doi:10.1093/eurheartj/ehy440

Take a Blood Pressure Pill or Benefit from Renal Denervation?

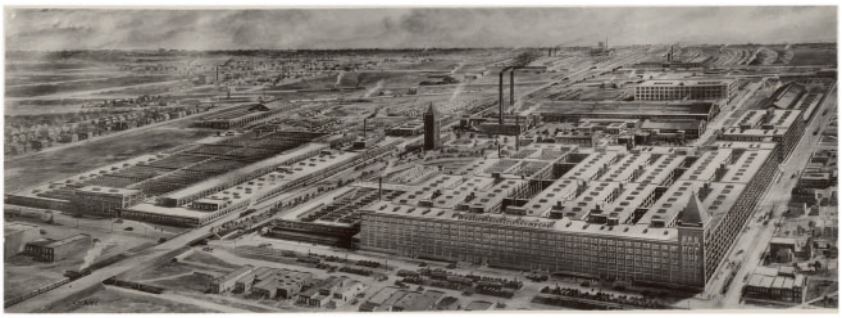
The RADIANCE-HTN SOLO and the SPYRAL HTN-ON and HTN-OFF MED randomized studies suggest that the blood pressure lowering effect of renal denervation corresponds to the effect of one antihypertensive drug

Renal denervation has been introduced as a new treatment modality for patients with hypertension. Until, recently, studies to test the efficacy of renal denervation in lowering blood pressure focused on patients with so-called treatment resistant hypertension; patients who had not achieved blood pressure control despite treatment with three or more antihypertensive drugs including a diuretic.

The SYMPLICITY HTN-2 trial[1] found a major reduction in systolic blood pressure with renal denervation in patients with treatment resistant hypertension measuring office blood pressure. However, ambulatory blood pressure is the state-of-the art technique for measuring blood pressure in patients with treatment resistant hypertension,[2] and with this method blood pressure reductions were less evident.[1] Furthermore, poor drug adherence is common in treatment resistant hypertension,[3] and it was not monitored in SYMPLICITY HTN-2. Interpretation of the study results[3] was thus confounded by the Hawthorne effect: 'patients started taking their drugs as prescribed in response to the additional attention devoted to them'.[4]

The SYMPLICITY HTN-3 study[5] included sham and ambulatory blood pressure measurements that balanced the Hawthorne and other patient and investigator non-specific effects, resulting in a blood pressure reduction of <2 mmHg in the renal denervation treatment group compared to control. Further, meta-analyses of the first 10 properly randomized and controlled studies of renal denervation did not show blood pressure lowering effects, whether or not SYMPLICITY HTN-3 was included in the analysis,[6] or whether or not a sham control was a part of the design.[7]

However, these disappointments, summarized above,[5–7] did not end the interest in renal denervation for several reasons. First, total abdominal sympathectomy resulting from surgical splanchnicectomy was effective blood pressure lowering treatment of severe hypertension in cohorts of patients reported in the 1930s[8] and 1950s.[9,10] Second, recent meta-analyses showed that renal denervation did not cause severe adverse events and could therefore be considered safe.[6,7] Third, the role of the sympathetic nervous system in the pathophysiology of hypertension is well documented.[11,12] Further, the procedural problems that contributed to the failure of early renal denervation trials to lower blood pressure could be resolved.[13,14] Therefore, new protocols were designed to assess the antihypertensive efficacy of renal denervation. One new approach in at least two studies was to perform renal denervation in untreated hypertensive patients in order to avoid any interference of drug therapies.



Hawthorne Illinois Works, Western Electric Company circa 1925. The Hawthorne effect (also referred to as the observer effect or viewing effect) is where individuals modify or improve an aspect of their behaviour in response to their awareness of being observed. The term was coined in 1950 by Henry A. Landsberger, when analysing earlier experiments from 1924–32 at the Hawthorne Works (a factory outside Chicago). The original study, which was designed to investigate the effect of different lighting levels on workers productivity, suggested that the experience of being a research subject per se could lead to productivity changes, irrespective of the lighting level.

The RADIANCE-HTN SOLO study[15] tested whether endovascular ultrasound renal denervation could reduce blood pressure in patients with hypertension who were untreated with antihypertensive drugs for 4 weeks, whereas the SPYRAL HTN-OFF MED[16] and HTN-ON MED trials[17] investigated whether renal denervation achieved by intravascular delivery of radiofrequency energy could lower blood pressure in patients off medication[16] or in patients on stable antihypertensive

Table 1 Comparisons of the main characteristics (approximate average for the patients randomized to renal denervation and to control) and the results of three new studies of intravascular renal denervation compared with the previous DENERHTN study

Variables	RADIANCE-HTN SOLO[15]	SPYRAL HTN-OFF MED[16]	SPYRAL HTN-ON MED[17]	DENERHTN[18]
No. randomized	146	80	80	106
Age (years)	54	54	53	55
% men	60	70	84	62
BMI (kg/m^2)	30	30	32	30
Office SBP (mmHg)	154	162	164	157
Office DBP (mmHg)	100	101	101	92
24-h SBP (mmHg)	143	152	152	149
24-h DBP (mmHg)	88	99	98	90
Results (mmHg) expressed as difference in reductions between renal denervation and control (SHAM in three new studies[15–17])				
Change Office-SBP	−6.5	−7.7	−6.8	−5.6
Change Office-DBP	−4.1	−4.9	−3.5	−3.1
Change 24h-SBP	−4.1	−5.0	−7.4	−5.9
Change 24h-DBP	−1.8	−4.4	−4.1	−3.1
Change daytime SBP	−6.3	−6.1		−5.9[a]
Change daytime DBP	−2.6	−4.1		−3.1

aPrimary endpoint, significant difference in DENERHTN. Except for DENERHTN, most of the differences in reductions between renal denervation and SHAM were statistically significant in the three new trials.[15–17]
SBP, systolic blood pressure; DBP, diastolic blood pressure.

medication.[17] Similar decreases in blood pressure were obtained in RADIANCE-HTN SOLO and the SPYRAL studies (*Table 1*), in patients either off or on hypertensive treatment.

However, the Hawthorne effect was not ruled out in RADIANCE-HTN SOLO,[15] as investigators relied on antihypertensive drug use reported by the patients themselves. Reported medication use was more common in the sham groups in the RADIANCE-HTN SOLO study[15] and in SPYRAL HTN-ON MED,[17] with a mean drug adherence of 60%. However, hidden use of drugs was not evaluated by direct measurements in blood or urine. Thus, assuming that hidden drug use was not more common in the treatment group, RADIANCE-HTN SOLO, together with the SPYRAL HTN-OFF[16] and HTN-ON MED trials,[17] show that renal denervation lowers blood pressure. Interestingly, the designs, inclusion and exclusion criteria, baseline characteristics, and results expressed as ambulatory and office blood pressure lowering were similar in all of the new trials (*Table 1*). This standardization of design of the recent renal denervation research studies likely relates to the same investigators being involved and to improvements in procedures, as indicated in *Table 1*, in which we have compared with DENERHTN as an example of previous studies—leading to similar statistically significant blood pressure reductions compared with control.[18]

The RADIANCE-HTN SOLO and the SPYRAL HTN-OFF and HTN-ON MED trials open a new chapter in renal denervation research[6,7] and take the renal denervation field into a new era. Together, these trials suggest that a renal denervation class effect may apply. Renal denervation achieved by intravascular delivery of radiofrequency energy or ultrasound energy may produce similar blood pressure lowering effects.

What is the clinical benefit of renal denervation? The net reduction in ambulatory systolic blood pressure of 6 mmHg reported in the new studies[15–17] approximates the effect of one antihypertensive drug.[19] However, there may be responders and non-responders, as shown in RADIANCE-HTN SOLO, and some subgroups of patients may benefit more than others. Further research is needed to identify the patients who will most likely benefit from renal denervation[20] and to confirm a sustained long-term blood pressure lowering effect, which could then make renal denervation cost-effective, at least for the treatment of resistant hypertension.[21] Long-term safety must also be established beyond the initial 6 months post-procedure.[6,7]

Future research needs to show that blood pressure reduction following renal denervation protects the brain, heart, kidneys, and large arteries and that renal denervation lowers cardiovascular morbidity and mortality.

RADIANCE-HTN SOLO and the SPYRAL studies inject new optimism into this field of research by demonstrating successful blood pressure reduction following renal denervation with both radiofrequency energy and ultrasound energy. After overcoming multiple problems with renal denervation in clinical research, with a dramatic fall in expectations from extremely high[1] down to almost nothing,[5–7] we may again be at the foot of an uphill spiral.[16–18,22]

Correspondence:
Sverre E. Kjeldsen
Department of Cardiology
Oslo University Hospital
Ullevaal, Kirkeveien 166
NO-0407 Oslo, Norway
Email: s.e.kjeldsen@medisin.uio.no

Krzysztof Narkiewicz
Department of Hypertension and Diabetology,
Medical University of Gdansk,
Gdansk, Poland

Michel Burnier
Service of Nephrology and Hypertension,
Centre Hospitalier Universitaire Vaudois,
Lausanne, Switzerland

Suzanne Oparil
Vascular Biology and Hypertension Program,
Department of Medicine,
University of Alabama at Birmingham,
Birmingham, AL, USA

Acknowledgements

A previous version of this commentary has been published in *Blood Pressure*[23] and this subsequent publication in *European Heart Journal* has been approved by the administrative editor of *Blood Pressure*.

Conflict of interest: S.E.K., K.N., and M.B. are the editors of *Blood Pressure* and report no relevant conflicts of interest to disclose related to this article. Outside the present work, S.E.K. has received ad hoc honoraria for lecturing from Bayer, Merck & Co., Sanofi, and Takeda, and honoraria from Takeda for study committee work within the past 3 years. S.O. is also editor of *Blood Pressure* and declares the following COI: ROX Medical, Inc. (Rox Control HTN 2 Study—US IDE Steering Committee Member); (multicenter study/ROX coupler-HTN); Vascular Dynamics, Inc. (site investigator, multicenter pivotal study/PMA for resistant HTN).

References

The list of references is available on the online version of this paper.

doi:10.1093/eurheartj/ehy494

Optimal Blood Pressure Goals Recommended by the Latest Hypertension Guidelines: India may benefit the most

Systemic hypertension is an important risk factor for chronic disease burden, premature morbidity, and excessive mortality. Despite the medical advances of the last few decades, hypertension remains rampant as a precursor of Atherosclerotic Cardiovascular Disease (ASCVD). Globally, over 1 billion adults have hypertension and will escalate to 1.5 billion in the decade ahead.

To provide standardized guidance for proper diagnosis and efficient blood pressure (BP) control, latest guidelines have been formulated by USA[1] and Europe.[2] The primary objective of these latest hypertension guidelines is to advocate methodologies and options to achieve safe 'goal blood pressure levels' to eliminate the consequences of hypertension. The American guidelines have lowered the threshold to define hypertension to $\geq$130/80 mmHg whereas the ESC/ESH guidelines have retained the previous threshold of $\geq$140/90 mmHg to define hypertension (*Table 1*).

The new definition of hypertension proposed by ACC/AHA has provoked criticism from some quarters as it instantly increases the prevalence of hypertension thereby challenging and probably straining the health care systems especially in the developing countries. Concerns have been raised about the newer lower thresholds to define hypertension. It has been argued that the lower thresholds not only raise the prevalence of hypertension but also pose a danger of inappropriate labelling of people as 'hypertensive' which may cause 'anxiety'.

While these views are to be expected, looking the other way does not resolve the disease burden imposed by chronic elevation in systemic blood pressure (SBP). Ignoring the consequences of modestly elevated BP levels for argument sake and due to unfounded fears, will likely worsen the pandemic of cardiovascular disease. Instead of crying foul on the new guidelines, we should concentrate on fostering global awareness of hypertension and devise practical strategies to revitalize the health care delivery systems to provide optimal care to patients with hypertension.

What would be the significance and connotations of the new guidelines for India with a population of 1.3 billion and an estimated prevalence of hypertension of 25%![3] At a time when the cardiovascular mortality is decreasing in the west, India is experiencing an escalating incidence of cardiovascular disease and a mounting expenditure to manage the complications triggered by hypertension (*Figure 1*). Uncontrolled hypertension is wrecking a havoc on public health in India. Unless this inexorable path is disrupted, India is heading towards a rising prevalence of ASCVD. The country should not tolerate the current BP control rates of $<$10% in the rural and $<$20% in the urban areas[4]; this status quo simply is not acceptable.

While the American and European guidelines differ in the definition of hypertension, the recommended therapeutic goal is the same, i.e. $<$130/80 mmHg (*Figure 2*, *Table 2*). This uniform BP goal is the catch! It is the hook and eye most relevant to India. Population studies have shown that in India, BP levels between 130–140/80–89 mmHg cause substantial CVD, stroke, and high death rates[5] (*Figure 3*). Given this observation and faced with the fringe of hypertension-mediated health calamity, it is apt for India to embrace the newer lower target BP levels recommend by the American and European guidelines. Already under the clutch of widespread CVD, we do not have time to debate endlessly on the social, economic, and cultural implications of the newer lower thresholds to diagnose and treat hypertension. India should endorse and welcome the new guidelines for the larger and long-term public health benefits to the nation and its productivity.

The newer (and lower) BP goals should be viewed as a blessed opportunity to utilize the resources for early diagnosis and proper