HELLENIC JOURNAL OF CARDIOLOGY VOL. ■, 2026: ■-■


REVIEW ARTICLE

# Consensus referral pathway for the clinical use of renal denervation in uncontrolled hypertension: a joint statement by the Hellenic Society of Hypertension, the Hellenic Society of Cardiology (WGs "Hypertension and Heart" and "Interventional Cardiology"), the Hellenic Society of Nephrology and the Hellenic Academy of General Practice/Family Medicine and Primary Health Care

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Manuscript received December 4, 2025; revised manuscript received December 17, 2025, accepted December 29, 2025. Available online xxx

ISSN 1109-9666 https://doi.org/10.1016/j.hjc.2025.12.004

**ABBREVIATIONS**

**ACC** = American College of Cardiology

**AHA** = American Heart Association

**BP** = Blood pressure

**CKD** = Chronic kidney disease

**CV** = Cardiovascular

**eGFR** = Estimated glomerular filtration rate

**ESC** = European Society of Cardiology

**ESH** = European Society of Hypertension

**HTN** = Hypertension

**RDN** = Renal denervation

**SNS** = Sympathetic nervous system

**SPC** = Single-pill combination

**ABSTRACT**

Growing evidence on the long-term efficacy and safety of sympathetic renal denervation (RDN) has established this neuromodulatory interventional therapy as the third therapeutic pillar for hypertension management, alongside lifestyle modification and pharmacotherapy. Accordingly, recent European and American guidelines have upgraded the role of RDN, recommending its consideration as an additional treatment option for selected patients with resistant or uncontrolled hypertension—particularly, for those at high cardiovascular risk—when performed in experienced centers with appropriate training and within a shared decision-making framework that respects patients' preferences. This consensus document, jointly developed by the Hellenic Society of Hypertension (Hellenic Excellence Centers of Hypertension), the Hellenic Society of Cardiology (Working Groups "Hypertension and Heart" and "Interventional Cardiology"), the Hellenic Society of Nephrology, and the Hellenic Academy of General Practice/Family Medicine and Primary Health Care, aims to provide a structured referral pathway for the clinical use of RDN in Greece. The proposed pathway integrates all contemporary therapeutic options in alignment with current hypertension guidelines and takes into account the structure of the Greek health care system. Ongoing and future research regarding antihypertensive therapies, including novel device-based and pharmacological interventions, is anticipated to further refine patient selection, procedural techniques, and long-term strategies to optimize cardiometabolic outcomes.

(Hellenic Journal of Cardiology 2026;■:■-■) 

## 1. INTRODUCTION – BACKGROUND

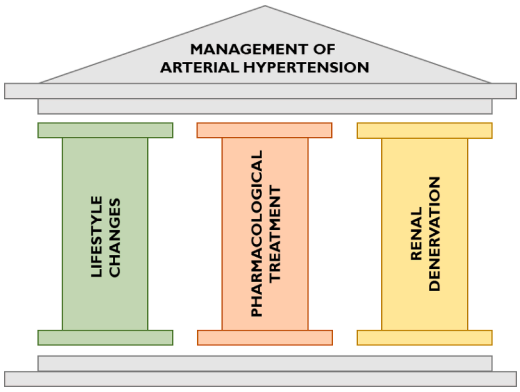
Hypertension (HTN) remains a major global public health challenge, accounting for approximately 12% of total mortality worldwide.[1] Despite its high prevalence and well-established adverse consequences, more than half of individuals with hypertension remain undiagnosed, and only about 1 in 5 achieve adequate blood pressure (BP) control.[1] Effective management of HTN through lifestyle modification and pharmacological treatment reduces the risk of future cardiovascular (CV) events significantly and remains the cornerstone of therapy.[2-4] However, multiple factors contribute to persistently high rates of uncontrolled HTN, including poor medication adherence, therapeutic inertia, inaccurate BP measurement, and other clinical or systemic barriers.[2-4]

Over the past 15 years, device-based approaches targeting the autonomic nervous system have emerged as a promising field of investigation.[5-7] Among these, sympathetic renal denervation (RDN) has demonstrated particular efficacy and safety. The "second-generation," randomized, sham-controlled RDN trials—using updated catheter systems such as the *Symplicity Spyral* (Medtronic) and the *Paradise* (ReCor Medical)—showed clinically meaningful, placebo-corrected reductions in office and 24-hour ambulatory systolic BP, with an excellent safety profile.[8-11] Long-term data from extended follow-up analyses and national registries exceeding 10 years of follow-up have confirmed the durability and safety of RDN.[12] This therapy also possesses unique advantages, including its *"always-on"* adherence-independent BP-lowering effect, and the potential pleiotropic benefits in hypertension associated comorbidities, such as obstructive sleep apnea, atrial fibrillation, heart failure, and metabolic syndrome.[9]

The previously mentioned accumulating evidence has been incorporated into recent international guidelines, rendering RDN as the third therapeutic pillar in HTN management—alongside lifestyle interventions and pharmacotherapy—within a shared decision-making framework (**Fig. 1**).[2-4] The 2023 European Society of Hypertension, 2024 European Society of Cardiology, and 2025 American Hypertension guidelines align in recognizing RDN as an appropriate therapeutic option for (i) patients with resistant HTN and (ii) those with uncontrolled HTN at high cardiovascular risk (**Fig. 2**).[2-4] In addition, RDN may be considered for patients who are non-adherent to medication, intolerant to multiple drug therapies, or experiencing a compromised quality of life due to adverse effects.[2-4]

To facilitate the effective implementation of these recommendations within the Greek national health care context, the Hellenic Society of Hypertension initiated a collaborative effort with the Hellenic Society of Cardiology (Working Groups "Hypertension and Heart," "Interventional Cardiology"), the Hellenic Society of Nephrology, and the Hellenic Academy of General Practice/Family Medicine and Primary Health Care. This consensus document aims

**FIGURE 1** The three pillars for the management of uncontrolled or resistant hypertension




to outline a structured referral pathway for patients with HTN, integrating all guideline-endorsed therapeutic options and adapting them to the organization of the Greek health care system.

## 2. THE REFERRAL PATHWAY TOWARD OPTIMAL HYPERTENSION CONTROL

The management of a patient with hypertension on the path toward optimal BP control can be conceptualized as a stepwise process—from the initial detection of elevated BP to the potential application of innovative therapies and subsequent follow-up by the treating physician. The rationale and workflow of this pathway, adapted to the structure and realities of the Greek health care system, are depicted in 7 sequential steps (Fig. 3, Steps A to G) and described in detail in the subsequent section.

**2.1. STEP A. DETECTION OF HIGH BP VALUES.** High BP values may be detected either by health care professionals or through a random BP measurement during a pharmacy visit or during home BP self-measurements. Health care professionals involved in high BP detection may be cardiologists, internists, nephrologists, or general practitioners/family doctors in primary health care units, private practice, hypertension outpatient clinics, hypertension excellence centers, or emergency departments. During this step, the role of pharmacists is also important because pharmacies are the most easily accessible health care institutions in Greece, with approximately 10,000 pharmacies in total.[13]

**2.2. STEP B. CONFIRMATION OF HYPERTENSION.** BP fluctuates over time and detection of high BP values during a single occasion cannot establish the diagnosis of HTN or ensure the uncontrolled status in already diagnosed patients with hypertension. Confirmation of HTN should be performed by health care professionals in the context of a formal scheduled office visit. Out-of-office BP measurements or meticulously performed standardized office BP measurements represent the most valuable tools for the confirmation of HTN.[2-4] Repeated office measurements and/or home BP monitoring can be used if ambulatory BP monitoring is not available. In Greece, home BP monitoring is largely available and should be wisely used following physicians' instructions to guide proper therapeutic decisions.

**2.3. STEP C. MANAGEMENT OF HYPERTENSION.** After careful assessment to confirm HTN in Step B, patients without known history of HTN can be either normotensives (not shown in Fig. 3/Step B) or newly diagnosed hypertensives (office BP ≥ 140/90 mmHg, or ambulatory 24-hour BP ≥ 130/80 mmHg, or home BP ≥ 135/85 mmHg). The latter should undergo a thorough clinical and routine laboratory assessment, including evaluation of secondary causes in case of clinical suspicion, and should be offered lifestyle interventions and pharmacotherapy in the form of a dual single-pill combination (SPC) for the most or monotherapy for selected cases (e.g., BP < 150/95 mmHg with low CV risk, high-normal BP with very high CV risk, frailty, and/or advanced age).[2] Patients with hypertension with a known history of HTN can be categorized in those with controlled HTN (office BP 120-130/70-80 mmHg, or ambulatory 24-hour BP 115-125/70-75 mmHg, or home BP 120-130/70-80 mmHg) and those with uncontrolled HTN (office BP ≥ 130/80 mmHg, or ambulatory 24-hour BP ≥ 125/75 mmHg, or home BP ≥ 120/80 mmHg). The former category can be regularly followed up by treating physicians and periodically checked with procedures as those described in Step B. On the other hand, patients with uncontrolled hypertension should be thoroughly assessed, instructed to intensify lifestyle modifications, and offered drug dose uptitration, such as to dual SPC if on monotherapy or to triple SPC if on dual SPC. A follow-up assessment should be arranged to assess the effect of the previously mentioned interventions.

**2.4. STEP D. FOLLOW-UP (1–3 MONTHS).** After a follow-up period of about 1-3 months, re-assessment of BP should be conducted. Patients with controlled hypertension can be regularly followed up by their treating physicians. In patients with uncontrolled HTN, the number of drugs received and their total CV risk should be taken into consideration. High/very high risk implies established CV disease or high estimated risk according to risk algorithms

**FIGURE 2** **Renal denervation recommendations in recent hypertension guidelines**

European Society of Hypertension

2023

| Recommendations and statements | CoR | LoE |
|---|---|---|
| RDN can be considered as a treatment option in patients with an eGFR >40 ml/min/1.73m$^2$ who have uncontrolled BP despite the use of antihypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life. | II | B |
| RDN can be considered as an additional treatment option in patients with true resistant hypertension if eGFR is >40 ml/min/1.73m$^2$. | II | B |
| Selection of patients to whom RDN is offered should be done in a shared decision-making process after objective and complete patient's information. | I | C |
| RDN should only be performed in experienced specialized centers to guarantee appropriate selection of eligible patients and completeness of the denervation procedure. | I | C |

ESC European Society of Cardiology

2024

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| To reduce BP, and if performed at a medium-to-high volume centre, catheter-based renal denervation may be considered for resistant hypertension patients who have BP that is uncontrolled despite a three BP-lowering drug combination (including a thiazide or thiazide-like diuretic), and who express a preference to undergo renal denervation after a shared risk-benefit discussion and multidisciplinary assessment.[564,566–568,586–590] | IIb | B |
| To reduce BP, and if performed at a medium-to-high volume centre, catheter-based renal denervation may be considered for patients with both increased CVD risk and uncontrolled hypertension on fewer than three drugs, if they express a preference to undergo renal denervation after a shared risk-benefit discussion and multidisciplinary assessment.[564,566–568,586–590] | IIb | A |
| Due to a lack of adequately powered outcomes trials demonstrating its safety and CVD benefits, renal denervation is not recommended as a first-line BP-lowering intervention for hypertension. | III | C |
| Renal denervation is not recommended for treating hypertension in patients with moderate-to-severely impaired renal function (eGFR <40 mL/min/1.73 m$^2$) or secondary causes of hypertension, until further evidence becomes available. | III | C |

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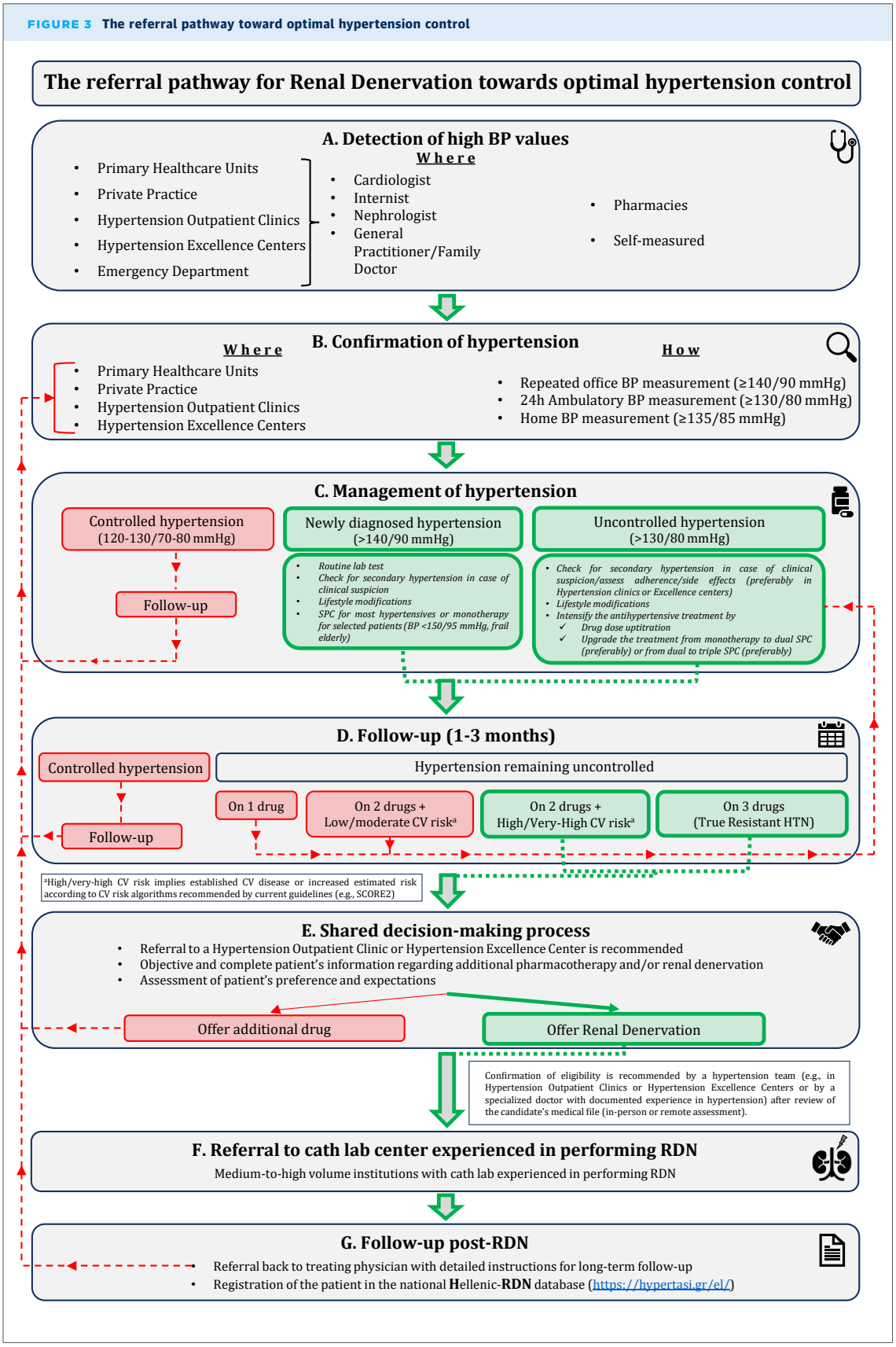
American Heart Association.

2025

| | |
|---|---|
| 2b B-R | 4. In carefully selected patients with systolic and diastolic hypertension (office SBP 140-180 mm Hg and DBP ≥90 mm Hg) and eGFR ≥40 mL/min/1.73 m$^2$ who have resistant hypertension despite optimal treatment, or intolerable side effects to additional antihypertensive drug therapy, renal denervation (RDN) may be reasonable as an adjunct treatment to BP medications and lifestyle modification to reduce BP.[12-14] |
| 1 B-NR | 5. All patients with hypertension who are being considered for RDN should be evaluated by a multidisciplinary team with expertise in resistant hypertension and RDN.[12-14] |
| 1 C-EO | 6. For patients with hypertension for whom RDN is contemplated, the benefits of lowering BP and potential procedural risks compared with continuing medical therapy should be discussed as part of a shared decision-making process to ensure patients choose the therapy that meets their expectations. |

**FIGURE 3** The referral pathway toward optimal hypertension control



**Box 1 High or very high cardiovascular risk definition according to recent guidelines**

- Established cardiovascular disease.
- Stage 4-5 chronic kidney disease.
- High/Very high risk according to SCORE-2, SCORE2-OP, SCORE2-Diabetes risk equations.
- High-normal BP (130-139/85-89 mmHg) with hypertension-mediated organ damage or stage 3 chronic kidney disease or diabetes.
- Grade 1 hypertension (140-159/90-99 mmHg) with ≥3 cardiovascular risk factors or with hypertension-mediated organ damage or stage 3 chronic kidney disease or diabetes.
- Grade 2 hypertension (160-179/100-109 mmHg) with ≥1 cardiovascular risk factors or with hypertension-mediated organ damage or stage 3 chronic kidney disease or diabetes.
- Grade 3 hypertension (≥180/110 mmHg).

recommended by current guidelines (Box 1).[14] Patients on 1 drug or 2 drugs with low/moderate total CV risk can be referred back to Step C procedures for uncontrolled HTN. Patients on 2 drugs and high/very high CV risk or those with uncontrolled HTN despite the use of 3 drugs (true resistant hypertension) should be thoroughly discussed at Steps E and F.

**2.5. STEP E. SHARED DECISION-MAKING PROCESS.** Patients should be thoroughly and objectively informed about their next therapeutic options either to receive additional drugs or be subjected to a non-pharmacological device-based intervention, namely, RDN. Patients should be actively involved in the final decision regarding their health status, discussing the risk of remaining uncontrolled HTN, the benefits of lowering BP, potential side effects of the additional medications, and the risk and benefits of the minimally invasive RDN procedure (Box 2). In patients who are willing to continue with the addition of medications, the treating physician will select—based on patients' clinical profile—either spironolactone or eplerenone or other drugs (β blocker, α blocker, centrally acting agents, or other). In patients willing to undergo RDN, confirmation of eligibility criteria for RDN (Box 3) should be conducted by a HTN team after careful review of the candidate's medical file, including a 24-hour ambulatory BP monitoring. The HTN team should ideally involve a hypertension outpatient clinic or hypertension excellence center or a specialized doctor with documented experience in HTN. Importantly, review of the patient's file can be conducted remotely in case an in-person visit is not feasible. During these sessions, any additional patients' queries about RDN can be discussed, taking into consideration patients' unique preferences and expectations.

**2.6. STEP F. REFERRAL TO CATH LAB CENTER EXPERIENCED IN PERFORMING RDN.** Patients who fulfill the eligibility criteria for undergoing RDN should be referred to medium-to-high volume institutions with cardiac catheterization laboratory and health care personnel experienced in performing the RDN procedure (Box 4). The procedure should be performed by a highly skilled interventionalist with experience in renal artery interventions to avoid complications and minimize the risk of ineffective treatments related to suboptimal interventions.

**2.7. STEP G. FOLLOW-UP POST-RDN.** After RDN, patients should be referred back to their treating

**Box 2 Strengths and limitations of renal denervation**

**STRENGTHS**

- Continuous, "always-on" blood pressure-lowering effect during daytime and night-time periods.
- Durable blood pressure reduction after the procedure.
- Clinically meaningful magnitude of blood pressure reduction.
- No permanent implant remains after the procedure, with either radiofrequency or ultrasound technologies.
- Potential pleiotropic benefits in hypertension-associated comorbidities, including heart failure, chronic kidney disease, sleep apnea syndrome, atrial fibrillation, and others.

**LIMITATIONS**

- Lack of reliable predictors of blood pressure response after the procedure; renal denervation remains a procedure performed without real-time feedback.

**Box 3 Eligibility criteria for renal denervation**

- True resistant hypertension.
- Uncontrolled hypertension based on ambulatory blood pressure monitoring despite treatment with more than two antihypertensive medications and confirmed high or very high cardiovascular risk.
- Exclusion of secondary causes of hypertension.
- Estimated glomerular filtration rate (eGFR) $> 40$ ml/min/1.73 $m^2$.
- Main renal artery diameter ≥4 mm and length ≥20 mm.
- Absence of significant renal artery stenosis, renal artery aneurysms, or fibromuscular dysplasia.
- No history of previous renal artery angioplasty or stenting.

physicians and be regularly followed up by them. Treating physicians should be clearly informed that the follow-up and future pharmacological options for a post-RDN patient do not differ substantially compared with those of a patient with hypertension who has not been subjected to RDN. Treating physicians will also be asked to register and insert their patients' data in the national **H**ellenic-**RDN** database (https://hypertasi.gr/el/) posted in the website of the Hellenic Society of Hypertension. In this way, the scientific community will be informed about valuable aspects of the implementation of RDN in a pragmatic setting and treating physicians will be instructed on how to follow-up their patients and receive support if any query arises.

## 3. CONCLUSIONS

The real-world applicability and implementation of renal denervation (RDN) remain limited due to several challenges related to the procedure, patients, and physicians or health care systems. Method-related challenges include the lack of robust markers to reliably assess procedural adequacy and success. Patient-related challenges involve identifying optimal patient selection strategies, particularly, for predicting BP response, as well as addressing patients' preferences and perspectives. Physician- and health care system-related barriers include clinical inertia, the need for experienced and specialized centers capable of performing RDN, and reimbursement issues, which play a crucial role in the widespread adoption of the procedure.

Real-world data are needed to confirm the feasibility and applicability of current guideline recommendations. In this context, the present consensus document establishes, for the first time, a structured referral pathway designed to optimize hypertension control rates by integrating all guideline-endorsed therapeutic options, including RDN, within the organizational framework of a national health care system.

## SOURCES OF FUNDING

None.

## CONFLICTS OF INTEREST

**Lampros K. Michalis**: Always: Indirect payment via the Institution; RCT's/Registries: Actelion, MSD, CSL Boehring, Pfizer, Novo Nordisk; advisory boards: Abbott, Chiesi, Bayer; Honararia: Menarini, Bayer, Novartis, Boehringer, Abbott, Innovis Pharma, Pfizer, Elpen, Novo Nordisk; Proctoring: Abbott, Medtronic; research grants: Elpen, Medtronic, Menarini, Abbott, Boehringer, Pfizer, SofMedica; leadership or fiduciary role in other board, societym or committee: Union of European Medical Specialists Cardiology Section, President Hellenic Society of Cardiology, Vice President.
**George S. Stergiou**: Received consulting fees from Menarini, Sanofi-Aventis, Servier, Lavipharm, Viatris; lecture fees from AstraZeneca, Sanofi-Aventis, Menarini, Servier, Viatris, WinMedica; and research

**Box 4 Minimum requirements for a medium-to high-volume RDN institution**

- Availability of laboratory, inpatient ward, cardiac, or intensive care unit.
- Experience in interventional cardiology procedures (access sites, radioprotection measures, selective renal artery catheterization).
- Experience with periprocedural blood pressure management and analgesia/sedation.
- Performance of at least five proctored cases with each system intended to be used.
- Use of RDN devices that have demonstrated efficacy and safety in clinical studies.

grants from AstraZeneca, Menarini, Servier, WinMedica.
None for all other authors.

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**KEYWORDS** **Consensus, Hypertension management, Pathway, Renal denervation, Sympathetic nervous system**