient clinic to screen and select hypertensive patients, who are eligible for RDN.<sup>83–85,88</sup> It is, however, debatable whether

these costs should be included if RDN is undertaken only in high volume centres with established hypertension clinics while low volume centres are excluded for both efficacy and efficiency reasons. The European Expert Group established that several health economics issues should be addressed in future clinical studies:

- (1) Individual patients' pathways flow charts for information about patients screened in hypertension clinics are needed.
- (2) Models need to be re-analysed when data on adverse event occurrence and on the sustainability of BP reduction are available.
- (3) Consistent data collection for resource utilization needs to be ensured.

## Summary and outlook

A number of important questions still need to be addressed in order to establish an evidence base for RDN that would permits its adoption for routine clinical use (Box 1). Much of the unmet need distils down to the issue of standardization. This applies to the technology and the technique, where different systems may not work equally well in all situations. It applies to the terminology used, as well as to markers of procedural success. And perhaps most of all, standardization will be key when designing clinical trials. Treatments, populations, methods, and adherence measures need to be highly consistent to avoid inconclusive or biased results. Finally, we urgently need to delineate predictors of BP response following RDN. Only then we will be able to individualize patient care and even expand this intervention to specific hypertension patient groups. The open questions around RDN touch upon a large number of specialties from interventional cardiologists to hypertension experts and

molecular biologists. The future of the therapy will depend on closer interactions at all levels, necessitating smaller projects targeting specific questions as well as large-scale multidisciplinary research programmes. RDN may or may not be a breakthrough therapy. Focused, collaborative high-quality research will be necessary to ensure that future patients are neither denied an effective therapy nor needlessly put at risk from procedures that bring no benefits.

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### Box 1: Recommendations for future randomized controlled trials on renal denervation in hypertension

#### Study population

- Include patients with moderate rather than resistant hypertension reflecting the pathogenetic importance of sympathetic activity in earlier stages.
- Exclude patients with stiff large arteries (e.g. isolated systolic hypertension) for the next pivotal trial.

#### Study design

- Perform wash out period only in highly experienced centers (safety concerns).
- Consider sham procedure with renal angiography as potentially unethical in mild to moderate hypertension.
- Standardize concomitant antihypertensive therapy (preferentially all treated with the combination of a RAS-blocker, calcium channel blocker and diuretic in the run-in period).
- Monitor drug adherence as potential confounder of blood pressure response (e.g. pill counting, electronic pill dispensers, toxicological drug analysis).

#### Study outcomes

- Use change in ambulatory blood pressure as the primary efficacy endpoint (strictly standardized), while change in office blood pressure should be considered as secondary parameter.
- Delineate clinically easy accessible predictors for blood pressure efficacy.
- Incorporate health-economic analysis beyond the Markov-models.

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## References

- Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Burnier M, Ambrosioni E, Caulfield M, Coca A, Olsen MH, Tsoufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Ferrari R, Hasdai D, Hoes AW, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Gillebert TC, Rosoi EA, Anker SD, Bauersachs J, Hiti J, Caulfield M, De Buyere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Ryden L, Sirenko Y, Stanton A, Struijker-Boudier H, Vlachopoulos C, Volpe M, Wood DA. 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). *Eur Heart J* 2013;**34**: 2159–2219.
- Judd E, Calhoun DA. Apparent and true resistant hypertension: definition, prevalence and outcomes. *J Hum Hypertens* 2014;**28**:463–468.
- Mahfoud F, Lüscher TF, Andersson B, Baumgartner I, Cifkova R, Dimario C, Doevendans P, Fagard R, Fajadet J, Komajda M, Lefevre T, Lotan C, Sievert H, Volpe M, Widimsky P, Wijns W, Williams B, Windecker S, Witkowski A, Zeller T, Böhm M. Expert consensus document from the European Society of Cardiology on catheter-based renal denervation. *Eur Heart J* 2013;**34**:2149–2157.
- Schmieder RE, Redon J, Grassi G, Kjeldsen SE, Mancia G, Narkiewicz K, Parati G, Ruilope L, van de Borne P, Tsoufis C. Updated ESH position paper on interventional therapy of resistant hypertension. *EuroIntervention* 2013;**9**(Suppl. R):R58–R66.
- Böhm M, Linz D, Ukena C, Esler M, Mahfoud F. Renal denervation for the treatment of cardiovascular high risk-hypertension or beyond? *Circ Res* 2014;**115**:400–409.
- Tsoufis C, Mahfoud F, Mancia G, Redon J, Damascelli B, Zeller T, Schmieder RE. 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* 2014;**9**:1027–1035.
- DiBona GF. Physiology in perspective: The Wisdom of the Body. Neural control of the kidney. *Am J Physiol Regul Integr Comp Physiol* 2005;**289**:R633–R641.
- Esler M. The 2009 Carl Ludwig lecture: pathophysiology of the human sympathetic nervous system in cardiovascular diseases: the transition from mechanisms to medical management. *J Appl Physiol* 2010;**108**:227–237.
- Smith PA, Graham LN, Mackintosh AF, Stoker JB, Mary DA. Relationship between central sympathetic activity and stages of human hypertension. *Am J Hypertens* 2004;**17**:217–222.
- Esler M. Sympathetic nervous system moves toward center stage in cardiovascular medicine: from Thomas Willis to resistant hypertension. *Hypertension* 2014;**63**: e25–e32.
- Parati G, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. *Eur Heart J* 2012;**33**:1058–1066.
- Smithwick RH. Surgical treatment of hypertension. *Am J Med* 1948;**4**:744–759.
- Smithwick RH, Thompson JE. Splanchnicectomy for essential hypertension: results in 1,266 cases. *J Am Med Assoc* 1953;**152**:1501–1504.
- Esler MD, Krum H, Schlaich M, Schmieder RE, Böhm M, Sobotka PA. Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the Symplicity HTN-2 randomized, controlled trial. *Circulation* 2012;**126**:2976–2982.
- Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. *Lancet* 2010;**376**:1903–1909.
- Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009;**373**:1275–1281.
- Mahfoud F, Ukena C, Schmieder RE, Cremers B, Rump LC, Vonend O, Weil J, Schmidt M, Hoppe UC, Zeller T, Bauer A, Ott C, Blessing E, Sobotka PA, Krum H, Schlaich M, Esler M, Böhm M. Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. *Circulation* 2013;**128**: 132–140.
- Persu A, Jin Y, Azizi M, Baelen M, Volz S, Elvan A, Severino F, Rosa J, Adiyaman A, Fadl Elmula FE, Taylor A, Pechere-Bertschi A, Wuertner G, Jokhaji F, Kahan T, Renkin J, Monge M, Widimsky P, Jacobs L, Burnier M, Mark PB, Kjeldsen SE, Andersson B, Sapoval M, Staessen JA. Blood pressure changes after renal denervation at 10 European expert centers. *J Hum Hypertens* 2014;**28**:150–156.
- Worthley SG, Tsoufis CP, Worthley MI, Sinhal A, Chew DP, Meredith IT, Malaipapan Y, Papademetriou V. Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial. *Eur Heart J* 2013;**34**:2132–2140.
- Sievert H, Schofer J, Ormiston J, Hoppe UC, Meredith IT, Walters DL, Azizi M, Diaz-Cartelle J, Cohen-Mazor M. Renal denervation with a percutaneous bipolar radiofrequency balloon catheter in patients with resistant hypertension: 6-month results from the REDUCE-HTN clinical study. *EuroIntervention* 2015;**10**:1213–1220.
- Ott C, Mahfoud F, Schmid A, Ditting T, Sobotka PA, Veelen R, Spies A, Ukena C, Laufs U, Uder M, Böhm M, Schmieder RE. Renal denervation in moderate treatment-resistant hypertension. *J Am Coll Cardiol* 2013;**62**:1880–1886.
- Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, Midulla M, Mounier-Vehier C, Courand PY, Lantelme P, Denolle T, Dourmap-Collass C, Trillaud H, Pereira H, Plouin PF, Chatellier G. The Renal Denervation for Hypertension i. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* 2015; doi: 10.1016/S0140-6736(14)61942-5.
- Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL, Investigators SH-. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014;**370**:1393–1401.
- Fadl Elmula FE, Hoffmann P, Fossum E, Brekke M, Gjonnaess E, Hjornholm U, Kjaer VN, Rostrop M, Kjeldsen SE, Os I, Stenehjem AE, Hoieggan A. Renal sympathetic denervation in patients with treatment-resistant hypertension after witnessed intake of medication before qualifying ambulatory blood pressure. *Hypertension* 2013;**62**:526–532.
- Fadl Elmula FEM, Hoffmann P, Larstorp AC, Fossum E, Brekke M, Kjeldsen SE, Gjonnaess E, Hjornholm U, Kjaer VN, Rostrop M, Os I, Stenehjem A, Hoieggan A. Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. *Hypertension* 2014;**63**:991–999.
- Zannad F, Stough WG, Mahfoud F, Bakris GL, Kjeldsen SE, Kieval RS, Haller H, Yared N, De Ferrari GM, Pina IL, Stein K, Azizi M. Design considerations for clinical trials of autonomic modulation therapies targeting hypertension and heart failure. *Hypertension* 2015;**65**:5–15.
- Schmieder RE. Hypertension: how should data from SYMPPLICITY HTN-3 be interpreted? *Nat Rev Cardiol* 2014;**11**:375–376.
- Mahfoud F, Lüscher TF. Renal denervation: simply trapped by complexity? *Eur Heart J* 2015;**36**:199–202.
- Kandzari DE, Bhatt DL, Brar S, Devireddy CM, Esler M, Fahy M, Flack JM, Katzen BT, Lea J, Lee DP, Leon MB, Ma A, Massaro J, Mauri L, Oparil S, O'Neill WW, Patel MR, Rocha-Singh K, Sobotka PA, Svetkey L, Townsend RR, Bakris GL. Predictors of blood pressure response in the SYMPPLICITY HTN-3 trial. *Eur Heart J* 2015;**36**:219–227.
- Lüscher TF, Mahfoud F. Renal nerve ablation after SYMPPLICITY HTN-3: confused at the higher level? *Eur Heart J* 2014;**35**:1706–1711.
- Tzafiriri AR, Mahfoud F, Keating JH, Markham PM, Spognardi A, Wong G, Fuimaono K, Böhm M, Edelman ER. Innervation patterns may limit response to endovascular renal denervation. *J Am Coll Cardiol* 2014;**64**:1079–1087.
- Mahfoud F, Bhatt DL. Catheter-based renal denervation: the black box procedure. *JACC Cardiovasc Interv* 2013;**6**:1092–1094.
- Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, Kolodgie FD, Virmani R, Joner M. Anatomic assessment of sympathetic peri-arterial renal nerves in man. *J Am Coll Cardiol* 2014;**64**:635–643.
- Mahfoud F, Edelman ER, Böhm M. Catheter-based renal denervation is no simple matter: lessons to be learned from our anatomy? *J Am Coll Cardiol* 2014;**64**:644–646.
- Henegar JR, Zhang Y, Hata C, Narciso I, Hall ME, Hall JE. Catheter-based radiofrequency renal denervation: location effects on renal norepinephrine. *Am J Hypertens* 2015; doi: 10.1093/ajh/hpu048.

36. Esler M. Illusions of truths in the simplicity HTN-3 trial: generic design strengths but neuroscience failings. *J Am Soc Hypertens* 2014;**8**:593–598.
37. Sakakura K, Roth A, Ladich E, Shen K, Coleman L, Joner M, Virmani R. Controlled circumferential renal sympathetic denervation with preservation of the renal arterial wall using intraluminal ultrasound: a next-generation approach for treating sympathetic overactivity. *EuroIntervention* 2015;**10**:1230–1238.
38. Persu A, Sapoval M, Azizi M, Monge M, Danse E, Hammer F, Renkin J. Renal artery stenosis following renal denervation: a matter of concern. *J Hypertens* 2014;**32**: 2101–2105.
39. Mahfoud F, Kjeldsen SE. Catheter-based renal denervation: a word of caution. *Euro-Intervention* 2013;**8**.
40. Zuern CS, Eick C, Rizas KD, Bauer S, Langer H, Gawaz M, Bauer A. Impaired cardiac baroreflex sensitivity predicts response to renal sympathetic denervation in patients with resistant hypertension. *J Am Coll Cardiol* 2013;**62**:2124–2130.
41. Gal P, de Jong MR, Smit JJJ, Adiyaman A, Staessen JA, Elvan A. Blood pressure response to renal nerve stimulation in patients undergoing renal denervation: a feasibility study. *J Hum Hypertens* 2015;**29**:292–295.
42. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, Shirokova N, Karaskov A, Mittal S, Steinberg JS. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol* 2012;**60**:1163–1170.
43. Verloop WL, Vink EE, Voskuil M, Vonken EJ, Rookmaaker MB, Bots ML, Doevendans PA, Blankestijn PJ, Spiering W. Eligibility for percutaneous renal denervation: the importance of a systematic screening. *J Hypertens* 2013;**31**:1662–1668.
44. Hering D, Lambert EA, Marusic P, Walton AS, Krum H, Lambert GW, Esler MD, Schlaich MP. Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. *Hypertension* 2013;**61**:457–464.
45. Vink EE, Verloop WL, Siddiqi L, van Schelven LJ, Liam Oey P, Blankestijn PJ. The effect of percutaneous renal denervation on muscle sympathetic nerve activity in hypertensive patients. *Int J Cardiol* 2014;**176**:8–12.
46. Zhang Y, Zhang X, Liu L, Zanchetti A, Group FS. Is a systolic blood pressure target <140 mmHg indicated in all hypertensives? Subgroup analyses of findings from the randomized FEVER trial. *Eur Heart J* 2011;**32**:1500–1508.
47. Franklin SS, Thijs L, Hansen TW, Li Y, Boggia J, Kikuya M, Bjorklund-Bodegard K, Ohkubo T, Jeppesen J, Torp-Pedersen C, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Imai Y, Wang J, Ibsen H, O'Brien E, Staessen JA, International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes I. Significance of white-coat hypertension in older persons with isolated systolic hypertension: a meta-analysis using the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes population. *Hypertension* 2012;**59**:564–571.
48. Logan AG. Hypertension in aging patients. *Expert Rev Cardiovasc Ther* 2011;**9**: 113–120.
49. Ewen S, Ukena C, Linz D, Kindermann I, Cremers B, Laufs U, Wagenpfeil S, Schmieder RE, Böhm M, Mahfoud F. Reduced effect of percutaneous renal denervation on blood pressure in patients with isolated systolic hypertension. *Hypertension* 2015;**65**:193–199.
50. Ott C, Schmid A, Toennes SW, Ditting T, Veelken R, Uder M, Schmieder R. Central pulse pressure predicts BP reduction after renal denervation in patients with treatment resistant hypertension. *EuroIntervention* 2015; in press.
51. Lobo MD, Sobotka PA, Stanton A, Cockcroft JR, Sulke N, Dolan E, van der Giet M, Hoyer J, Furniss SS, Foran JP, Witkowski A, Januszewicz A, Schoors D, Tsioufis K, Rensing BJ, Scott B, Ng GA, Ott C, Schmieder RE, for the ROXCHTNI. Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial. *Lancet* 2015; **385**:1634–1641.
52. Julius S, Majahalme S. The changing face of sympathetic overactivity in hypertension. *Ann Med* 2000;**32**:365–370.
53. Esler M, Jennings G, Biviano B, Lambert G, Hasking G. Mechanism of elevated plasma noradrenaline in the course of essential hypertension. *J Cardiovasc Pharmacol* 1986; **8**(Suppl. 5):S39–S43.
54. Scheffers JJ, Kroon AA, Schmidli J, Jordan J, Tordoir JJ, Mohaupt MG, Luft FC, Haller H, Menne J, Engeli S, Ceral J, Eckert S, Erglis A, Narkiewicz K, Philipp T, de Leeuw PW. Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study. *J Am Coll Cardiol* 2010;**56**:1254–1258.
55. Veelken R, Schmieder RE. Renal denervation – implications for chronic kidney disease. *Nat Rev Nephrol* 2014;**10**:305–313.
56. de Beus E, de Jager R, Joles JA, Grassi G, Blankestijn PJ. Sympathetic activation secondary to chronic kidney disease: therapeutic target for renal denervation? *J Hypertens* 2014;**32**:1751–1761.
57. Vink EE, Verloop WL, Bost RB, Voskuil M, Spiering W, Vonken EJ, Bots ML, Blankestijn PJ. The blood pressure-lowering effect of renal denervation is inversely related to kidney function. *J Hypertens* 2014;**32**:2045–2053.
58. Hering D, Mahfoud F, Walton AS, Krum H, Lambert GW, Lambert EA, Sobotka PA, Böhm M, Cremers B, Esler MD, Schlaich MP. Renal denervation in moderate to severe CKD. *J Am Soc Nephrol* 2012;**23**:1250–1257.
59. Ott C, Mahfoud F, Schmid A, Toennes SW, Ewen S, Ditting T, Veelken R, Ukena C, Uder M, Böhm M, Schmieder R. Renal denervation preserves renal function in patients with chronic kidney disease and resistant hypertension. *J Hypertens* 2015; **33**:1261–1266.
60. European Medicines Agency. *Guideline on clinical investigation of medicinal products in the treatment of hypertension*. London, 2010; EMA/238/1995/Rev. 3.
61. Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beveers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H, Group LS. Cardiovascular morbidity and mortality in the Losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;**359**:995–1003.
62. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A, group Vt. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;**363**:2022–2031.
63. Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. *N Engl J Med* 2006;**354**:2368–2374.
64. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, Clement D, de la Sierra A, de Leeuw P, Dolan E, Fagard R, Graves J, Head GA, Imai Y, Kario K, Lurbe E, Mallion JM, Mancia G, Mengden T, Myers M, Ogedegbe G, Ohkubo T, Ombroni S, Palatini P, Redon J, Ruilope LM, Shennan A, Staessen JA, vanMontfrans G, Verdecchia P, Waeber B, Wang J, Zanchetti A, Zhang Y, European Society of Hypertension Working Group on Blood Pressure M, Cardiovascular V. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 2014;**32**:1359–1366.
65. Redon J, Lurbe E. Ambulatory blood pressure monitoring is ready to replace clinic blood pressure in the diagnosis of hypertension: con side of the argument. *Hypertension* 2014;**64**:1169–1174.
66. Redon J, Campos C, Narciso ML, Rodicio JL, Pascual JM, Ruilope LM. Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. *Hypertension* 1998;**31**:712–718.
67. Mancia G, Bombelli M, Facchetti R, Madotto F, Quarti-Trevano F, Polo Friz H, Grassi G, Sega R. Long-term risk of sustained hypertension in white-coat or masked hypertension. *Hypertension* 2009;**54**:226–232.
68. Mancia G, Parati G. Ambulatory blood pressure monitoring and organ damage. *Hypertension* 2000;**36**:894–900.
69. Mancia G, Parati G. Office compared with ambulatory blood pressure in assessing response to antihypertensive treatment: a meta-analysis. *J Hypertens* 2004;**22**:435–445.
70. Mancia G, Zanchetti A, Agabiti-Rosei E, Benemio G, De Cesaris R, Fogari R, Pessina A, Porcellati C, Rappelli A, Salvetti A, Trimarco B. Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy. SAMPLE Study Group. Study on ambulatory monitoring of blood pressure and lisinopril evaluation. *Circulation* 1997;**95**: 1464–1470.
71. Schmieder RE, Schmidt ST, Riemer T, Dechend R, Hagedorn I, Senges J, Messerli FH, Zeymer U. Disproportional decrease in office blood pressure compared with 24-hour ambulatory blood pressure with antihypertensive treatment: dependency on pretreatment blood pressure levels. *Hypertension* 2014;**64**:1067–1072.
72. Lobo MD, de Belder MA, Cleveland T, Collier D, Dasgupta I, Deanfield J, Kapil V, Knight C, Matson M, Moss J, Paton JFR, Poulter N, Simpson I, Williams B, Caulfield MJ. Joint UK societies' 2014 consensus statement on renal denervation for resistant hypertension. *Heart* 2015;**101**:10–16.
73. Mancia G, Ombroni S, Parati G, Ravogli A, Villani A, Zanchetti A. Lack of placebo effect on ambulatory blood pressure. *Am J Hypertens* 1995;**8**:311–315.
74. Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, Gheeraert PJ, Missault LH, Braun JJ, Six RO, Van Der Niepen P, O'Brien E, Investigators OvAPS. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003;**348**: 2407–2415.
75. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, Toennes SW. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens* 2013;**31**:766–774.
76. Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J, Samani NJ, Gupta P, Madira W, Stanley A, Williams B. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart* 2014;**100**:855–861.
77. Hill MN, Miller NH, Degeest S. Adherence and persistence with taking medication to control high blood pressure. *J Am Soc Nephrol* 2011;**5**:56–63.
78. Patel HC, Hayward C, Ozdemir BA, Rosen SD, Krum H, Lyon AR, Francis DP, di Mario C. Magnitude of blood pressure reduction in the placebo arms of modern hypertension trials: implications for trials of renal denervation. *Hypertension* 2015; **65**:401–406.



79. Waeber B, Feihl F. Assessment of drug compliance in patients with high blood pressure resistant to antihypertensive therapy. *EuroIntervention* 2013;**9**(Suppl. R): R29–R34.
80. Burnier M, Wuerzner G, Struijker-Boudier H, Urquhart J. Measuring, analyzing, and managing drug adherence in resistant hypertension. *Hypertension* 2013;**62**:218–225.
81. Santschi V, Chiolerio A, Burnier M. Electronic monitors of drug adherence: tools to make rational therapeutic decisions. *J Hypertens* 2009;**27**:2294–2295; author reply 2295.
82. Messerli FH, Bangalore S. Renal denervation for resistant hypertension? *N Engl J Med* 2014;**370**:1454–1457.
83. Geisler BP, Egan BM, Cohen JT, Garner AM, Akehurst RL, Esler MD, Pietzsch JB. Cost-effectiveness and clinical effectiveness of catheter-based renal denervation for resistant hypertension. *J Am Coll Cardiol* 2012;**60**:1271–1277.
84. Henry TL, DeBrouwer BF, Van Keep MM, Blankstijn PJ, Bots ML, Koffijberg H. Cost-effectiveness of renal denervation therapy for the treatment of resistant hypertension in The Netherlands. *J Med Econ* 2015;**18**:76–87.
85. Dorenkamp M, Bonaventura K, Leber AW, Boldt J, Sohns C, Boldt LH, Haverkamp W, Frei U, Roser M. Potential lifetime cost-effectiveness of catheter-based renal sympathetic denervation in patients with resistant hypertension. *Eur Heart J* 2013;**34**:451–461.
86. Revicki DA, Frank L. Pharmacoeconomic evaluation in the real world. Effectiveness versus efficacy studies. *Pharmacoeconomics* 1999;**15**:423–434.
87. Pratley RE. The efficacy and effectiveness of drugs for diabetes: how do clinical trials and the real world compare? *Diabetologia* 2014;**57**:1273–1275.
88. Olivier HE, Jamero D. Implementation of a hypertension clinic using a streamlined treatment algorithm. *Am J Health Syst Pharm* 2012;**69**:664–667.

## CARDIOVASCULAR FLASHLIGHT

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### Fulminant lymphocytic myocarditis mimicking ST-elevation myocardial infarction

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A 74-year-old lady with hypertensive cardiomyopathy and COPD (GOLD II) was admitted to our hospital because of angina and worsening dyspnoea over the last 3 days. The admission electrocardiogram showed ST-elevation and Q waves in the antero-lateral leads, compatible with subacute anterior myocardial infarction. Troponin I was 52 µg/L and CK 2061 U/L. Urgent coronary angiography excluded coronary artery disease, so transthoracic echocardiography (TTE) and cardiac magnetic resonance (CMR) were performed. TTE showed diffuse in left ventricular hypokinesia and increased thickness of the antero-septal wall, while CMR revealed a corresponding extensive myocardial oedema and necrosis with predominant sub-epicardial/mid-myocardial distribution highly suggestive of a myocarditis pattern. The diagnosis of fulminant lymphocytic myocarditis was confirmed by myocardial biopsy. The ejection fraction dropped from 45 to 15% but recovered 3 weeks later (temporary ECMO support) until 40%.

Panel A: ST-elevation in V1–V4 and DI–aVL leads (red boxes), admission ECG. Panel B: significant QRS widening and diffuse ST-elevation (yellow boxes), day 4 ECG. Panels C, D and F: short-axis (C) and three-chamber long-axis (D) MR T2 mapping with extensive circumferential sub-epicardial myocardial oedema, particularly on the right-ventricular side of the interventricular septum (green arrows; the light purple myocardium marks myocardial oedema with T2 value increased to 68 ms). Three-chamber, long-axis MR late enhancement view (Panel F) with an analogous distribution of myocardial necrosis (blue arrows). Panel E: myocardial biopsy showing diffuse lymphocytic–histiocytic infiltrate and myocyte necrosis.

