



Interventional Treatment of Arterial Hypertension in The Modern Era: An Updated Review from the Young Investigator Group of the European Society of Hypertension

Yusuf Ziya Şener¹ · Costantino Mancusi² · Alexandr Ceasovschih³ · Andrej Belančić⁴ · Ariadni Menti⁵ · Christina Antza⁶ · Diana Ferrao⁷ · Jelena Petrović⁸ · Justine Huart⁹ · Karel Lábr¹⁰ · Ilaria Fucile² · Marijana Vučković¹¹ · Andrej Porcnik¹² · Petra Sinigoj^{13,14} · Niki Katsiki^{15,16}

Received: 4 May 2026 / Accepted: 12 August 2026
© The Author(s) 2026

Abstract

Achievement of blood pressure targets in hypertensive patients is a challenge for clinicians despite the different classes of drugs currently available. For this reason, taking advantage of the technological progress, new interventional strategies have been proposed. Each of these approaches acts on autonomic and vascular regulation, critical components of hypertension pathophysiology with the aim to recalibrate aberrant sympathetic activation and vascular dysfunction. Renal artery denervation is the only modality currently supported by guideline recommendations in selected patients. Baroreflex activation therapy, and carotid body modulation, thanks to good experimental results, are under evaluation as promising strategies. Concurrently, newer modalities, such as deep brain stimulation, cardiac neuromodulation, and arteriovenous shunts, are emerging with promising early data. The present narrative review provides an overview of interventional treatments for hypertension, describing their efficacy, mechanism of action, safety, and side effects. As clinical research progresses, there is the possibility that these techniques will emerge as promising treatment options for patients with resistant hypertension in the near future.

Keywords Baroreflex activation therapy · Carotid body ablation · Cardiac neuromodulation therapy · Deep brain stimulation · Arteriovenous shunts · Sphenopalatine ganglion block

1 Introduction

Hypertension remains the foremost modifiable risk factor for cardiovascular (CV) morbidity and mortality, yet conventional pharmacotherapy often fails to achieve adequate blood pressure (BP) control in a substantial subset of patients [1]. This therapeutic gap has catalyzed the development of interventional strategies that target the autonomic and vascular underpinnings of hypertension, signaling a paradigm shift in its management [2].

The last decade has witnessed a resurgence of device-based therapies, challenging traditional dogma and redefining treatment-resistant hypertension. Grounded in mechanistic insights into neurovascular modulation, these

interventions strive to recalibrate aberrant sympathetic activation and vascular dysfunction [3, 4]. The trajectory from early enthusiasm to evidence-driven refinement underscores the iterative nature of this field, where technological advances and rigorous clinical evaluation continuously reshape therapeutic paradigms.

Key interventions, including renal artery denervation (RDN), baroreflex activation therapy, and carotid body modulation, have progressed from experimental concepts to clinically evaluated strategies. Concurrently, newer modalities, such as deep brain stimulation, cardiac neuromodulation, and arteriovenous shunts, are emerging with promising early data [4, 5]. Each of these approaches presents unique physiological rationales and technical challenges, reflecting

Yusuf Ziya Şener and Costantino Mancusi shared first authorship.

Extended author information available on the last page of the article

the complexity of autonomic and vascular regulation in hypertension pathophysiology.

Despite growing evidence supporting interventional strategies, critical questions remain regarding optimal patient selection, procedural durability, and long-term safety. Current guideline recommendations are evolving as newer trials provide refined insights into their comparative efficacy and integration with existing pharmacological regimens [5, 6]. The need for precision medicine in hypertension management has never been greater, necessitating a multidisciplinary approach that aligns cutting-edge interventions with individualized patient profiles [7].

The present narrative review synthesizes the state of knowledge in hypertension management, critically evaluating the mechanistic underpinnings, procedural refinements, and clinical outcomes of interventional therapies. By contextualizing their role within contemporary treatment frameworks, we aim to delineate the trajectory of device-based hypertension management, bridging the gap between innovation and clinical implementation (Fig. 1).

2 Search Methodology

References for this narrative review were identified by a PubMed electronic database search, with data extraction from 1 January 2010 to 30 January 2026. A combination of Medical Subject Heading (MeSH) terms and non-MeSH terms was used, including hypertension interventional treatment, renal artery denervation, baroreflex activation therapy, endovascular baroreflex amplification, carotid body ablation, cardiac neuromodulation therapy, deep brain stimulation, arteriovenous shunts and sphenopalatine ganglion block. All selected articles were in English and were peer-reviewed. Reference lists of selected publications were also searched. As in all narrative reviews, selection bias cannot be excluded.

3 Renal Artery Denervation (RDN)

3.1 Rationale

Since the sympathetic nervous system overactivity underlies the pathophysiology of hypertension, RDN with the interruption of renal sympathetic nerves appeared as a promising solution providing a sustainable BP-lowering effect [8, 9]. The activation of sympathetic efferent nerves along the

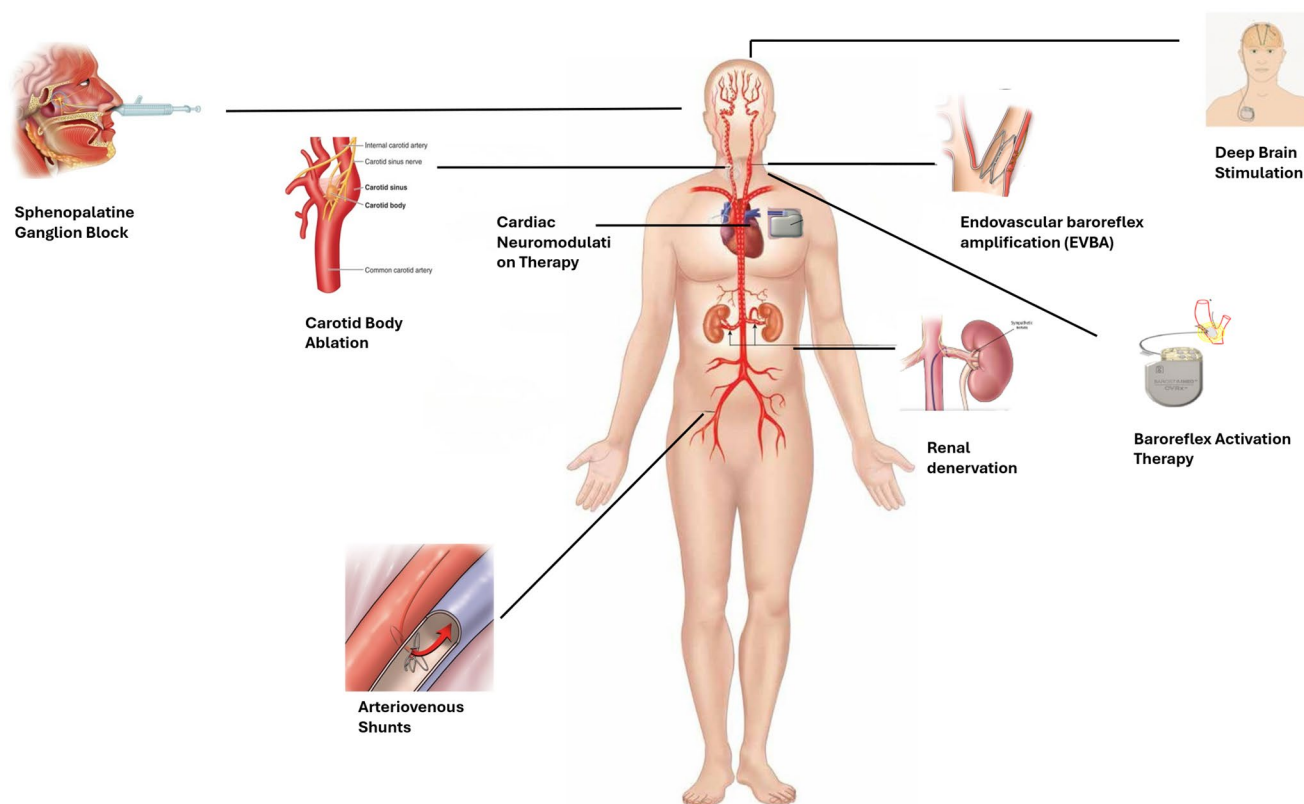


Fig. 1 Interventional treatment of arterial hypertension.

vascular and parenchymal renal structures leads to renin release, fluid retention and increased renal vascular resistance [9, 10]. Concomitantly, afferent renal sensory nerves modulate sympathetic outflow to the periphery through the hypothalamic paraventricular nucleus in the brain [10]. The interruption of both nerve types is necessary to mediate the effects of RDN on the CV system [11].

Three types of RDN are currently available [12–14] with long-lasting results [8]. Besides BP lowering, possible benefits have been suggested in patients with heart failure (HF) and increased sympathetic activity [15]. However, several aspects of RDN remain to be reconsidered, such as the modest treatment effect together with the high cost and the possibility of variable response among individuals. Additionally, long-term safety and the risk of rebound hypertension in case of late procedural complications need to be time-tested [8].

3.2 Procedure

RDN is a minimally invasive procedure aimed at disrupting the sympathetic nervous system to reduce hypertension, particularly in patients with treatment-resistant essential hypertension. The procedure involves catheter-based delivery of radiofrequency or ultrasound energy to ablate the renal sympathetic nerves located in the adventitia of the renal arteries. This intervention is performed under local anesthesia, typically via a femoral artery approach, and is guided by fluoroscopy, with the use of intravascular ultrasound or angiography for precise catheter placement. The main goal of RDN is to reduce systemic BP by interrupting the overactive sympathetic signaling associated with hypertension, which can contribute to a range of CV and renal complications.

3.3 Patient Selection

Patient selection for RDN is critical to ensuring optimal outcomes. Ideal candidates include those with treatment-resistant hypertension, defined as BP remaining above target despite the use of at least three antihypertensive medications, including a diuretic [16]. It is important to exclude patients with secondary hypertension, such as hyperaldosteronism or pheochromocytoma. Additionally, patients with significant renal artery stenosis, renal failure, or poorly managed CV comorbidities should not undergo RDN, as these conditions may compromise the procedure's safety and efficacy. Recent clinical trials, such as the SYMPPLICITY HTN-3 trial, have highlighted the importance of selecting patients who are likely to benefit from the sympathetic blockade, as the procedure's efficacy can vary depending

on the individual's baseline sympathetic tone and comorbid conditions [17].

4 Types of RDN

4.1 Radiofrequency Method

The radiofrequency (RF) method is the most widely used technique in renal artery denervation. It involves the application of RF energy through a catheter placed in the renal artery. The catheter emits heat, which ablates the sympathetic nerve fibers in the renal artery wall, thereby reducing sympathetic activity. The procedure is typically performed using a multi-electrode catheter, allowing for the delivery of RF energy at multiple points along the renal artery.

The most notable trial investigating this method is the SYMPPLICITY HTN-3, a randomized, sham-controlled study that enrolled 535 patients with resistant hypertension [15]. While it initially failed to demonstrate a significant BP reduction compared with sham at 6 months, the trial revealed critical lessons regarding patient selection, operator experience, and medication adherence, which shaped the design of subsequent studies [15]. Later trials incorporating these insights have shown more consistent efficacy of RF-based renal artery denervation in appropriately selected patients [17].

4.2 Ultrasound-Based Method

The Paradise catheter (ReCor Medical, Palo Alto, CA) is an endovascular device that delivers circumferential ablation to both afferent and efferent renal nerves using high-frequency ultrasound, without requiring contact with the arterial wall [16]. This feature enhances the safety and efficacy of RDN [18]. The catheter was used in the RADIANCE-HTN SOLO trial, in which ultrasound-based RDN significantly reduced 24-h ambulatory systolic BP in 146 untreated patients compared with sham control [18]. A meta-analysis of 13 randomized trials on 2285 patients showed that both RF and ultrasound-based RDN lower BP, with ultrasound showing greater reductions of BP during 24h ABPM (ME 2.4 mmHg, 95%CI 0.09–4.71) [17]. A direct comparison trial is needed.

4.3 Alcohol-Mediated Method

Alcohol-mediated RDN was first introduced in 2016 and has since been evaluated in two sham-controlled, randomized, blinded trials - with and without concurrent antihypertensive medications [12–14]. The technique relies on the chemical ablation of renal nerves using absolute alcohol,

which induces cellular dehydration, protein denaturation, and inflammation leading to neurolysis.

The procedure is performed using the Peregrine System Kit (Ablative Solutions, San Jose, CA, USA), designed for renal arteries 4–7 mm in diameter. Three micro-needles positioned 120° apart deliver alcohol circumferentially into the perivascular space at a penetration depth of approximately 3.5 mm. A single 0.6 mL injection is administered per renal artery over 2–3 minutes, with a maximum of 1.2 mL per side if accessory arteries are treated. The total dose per subject should not exceed 2.4 mL. This approach has demonstrated significant BP reductions and acceptable safety profiles in early studies [12–14].

4.4 Current Evidence

RDN is currently included in the hypertension treatment algorithm [10, 19]. It is evaluated through 4 key pillars: (i) efficacy, (ii) durability, (iii) safety, and (iv) indications (Fig. 2).

4.4.1 Efficacy

Randomized sham-controlled trials proved that RDN lowers 24-h BP, independently of medication effects [5, 13]. This “always on” benefit is important for patients with poor adherence [5]. RDN may have a positive impact on target-organ damage but current evidence suggesting regression of left ventricular hypertrophy and improvement in cardiac structure even if encouraging, remains based on relatively limited datasets and surrogate endpoints [20, 21]. RDN is under investigation as an adjunct therapy in sympathetic overactivity conditions, including atrial fibrillation. In a randomized trial of 302 patients with atrial fibrillation and uncontrolled hypertension, RDN plus catheter ablation reduced arrhythmia episodes (HR 0.57; 95% CI 0.38 to 0.85; $P = .006$) [22].

4.4.2 Durability

BP reduction was sustained for ≥ 3 years [5, 13], with Global SYMPPLICITY Registry data suggesting durability for up to 10 years [23].

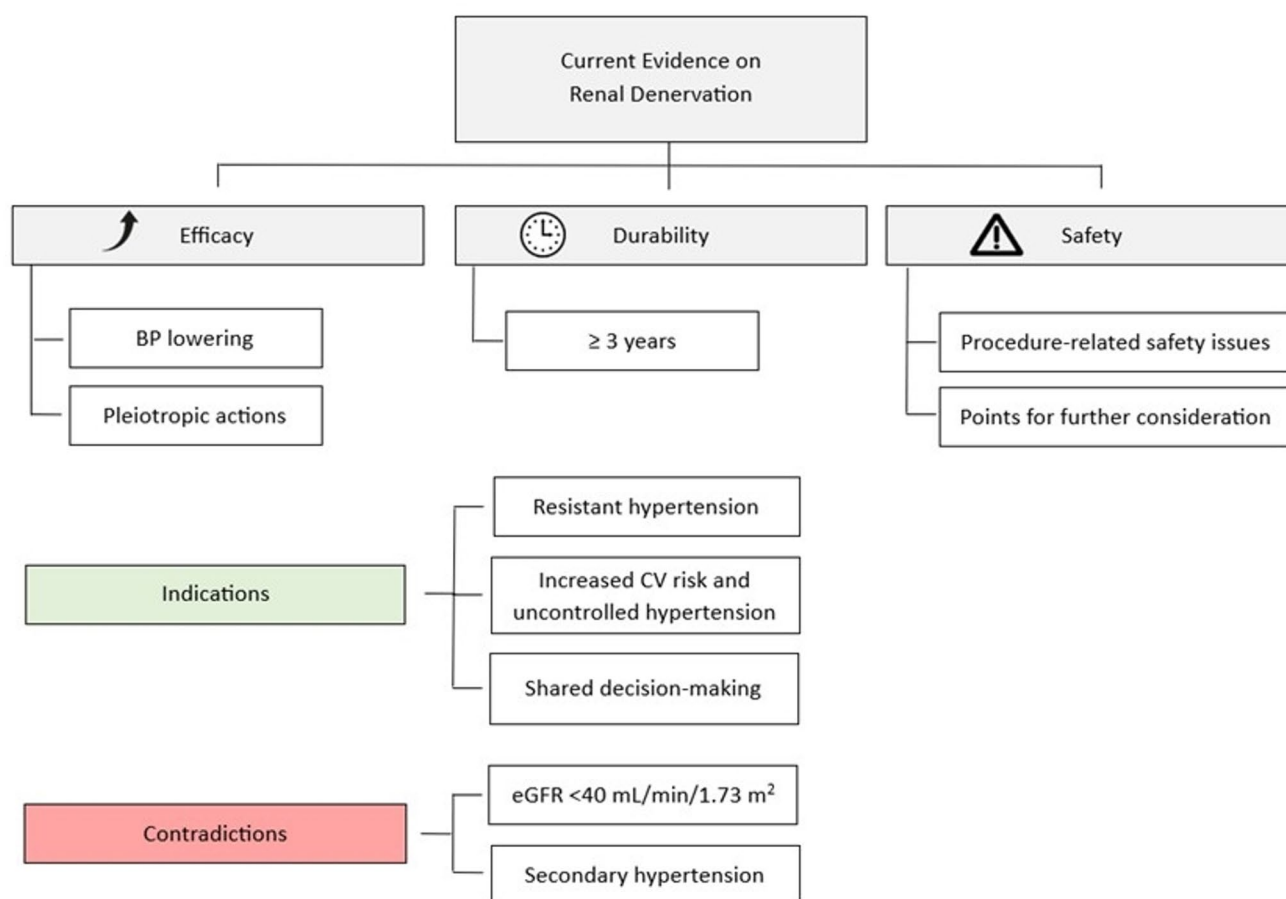


Fig. 2 Current evidence on renal denervation therapy

4.4.3 Safety

Procedure-related issues include access-site complications (e.g., bleeding), renal artery events (e.g., dissection), and contrast-induced kidney injury. These can be minimized with ultrasound guidance, proper technique, stenting, and adequate hydration [13].

Additional considerations [19]:

- Most patients still require medication post-RDN.
- Cost-effectiveness remains uncertain.
- No proven reduction in CV events.
- The procedure is irreversible.
- Procedural success and reinnervation cannot currently be verified.

4.4.4 Indications

RDN may be considered in experienced centers for patients with resistant hypertension or high-risk individuals with uncontrolled BP who accept intervention after shared decision-making [10, 19] (Table 2).

5 Baroreflex Activation Therapy

5.1 Rationale

Arterial baroreceptors located in carotid arteries are responsible for regulating BP. When BP rises, they stretch, which sends a signal to the medulla oblongata with a subsequent efferent message to lower sympathetic tone, with a correspondent drop in heart rate, systemic vascular resistance and renin production, thereby decreasing BP in the short and long term [24, 25]. Patients with chronic hypertension seem to have a higher threshold for baroreceptor activation, which allows for higher values of BP [26]. Electrical impulses that simulate the afferent stretch signals and, thus, cause a drop in BP are appealing and have been tested for several years [7].

5.2 Procedure

There are 2 main devices for baroreceptor activation, requiring different procedures. The CVRx Rheos device (CVRx, Minneapolis, MN, USA) has a RF programmer, a pulse generator that is surgically implanted in a procedure similar to endarterectomy and 2 leads that are implanted subcutaneously near the carotid sinuses [27]. The second-generation CVRx Barostim Neo (CVRx, Minneapolis, MN, USA) has several improvements over the Rheos device since the generator is smaller and allows for less invasive implantation,

has a longer-lasting battery life and a sole lead placed unilaterally [28].

5.3 Current Evidence

The first study using the Rheos pacemaker was a phase II study in 10 patients and showed significant drops in BP with a mean reduction in systolic blood pressure of 41 mm Hg without significant bradycardia or perceptible side effects [29]. These results encouraged the follow-up DEBuT-HT trial, a non-randomized study in 45 patients with resistant hypertension [30]. A decrease in BP was sustainably observed, with BP reductions of 21/12, 30/20 and 33/22 mmHg at 3 months, 1 year and 2 years, respectively [27]. There was 1 post-op death with no definite cause, 3 device-related infections and 1 stroke, besides other minor complications. In 2011, the Rheos system was tested in a randomized, double-blind, placebo-controlled manner; the device was implanted in 265 patients with resistant hypertension, who were afterwards randomized to either receive its immediate or delayed (after 6 months) activation [31]. There were significant differences in BP over the 12 months, but not at 6. It also showed several adverse events, including permanent nerve injury, stroke and infections, thus it was not approved by the Food and Drug Administration (FDA) [28]. The Barostim Neo device (CVRx, Minneapolis, MN, USA) was tested in an open-label, single-arm trial with 30 patients with resistant hypertension and revealed a mean 26/12 mmHg drop in BP. [32]. As expected by the characteristics of the device and implantation requirements, the complications were fewer, minor and resolved over time. However, the following randomized trial was suspended and the focus diverted to HF [33]. Due to the limited size of the study performed and safety concerns related to the occurrence of neurological adverse events, baroreceptor activation is not currently recommended by guidelines and larger randomized studies are still required before clinical implementation can be considered [16, 19].

6 Endovascular Baroreflex Amplification

6.1 Rationale

Endovascular baroreflex amplification (EVBA) is a device-based therapy to lower BP that targets the arterial baroreflex, which plays a critical role in maintaining adrenergic balance [34]. The baroreflex is a closed-loop system that regulates BP and heart rate. The most important pressure sensors are located in the carotid sinus, which reports to the brainstem [35]. In resistant hypertension, this system is often out of

balance. EVBA aims to restore the balance by increasing the activity of the baroreceptors [34].

6.2 Procedure

The EVBA procedure involves implanting a MobiusHD device (Vascular Dynamics, Inc.; Mountain View, California, USA) into the internal carotid artery near the carotid baroreceptors [34, 36]. The MobiusHD device is a self-expanding nitinol implant which exerts a pulsatile strain, meaning the strain varies during the cardiac cycle [37]. The device increases the wall stretch of the carotid sinus, which activates the baroreflex and reduces sympathetic activity [38]. This dynamic change in the geometric shape of the carotid sinus leads to a significant localized increase in vessel diameter [37].

6.3 Current Evidence

The Controlling And Lowering BP with the MobiusHD, First In Man, in EUROpe study (CALMFIM_EUR), a prospective open-label study, investigated the safety and efficacy of this device in 30 participants aged 18–80 years with resistant hypertension [34]. The study showed that the office BP was reduced by 27/14 (18–37/8–21) mmHg at 1 week, 22/10 (12–31/3–16) mmHg at 1 month, 24/11 (12–35/4–18) mmHg at 3 months and 24/12 (13–34/6–18) mmHg after 6 months. Mean reduction in 24-h ambulatory BP was 15/8 (7–23/3–13) mmHg at 3 months and 21/12 (14–29/7–16) mmHg at 6 months ($p < 0.0001$ for systolic and diastolic blood pressure) [34]. Symptomatic hypotension was observed in 17% of the participants, which was controlled by a change in therapy. Two patients treated in one study centre experienced ipsilateral focal neurological events immediately after implantation of the device [36]. A 3-year follow-up of 47 patients in the CALM-FIM study (European and USA participants) was performed [37].

The target value for office systolic BP of <140 mmHg was achieved in 33% of patients after 1 year, in 23% after 2 years and in 37% after 3 years. A clinically relevant response (reduction in office systolic BP by more than 10 mmHg or reduction in antihypertensive medication by 1 daily dose or more without an increase in office systolic BP) was observed in 73% of patients at 6 months and remained stable at 1, 2 and 3 years (72%, 73% and 77% respectively) [37]. The proportion of patients achieving a clinically relevant response at 6 months increased to 87% when the requirement for 24-h ambulatory systolic BP was added. There were no significant changes in heart rate from baseline to 3 years [39].

In terms of adverse events, 6 serious adverse or cerebrovascular events occurred, of which 2 patients suffered

a stroke 24 and 31 months after implantation of the device [37]. One patient experienced transient neurological symptoms in the ipsilateral vascular territory of the device 30 months after implantation of MobiusHD. Furthermore, 1 patient was hospitalized for hypertension 3 months after treatment and 2 patients experienced severe hypotension with syncope 11 and 32 months after implantation [39].

These studies provided promising results demonstrating both the safety and efficacy of EVBA in the treatment of resistant hypertension. Randomized controlled trials are underway to further investigate EVBA.

7 Carotid Body Ablation

7.1 Rationale

Carotid body (CB) hyperactivity increases central sympathetic tone and contributes to hypertension by increasing renal neurogenic sodium avidity and enhancing renal secretion of renin, as well as neurogenically mediated increases in vascular resistance. Acute reversible inactivation of the CB, with hyperoxia, caused a transient reduction in BP in patients with hypertension [40]. In rats with hypertension, interrupting the connection between the CBs and brain lowered both arterial pressure and sympathetic activity chronically [41]. CB denervation significantly lowered mean BP in spontaneously hypertensive rats and prevented the development of left ventricular hypertrophy [42].

7.2 Procedure

The ultimate Cibiem transvenous ultrasound system consists of an ultrasound catheter, a transvenous sheath, and an ultrasound generator. After obtaining a venous femoral access, a 16F sheath is placed for introduction of the ultrasound catheter which should be correctly positioned in the jugular vein adjacent to the region of the right-carotid bifurcation guided by fluoroscopy. Therapeutic ablations lasting 8 to 12 s are then applied to target the CB and its afferent nerve fibers.

7.3 Current Evidence

Two small, proof-of-concept, studies were performed to demonstrate the feasibility of surgical CB [41, 42]. Despite no major safety concerns, there was no significant reduction in office or ambulatory BP, despite some benefit related to reduced sympathetic nerve activity [43, 44]. More recently catheter-based interventional approaches via arterial access through the carotid artery or via a transvenous access have been tested. The unilateral right CB ablation was performed

using an ablation catheter system (Cibiem, USA) delivering ultrasound waves through the jugular vein under intravascular imaging guidance. However, available evidence remains heterogeneous and derives from relatively small populations.

8 Cardiac Neuromodulation Therapy

8.1 Rationale

Cardiac pump function is a principal determinant of BP, and its performance is modulated by preload in accordance with the Frank-Starling law [45]. Atrial contraction contributes approximately 15% to left ventricular filling during sinus rhythm [46]. Dual-chamber pacemakers are implanted in patients with advanced bradyarrhythmia, with reported prevalence rates ranging from 40 to 1,102 per 100,000 individuals, varying across countries and increasing with age. Moreover, prevalence demonstrates a rising trend over time [47]. Epidemiological data indicate that over 70% of patients requiring pacemaker implantation have concomitant hypertension, largely attributable to the advanced age of this population [48]. In patients with hypertension and implanted pacemakers, modulation of atrioventricular delay, and consequently left ventricular filling, has been proposed as a potential therapeutic strategy. This concept has led to the development of cardiac neuromodulation therapy (CNT).

8.2 Procedure

The Moderato System (BackBeat Medical, New Hope, PA) is an implantable, dual-chamber, rate-responsive pacemaker that integrates programmable hypertension control (PHC) algorithms. In contrast to conventional pacemakers, its distinguishing feature is its software that is designed to deliver alternating atrioventricular (AV) intervals, typically 8 to 13 beats with a shortened AV delay (20–80 ms), followed by 1 to 3 beats with a prolonged AV delay (100–180 ms). The device is implanted using standard dual-chamber pacemaker techniques, with the PHC algorithm constituting its principal innovation [45].

8.3 Current Evidence

In the BackBeat pilot study, patients requiring dual-chamber pacing with office systolic BP >150 mmHg despite stable antihypertensive therapy received the Moderato™ device with the PHC algorithm [43]. After a 1-month run-in period of conventional pacing, those with persistent office SBP >140 mmHg continued with PHC activation. Of 35

implanted patients, 27 qualified for PHC initiation (baseline office SBP $166 \pm 11/80 \pm 10$ mmHg on an average of 3.2 medications). During the run-in period, office SBP and 24-h ambulatory systolic BP decreased modestly (-8 ± 13 and -5 ± 12 mmHg, respectively) [43]. At 3 months post-activation, additional reductions were observed (-16 ± 15 mmHg in office SBP; -10 ± 13 mmHg in ambulatory systolic BP; both $p < 0.01$). Patients demonstrated sustained reductions in BP over a 2-year follow-up period. No device-related serious adverse events occurred [45]. The double-blinded Moderato II trial included patients with uncontrolled hypertension and an indication for dual-chamber pacing that received the Moderato system [46]. After a 1-month run-in, 47 patients were randomized to active CNT or inactive control. At 6 months, CNT reduced 24-h ambulatory SBP by 11.1 ± 10.5 mmHg versus 3.1 ± 9.5 mmHg in controls, yielding a net effect of 8.1 ± 10.1 mmHg ($p = 0.012$), with no device- or therapy-related adverse events [48]. Although these small studies report favorable outcomes, CNT is still experimental and restricted to patients with a pacing indication and therefore cannot currently be considered a broadly applicable treatment strategy for resistant hypertension.

9 Deep Brain Stimulation

9.1 Rationale

Deep brain stimulation (DBS) has been effectively used for the treatment of neurological disorders, such as Parkinson's disease, dystonia, tremor, epilepsy, pain, and Tourette syndrome [49]. It provides symptom improvement by electrical stimulation of specific brain regions, disrupting neuronal firing and inducing targeted modulation of neural circuits [49–51].

The potential of DBS in the treatment of arterial hypertension was first observed in 15 patients treated for chronic neuropathic pain [52]. Notably, stimulation of the ventral periaqueductal gray (PAG) in these patients led to significant reductions in BP, presumably by modulating autonomic and baroreflex function [52–54]. In addition to the PAG, subsequent studies have also identified other potential targets for DBS in the management of hypertension, including subcallosal neocortex and subthalamic nucleus [49, 53, 55, 56].

9.2 Procedure

DBS is a neurosurgical procedure that involves implanting electrodes into specific areas of the brain. These electrodes are connected to a neurostimulator (a battery-powered device) implanted under the skin in the chest or abdomen.

Firstly, computed tomography or magnetic resonance imaging is performed to map the brain and guide precise electrode placement. Following burr hole trepanation, the electrodes are inserted into the brain – for certain indications, the patient may remain awake during this stage. In the second stage, under general anesthesia, the neurostimulator is implanted and connected to the electrodes. The device is then externally programmed to deliver electrical impulses that modulate neural activity. DBS requires regular follow-ups for device adjustments and monitoring for potential complications. As with any invasive surgical procedure, DBS carries risks such as infection, haemorrhage, other procedure-related neurological impairment, and adverse reactions to anaesthesia [51].

9.3 Current Evidence

There is growing evidence from preclinical and animal studies, which apart from conventional electrostimulation also explore other forms of neuromodulation (e.g., light-based, magnetothermal, focused ultrasound) [54, 57–60]. The existing evidence from human studies primarily consists of few case reports [61–64] and small-scale studies [52, 53, 65]. In 2005, Green et al. examined BP response to DBS of the PAG in 15 awake study participants who were treated for neuropathic pain [50]. Stimulation of the ventral part caused a mean reduction in systolic BP of 14.2 ± 3.6 mmHg in 7 patients (without significant changes in pain severity), while stimulation of the dorsal part of PAG was associated with an increase in BP [52]. In 2014, Sverrisdóttir et al. evaluated sympathetic outflow after DBS of specific mid-brain nuclei known to regulate CV function in 17 patients treated for chronic neuropathic pain and Parkinson's disease [51]. Stimulation of the dorsal part of the subthalamic nucleus and ventrolateral PAG resulted in improved vasomotor baroreflex sensitivity, decreased BP, and a reduced fall in BP after tilt [53].

While these studies offer promising insights, further research is crucial to better understand the role of abnormal sympathetic activity in CV disease, to elucidate the mechanisms by which DBS modulates CV function and regulates BP, and to assess its potential as a novel interventional approach for hypertension management. At present, the use of DBS for hypertension treatment remains investigational since current evidence is derived primarily from secondary observations in patients undergoing DBS for other neurological indications rather than from dedicated hypertension trials [16, 19, 66, 67].

10 Arteriovenous Shunts

10.1 Rationale

Arteriovenous (AV) shunts have been developed for treating resistant arterial hypertension. This procedure creates a direct connection between an artery and a vein, bypassing the capillary bed, which lowers total peripheral resistance and increases venous return. These changes can reduce BP but also raise cardiac output. Proposed mechanisms of action include restoring Windkessel function, reducing effective arterial volume and systemic vascular resistance, increasing cardiac natriuretic peptide secretion, and mitigating central arterial stiffness, although direct evidence for these mechanisms is lacking [5, 68–70]. The concept of using AV shunts to reduce BP is not new and has been observed with AV fistulas used for hemodialysis [71].

10.2 Procedure

The procedure has evolved to become less invasive, notably with the ROX Anastomotic Coupler device, which is used to create a central iliac arteriovenous shunt. This device is introduced percutaneously using fluoroscopic guidance. After creating a shunt to connect the external iliac artery and vein, the ROX device is implanted to maintain the shunt's patency with a 4 mm opening, ensuring it remains open while avoiding excessive flow rates that could cause high-output cardiac failure. Potential complications include lower extremity edema, venous stenosis, right heart failure, and deep venous thrombosis [68, 72, 73].

10.3 Current Evidence

The ROX CONTROL HTN study [72, 74], a randomized trial with 83 treatment-resistant hypertensive patients, compared AV shunt formation with the ROX Coupler device to medical therapy. After 6 months, the device group had a mean systolic office BP reduction of 27 ± 24 mmHg and ambulatory systolic BP reduction of 14 ± 19 mmHg ($p < 0.001$) [72]. BP reduction persisted at one year, and significant reductions were also found in a subgroup of patients who had previously undergone renal artery denervation, suggesting that hemodynamic modulation could be effective for patients unresponsive to neuromodulatory therapies. Late ipsilateral venous stenosis requiring treatment has been found in 33% of patients in the device group [74]. Key advantages of the ROX Coupler system include verifiable deployment, reversibility, and immediate BP-lowering effects [5, 68–70, 74].

The ROX CONTROL HTN-2 study (NCT02895386), a randomized, double-blind, sham-controlled trial, began in 2017 but was terminated in 2019 after a potential heart

failure signal was observed in coupler-treated patients during long-term follow-up. The technology is no longer being pursued, with concerns about a high incidence of venous stenosis and uncontrolled, sustained increases in cardiac output [5, 16].

11 Sphenopalatine Ganglion Block

11.1 Rationale

The sphenopalatine ganglion (SPG), which is connected to the trigeminal nerve and the superior salivatory nucleus as part of the trigemino-autonomic reflex arc, plays a key role in autonomic regulation of vascular tone, making its modulation a potential therapeutic target for hypertension [75, 76].

11.2 Procedure

The SPG block is performed using a small, flexible sheath with a curved tip, inserted through the anterior nasal passage parallel to the nasal septum and above the middle turbinate. The inner catheter is then advanced to administer 2 mL of 2% lidocaine. Following the block, patients typically exhibit a 1–2 °C increase in facial temperature and/or lacrimation, indicative of successful ganglion engagement [77].

11.3 Current Evidence

In a study of 33 hypertensive patients, bilateral SPG block with 2% lidocaine was performed, with 11 patients receiving a sham procedure as controls [73]. One month after SPG block, the study group demonstrated significant reductions in 24-h and daytime diastolic BP ($p=0.02$) and daytime diastolic load ($p=0.03$). Additionally, 12 of 33 patients (36%) exhibited significant decreases in systolic and diastolic BP across 24-h, daytime, nighttime, pre-awake, and early morning periods, whereas no changes were observed in the sham control group [75]. A follow-up study involving a larger cohort of 47 treatment-naïve hypertensive patients confirmed previous observations, showing that SPG block produced modest but significant reductions in 24-h and daytime diastolic BP (-1.6 ± 5 mmHg, $p=0.04$; -1.9 ± 5 mmHg, $p=0.01$) and in daytime systolic BP variability (11 ± 2 vs. 10 ± 2 mmHg, $p<0.05$), with effects sustained at one month [78].

11.4 Guideline Recommendations Regarding Interventional Treatment of Hypertension

Among the aforementioned interventional approaches for hypertension, RDN is the only modality currently supported by guideline recommendations, with an expanding evidence base [31]. In this context, and according to the 2023 ESH guidelines, RDN may be considered in patients with an $\text{eGFR} > 40$ mL/min/1.73 m² who exhibit uncontrolled BP despite combination antihypertensive therapy or experience significant drug-related adverse effects compromising quality of life (Class IIa) [31]. Furthermore, RDN can be offered as an adjunctive therapy in patients with true resistant hypertension and $\text{eGFR} > 40$ mL/min/1.73 m² (Class IIa). The procedure should be performed exclusively in experienced specialized centers to ensure proper patient selection and procedural completeness (Class I) [16]. However, according to the 2024 ESC guidelines, RDN carries a Class IIb recommendation for BP reduction [18]. In medium- to high-volume centers, catheter-based RDN may be considered for patients with resistant hypertension whose BP remains uncontrolled on a three-drug regimen, provided they consent following a shared risk-benefit discussion and multidisciplinary evaluation [19]. The 2025 AHA guidelines assign a Class IIb recommendation to RDN in carefully selected patients with systolic and diastolic hypertension (office SBP 140–180 mmHg and DBP ≥ 90 mmHg) and an $\text{eGFR} \geq 40$ mL/min/1.73 m², who exhibit resistant hypertension despite optimal therapy or experience intolerable side effects from additional antihypertensive medications [77]. In such patients, RDN may be considered as an adjunct to pharmacologic treatment and lifestyle modification to reduce BP [79]. In summary, current guidelines endorse RDN for selected patients with resistant hypertension, with recommendations classified as Class IIa or IIb depending on the guideline and patient context (Table 1). Based on available evidence, recommendations for current use of RDN have been captured starting from 2012 from a dedicated study group of the Italian Society of Hypertension. The evaluation of RDN has shifted from strictly treating resistant patients failing a three-drug regimen to a comprehensive approach centred on individual patient adherence, tolerability, and preferences. Clinical eligibility has expanded from heavily medicated individuals including untreated or drug-intolerant patients with lower grades of hypertension. Technological advancements have also introduced multi-electrode and ultrasound devices that allow safer, faster, and more precise circumferential ablation extending into distal arterial branches [80, 81]. Pros and cons of the different interventional modalities are reported in Table 2.

Table 1 Clinical Indications and current recommendations for device-based interventions (renal denervation) in arterial hypertension according to major international guidelines

	Guideline	Class of recommendation (level of evidence)	Target patient population	Renal function threshold (eGFR)	Core procedural and clinical requirements
ACC, American College of Cardiology; AHA, American Heart Association; BP, blood pressure; DBP, diastolic blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.	ESH 2023	Class IIb (Level B)	True resistant hypertension. Uncontrolled hypertension with ongoing drug intolerance or severe treatment-related impaired quality of life.	> 40 mL/min/1.73m²	Mandatory execution within a shared decision-making framework. Restricted to highly specialized excellence centers. Objective ruling out of pseudo-resistance.
	ESC 2024	Class IIb (Level B)	Uncontrolled or resistant hypertension despite comprehensive lifestyle changes and appropriate combination pharmacotherapy.	> 40 mL/min/1.73m²	Strong emphasis on patient preferences. Highlights the "always-on" continuous effect of the device to counterbalance suboptimal drug adherence.
	ACC / AHA 2025	Class IIb (Level B-R)	Uncontrolled or resistant hypertension as an adjunctive, rather than substitutive, treatment strategy.	≥ 40–45 mL/min/1.73m² (per clinical trial protocols)	Requires specific baseline office BP thresholds (typically SBP 140–180 mmHg and DBP ≥ 90 mmHg). Validates both radiofrequency and ultrasound systems.

11.5 Future directions

The future of interventional treatment for arterial hypertension lies in appropriate patient selection, the improvement of long-term outcomes, and the integrating novel technologies into clinical practice. The most important aim for the future is the accumulation of long-term efficacy and safety data from large-scale randomized controlled trials and real-world registries, which will establish the effectiveness of interventions on BP reduction and their impact on CV morbidity and mortality. Digital health platforms, wearable sensors, and artificial intelligence, could play a key role in post-procedural monitoring, allowing continuous assessment of hemodynamic responses and the safety and efficacy of therapy.

Future strategies may also explore synergistic combinations of interventional procedures with pharmacological therapies, or novel approaches in patients with comorbidities, such as chronic kidney disease, metabolic syndrome, or advanced heart failure. Furthermore, cost-effectiveness analyses will be needed to evaluate the economic aspect of these therapies compared with lifelong medical treatment, particularly in settings where healthcare resources are limited. The transition toward precision medicine enables the optimization of device-based cardiovascular interventions, moving beyond a one-size-fits-all approach by integrating genomic profiles and phenotypic data to identify specific patient endotypes. This personalized strategy, which

accounts for patient-specific comorbidities and aims to mitigate residual cardiovascular risk, repositions these therapies as proactive tools for target-organ protection and long-term outcome improvement.

Table 2 Pros and cons of different interventional modalities for hypertension treatment

	PROS	CONS
<i>Renal Artery Denervation</i>		
Class IIb (Level B) recommendation in ESH 2023/ESC 2024 guidelines; fully approved for clinical use as a safe, device-based adjunctive therapy	Safe and minimally invasive medical procedure. Mean ambulatory systolic and diastolic BP were significantly reduced from baseline up to 36 months of follow-up	High cost Variable response among individuals Risk of rebound hypertension The most common complications are procedure-related, such as hematoma at the access site, renal artery dissection, pseudoaneurysm formation, retroperitoneal bleeding, and contrast-mediated acute kidney injury
<i>Baroreflex Activation Therapy</i>		
Approved exclusively for heart failure with reduced ejection fraction; currently not recommended (Class III) for isolated hypertension due to lack of large-scale RCTs	Systolic BP was reduced by 26 mmHg and diastolic BP reduced by 12.4 mmHg at 6 months (29)	Lack of strong evidence regarding efficacy and safety from appropriately designed, randomized controlled trials
<i>Endovascular Baroreflex Amplification</i>		
Restricted to investigational use; clinical validation is pending large-scale, sham-controlled randomized clinical trials	In patients with resistant hypertension, the office BP was reduced by 22/10 mmHg at 1 month and 24/12 mmHg after 6 months	Symptomatic hypotension Ipsilateral focal neurological events
<i>Carotid Body Ablation</i>		
Confined to early-stage experimental research	The 24-h ambulatory BP was reduced by an average of 9.1/6.7 mmHg at 6 months post-procedure with similar reductions observed already at 1 and 3 months	More prospective randomized clinical trials are missing
<i>Cardiac Neuromodulation Therapy (CNT)</i>		
Limited to niche clinical investigation; applicable solely as a protocol-based therapy in patients with a primary pacemaker indication	CNT reduced 24-h ambulatory systolic BP by 11.1 mmHg versus 3.1 mmHg in controls, yielding a net effect of 8.1±10.1 mmHg ($p=0.012$) at 6 months, No device- or therapy-related adverse events (46)	Applicable only to patients requiring cardiac pacemaker
<i>Deep Brain Stimulation</i>		
No clinical validation for hypertension	Stimulation of the ventral periventricular/periaqueductal gray matter at 10 Hz consistently lowered continuous on-table intraarterial systolic BP/diastolic BP by 14.2/4.9 mmHg(50)	Potential complications from neurosurgical intervention. Few cases treated
<i>Arteriovenous Shunts</i>		
Broadly contraindicated (Class III) by international guidelines and clinically abandoned due to severe long-term hemodynamic complications like high-output heart failure	Reversibility, and immediate BP-lowering effects It is revealed a large reduction in office systolic and diastolic BP (26.9 and 20.1 mmHg, respectively) at 6 months; These reductions persisted to 12-month follow-up	May cause high-output heart failure Potential complications: hemorrhage, infection, device migration, thrombosis, and stenosis It has high cost
<i>Sphenopalatine Ganglion Block</i>		
Lacks clinical validation and structured trials for hypertension; currently approved and used only for chronic craniofacial pain management	Modest but significant reductions of BP (in never treated patients with stage I–II essential hypertension), 24-h average diastolic BP and daytime diastolic BP were reduced by 1.6 mmHg and 1.9 mmHg respectively (76) Minimally invasive option. Effect is only anesthetic	Effect is non-permanent

ESH, European Society of Hypertension; BP: blood pressure

Acknowledgements We gratefully acknowledge the European Society of Hypertension for bringing together the co-authors (ESH Young Fellows) of this manuscript.

Author Contributions Yusuf Ziya Şener had the idea for the article, Alexandr Ceasovschi, Andrej Belančić, Ariadni Menti, Christina Antza, Diana Ferrao, Jelena Petrović, Justine Huart, Karel Lábr, Ilaria Fucile, performed the literature search and data analysis, Costantino Mancusi, Marijana Vučković, Andrej Porcnik, Petra Sinigoj, Niki Katsiki drafted the manuscript. Costantino Mancusi, Yusuf Ziya Şener critically revised the work. All authors have approved the manuscript.

Funding Open access funding provided by Università degli Studi di Napoli Federico II within the CRUI-CARE Agreement. The authors have no relevant financial or non-financial interests to disclose.

Declarations

Conflict of interest The authors declare no conflict of interest

Consent to participate Not applicable.

Ethical approval

Not applicable

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet*. 2021;398(10304):957–80.
2. Lobo MD, Sobotka PA, Pathak A. Interventional procedures and future drug therapy for hypertension. *Eur Heart J*. 2017;38(15):1101–11.
3. Schmieder RE, Redon J, Grassi G, Kjeldsen SE, Mancia G, Narkiewicz K, et al. ESH position paper: renal denervation—an interventional therapy of resistant hypertension. *J Hypertens*. 2012;30(5):837–41.
4. Jami O, Tijani Y, Et-Tahir A. Device-based therapy for resistant hypertension: an up-to-date review. *High Blood Press Cardiovasc Prev*. 2022;29(6):537–46.
5. Mahfoud F, Schlaich MP, Lobo MD. Device therapy of hypertension. *Circ Res*. 2021;128(7):1080–99.
6. Wang TD. Renal denervation: new evidence supporting long-term efficacy, alternative access routes, and cost-effectiveness. *J Clin Hypertens*. 2024;26(12):1528–30.
7. Dzau VJ, Hodgkinson CP. Precision hypertension. *Hypertension*. 2024;81(4):702–8.
8. Katsurada K, Shinohara K, Aoki J, Nanto S, Kario K. Renal denervation: basic and clinical evidence. *Hypertens Res*. 2022;45(2):198–209.
9. Iyer A, Roh S, Muhammad H, Hammad A, Kumar V, Patel D, et al. Renal denervation for resistant hypertension: a review of current literature. *Cardiovasc Revasc Med*. 2025;77:122–7.
10. Barbato E, Azizi M, Schmieder RE, Lauder L, Böhm M, Brouwers S, et al. Renal denervation in the management of hypertension in adults. A clinical consensus statement of the ESC council on hypertension and the European association of percutaneous cardiovascular interventions (EAPCI). *Eur Heart J*. 2023;44(15):1313–30.
11. Mahfoud F, Renkin J, Sievert H, Bertog S, Ewen S, Böhm M, et al. Alcohol-mediated renal denervation using the Peregrine system infusion catheter for treatment of hypertension. *JACC Cardiovasc Interv*. 2020;13(4):471–84.
12. Fischell TA, Ebner A, Gallo S, Ikeno F, Minarsch L, Vega F, et al. Transcatheter alcohol-mediated perivascular renal denervation with the peregrine system: first-in-human experience. *JACC Cardiovasc Interv*. 2016;9(6):589–98.
13. Kandzari DE, Weber MA, Pathak A, Zidar JP, Saxena M, David SW, et al. Effect of alcohol-mediated renal denervation on blood pressure in the presence of antihypertensive medications: primary results from the TARGET BP I randomized clinical trial. *Circulation*. 2024;149(24):1875–84.
14. Mahfoud F, Weber M, Schmieder RE, Lobo MD, Blankestijn PJ, Persu A, et al. Catheter-based alcohol-mediated renal denervation for the treatment of uncontrolled hypertension: design of two sham-controlled, randomized, blinded trials in the absence (TARGET BP OFF-MED) and presence (TARGET BP I) of antihypertensive medications. *Am Heart J*. 2021;239:90–9.
15. Lamirault G, Artifoni M, Daniel M, Barber-Chamoux N. Nantes University hospital working group on H. Resistant hypertension: novel insights. *Curr Hypertens Rev*. 2020;16(1):61–72.
16. Mancia G, Kreutz R, Brunstrom M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European Society of hypertension: endorsed by the international society of hypertension (ISH) and the European renal association (ERA). *J Hypertens*. 2023;41(12):1874–2071.
17. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370(15):1393–401.
18. Azizi M, Sanghvi K, Saxena M, Gosse P, Reilly JP, Levy T, et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. *Lancet*. 2021;397(10293):2476–86.
19. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, Christodorescu RM, Daskalopoulou SS, Ferro CJ, Gerds E, Hanssen H, Harris J, Lauder L, McManus RJ, Molloy GJ, Rahimi K, Regitz-Zagrosek V, Rossi GP, Sandset EC, Scheenaerts B, Staessen JA, Uchmanowicz I, Volterrani M, Touyz RM; ESC Scientific Document Group. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J*. 2024;45(38):3912–4018.
20. Xie L, Li Y, Luo S, Huang B. Impact of renal denervation on cardiac remodeling in resistant hypertension: a meta-analysis. *Clin Cardiol*. 2024;47(2):e24222.
21. Kordalis A, Tsiachris D, Pietri P, Tsioufis C, Stefanadis C. Regression of organ damage following renal denervation in resistant hypertension: a meta-analysis. *J Hypertens*. 2018;36(8):1614–21.
22. Steinberg JS, Shabanov V, Ponomarev D, Losik D, Ivanki E, Kropotkin E, et al. Effect of renal denervation and catheter ablation vs catheter ablation alone on atrial fibrillation recurrence among patients with paroxysmal atrial fibrillation and

- hypertension: the ERADICATE-AF randomized clinical trial. *JAMA*. 2020;323(3):248–55.
23. Al Ghorani H, Kulenthiran S, Recktenwald MJM, Lauder L, Kunz M, Götzinger F, et al. 10-year outcomes of catheter-based renal denervation in patients with resistant hypertension. *J Am Coll Cardiol*. 2023;81(5):517–9.
 24. Lohmeier TE, Irwin ED, Rossing MA, Serdar DJ, Kieval RS. Prolonged activation of the baroreflex produces sustained hypotension. *Hypertension*. 2004;43(2):306–11.
 25. Mohaupt MG, Schmidli J, Luft FC. Management of uncontrollable hypertension with a carotid sinus stimulation device. *Hypertension*. 2007;50(5):825–8.
 26. Victor RG. Carotid baroreflex activation therapy for resistant hypertension. *Nat Rev Cardiol*. 2015;12(8):451–63.
 27. Tordoir JH, Scheffers I, Schmidli J, Savolainen H, Liebeskind U, Hansky B, et al. An implantable carotid sinus baroreflex activating system: surgical technique and short-term outcome from a multi-center feasibility trial for the treatment of resistant hypertension. *Eur J Vasc Endovasc Surg*. 2007;33(4):414–21.
 28. Briasoulis A, Bakris G. Efficacy of baroreflex activation therapy for the treatment of resistant hypertension. *EuroIntervention*. 2013;9(Suppl R):R136.
 29. Illig KA, Levy M, Sanchez L, Trachiotis GD, Shanley C, Irwin E, et al. An implantable carotid sinus stimulator for drug-resistant hypertension: surgical technique and short-term outcome from the multicenter phase II Rheos feasibility trial. *J Vasc Surg*. 2006;44(6):1213–8.
 30. Scheffers IJ, Kroon AA, Schmidli J, Jordan J, Tordoir JJ, Mohaupt MG, et al. Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study. *J Am Coll Cardiol*. 2010;56(15):1254–8.
 31. Bisognano JD, Bakris G, Nadim MK, Sanchez L, Kroon AA, Schafer J, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. *J Am Coll Cardiol*. 2011;58(7):765–73.
 32. Hoppe UC, Brandt MC, Wachter R, Beige J, Rump LC, Kroon AA, et al. Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: results from the Barostim neo trial. *J Am Soc Hypertens*. 2012;6(4):270–6.
 33. Seravalle G, Grassi G. Carotid baroreceptor stimulation in resistant hypertension and heart failure. *High Blood Press Cardiovasc Prev*. 2015;22(3):233–9.
 34. van Kleef M, Bates MC, Spiering W. Endovascular baroreflex amplification for resistant hypertension. *Curr Hypertens Rep*. 2018;20(5):46.
 35. Gierthmuehlen M, Plachta DTT, Zentner J. Implant-mediated therapy of arterial hypertension. *Curr Hypertens Rep*. 2020;22(2):16.
 36. Spiering W, Williams B, Van der Heyden J, van Kleef M, Lo R, Versmissen J, et al. Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle clinical study. *Lancet*. 2017;390(10113):2655–61.
 37. Bates MC, Stone GW, Chen CY, Spiering W. Device profile of the MobiusHD EVBA system for the treatment of resistant hypertension: overview of its mechanism of action, safety and efficacy. *Expert Rev Med Devices*. 2020;17(7):649–58.
 38. Halim J, Lycke M, Van der Heyden J. Endovascular baroreflex amplification for resistant hypertension: what you need to know. *Future Cardiol*. 2020;16(3):151–8.
 39. van Kleef MEAM, Devireddy CM, van der Heyden J, Bates MC, Bakris GL, Stone GW, Williams B, Spiering W; CALM-FIM Investigators. Treatment of resistant hypertension with endovascular Baroreflex amplification: 3-year results from the CALM-FIM study. *JACC Cardiovasc Interv*. 2022; 15(3):321–32.
 40. Sinski M, Lewandowski J, Przybylski J, Zalewski P, Symonides B, Abramczyk P, et al. Deactivation of carotid body chemoreceptors by hyperoxia decreases blood pressure in hypertensive patients. *Hypertens Res*. 2014;37(9):858–62.
 41. McBryde FD, Abdala AP, Hendy EB, Pijacka W, Marvar P, Moraes DJ, et al. The carotid body as a putative therapeutic target for the treatment of neurogenic hypertension. *Nat Commun*. 2013;4:2395.
 42. Abdala AP, McBryde FD, Marina N, Hendy EB, Engelman ZJ, Fudim M, et al. Hypertension is critically dependent on the carotid body input in the spontaneously hypertensive rat. *J Physiol*. 2012;590(17):4269–77.
 43. Narkiewicz K, Ratcliffe LE, Hart EC, Briant LJ, Chrostowska M, Wolf J, et al. Unilateral carotid body resection in resistant hypertension: a safety and feasibility trial. *JACC Basic Transl Sci*. 2016;1(5):313–24.
 44. Niewinski P, Janczak D, Rucinski A, Tubek S, Engelman ZJ, Piesiak P, et al. Carotid body resection for sympathetic modulation in systolic heart failure: results from first-in-man study. *Eur J Heart Fail*. 2017;19(3):391–400.
 45. Neuzil P, Merkely B, Erglis A, Marinskis G, de Groot JR, Schmidinger H, Rodriguez Venegas M, Voskuil M, Sturmberger T, Petru J, Jongejan N, Aichinger J, Kamzola G, Aidietis A, Geller L, Mraz T, Osztheimer I, Mika Y, Evans S, Burkhoff D, Kuck KH; BackBeat Study Investigators. Pacemaker-mediated programmable hypertension control therapy. *J Am Heart Assoc*. 2017;6(12):e006974.
 46. Alhogbani T, Strohm O, Friedrich MG. Evaluation of left atrial contraction contribution to left ventricular filling using cardiovascular magnetic resonance. *J Magn Reson Imaging*. 2013;37(4):860–4.
 47. Bradshaw PJ, Stobie P, Knuiman MW, Briffa TG, Hobbs MS. Trends in the incidence and prevalence of cardiac pacemaker insertions in an ageing population. *Open Heart*. 2014;1(1):e000177.
 48. Kalarus Z, Merkely B, Neuzil P, Grabowski M, Mitkowski P, Marinskis G, et al. Pacemaker-based cardiac neuromodulation therapy in patients with hypertension: a pilot Study. *J Am Heart Assoc*. 2021;10(16):e020492.
 49. Ems R, Garg A, Ostergard TA, Miller JP. Potential deep brain stimulation targets for the management of refractory hypertension. *Front Neurosci*. 2019;13:93.
 50. Johnson MD, Lim HH, Netoff TI, Connolly AT, Johnson N, Roy A, et al. Neuromodulation for brain disorders: challenges and opportunities. *IEEE Trans Biomed Eng*. 2013;60(3):610–24.
 51. Greenberg's Handbook of Neurosurgery. 10th Edition ed: Thieme; 2023.
 52. Green AL, Wang S, Owen SL, Xie K, Liu X, Paterson DJ, et al. Deep brain stimulation can regulate arterial blood pressure in awake humans. *NeuroReport*. 2005;16(16):1741–5.
 53. Sverrisdóttir YB, Green AL, Aziz TZ, Bahuri NF, Hyam J, Basnayake SD, et al. Differentiated baroreflex modulation of sympathetic nerve activity during deep brain stimulation in humans. *Hypertension*. 2014;63(5):1000–10.
 54. Inui K, Murase S, Nosaka S. Facilitation of the arterial baroreflex by the ventrolateral part of the midbrain periaqueductal grey matter in rats. *J Physiol*. 1994;477(Pt 1):89–101.
 55. Hyam JA, Kringelbach ML, Silburn PA, Aziz TZ, Green AL. The autonomic effects of deep brain stimulation—a therapeutic opportunity. *Nat Rev Neurol*. 2012;8(7):391–400.
 56. Lacuey N, Hampson JP, Theeranaew W, Zonjy B, Vithala A, Hupp NJ, et al. Cortical structures associated with human blood pressure control. *JAMA Neurol*. 2018;75(2):194–202.
 57. Chomanskis Ž, Jonkus V, Danielius T, Paulauskas T, Orvydaitė M, Melaika K, et al. Hypotensive effect of electric stimulation of caudal ventrolateral medulla in freely moving rats. *Medicina (Kaunas)*. 2023;59(6):1046.

58. Chomanskis Ž, Jonkus V, Danielius T, Paulauskas T, Orvydaitė M, Melaika K, et al. Remotely programmable deep brain stimulator combined with an invasive blood pressure monitoring system for a non-tethered rat model in hypertension research. *Brain Sci.* 2023;13(3):504.
59. Mun J, Lee J, Park SM. Real-time closed-loop brainstem stimulation modality for enhancing temporal blood pressure reduction. *Brain Stimul.* 2024;17(4):826–35.
60. Lea-Banks H, Chauhan N, Hynynen K. Investigating the hypotensive effect of focused ultrasound neuromodulation and barbiturate-loaded nanodroplets in healthy and hypertensive rats. *Brain Stimul.* 2024;17(6):1317–27.
61. Green AL, Wang S, Bittar RG, Owen SL, Paterson DJ, Stein JF, et al. Deep brain stimulation: a new treatment for hypertension? *J Clin Neurosci.* 2007;14(6):592–5.
62. Pereira EA, Wang S, Paterson DJ, Stein JF, Aziz TZ, Green AL. Sustained reduction of hypertension by deep brain stimulation. *J Clin Neurosci.* 2010;17(1):124–7.
63. Patel NK, Javed S, Khan S, Papouchado M, Malizia AL, Pickering AE, et al. Deep brain stimulation relieves refractory hypertension. *Neurology.* 2011;76(4):405–7.
64. O'Callaghan EL, Hart EC, Sims-Williams H, Javed S, Burchell AE, Papouchado M, et al. Chronic deep brain stimulation decreases blood pressure and sympathetic nerve activity in a drug- and device-resistant hypertensive patient. *Hypertension.* 2017;69(4):522–8.
65. Green AL, Hyam JA, Williams C, Wang S, Shlugman D, Stein JF, et al. Intra-operative deep brain stimulation of the periaqueductal grey matter modulates blood pressure and heart rate variability in humans. *Neuromodulation.* 2010;13(3):174–81.
66. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *Hypertension.* 2018;71(6):1269–324.
67. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension global hypertension practice guidelines. *J Hypertens.* 2020;38(6):982–1004.
68. Brier TJ, Jain AK, Lobo MD. Central arteriovenous anastomosis for hypertension: it is not all about sympathomodulation. *Future Cardiol.* 2015;11(5):503–6.
69. Kapil V, Sobotka PA, Lobo MD, Schmieder RE. Central arteriovenous anastomosis to treat resistant hypertension. *Curr Opin Nephrol Hypertens.* 2018;27(1):8–15.
70. Paivanas N, Bisognano JD, Gassler JP. Carotid baroreceptor stimulation and arteriovenous shunts for resistant hypertension. *Methodist Debaque Cardiovasc J.* 2015;11(4):223–7.
71. Masson G, Viva T, Huart J, Weekers L, Bonvoisin C, Bouqueneau A, et al. The effect of elective ligation of the arteriovenous fistula on cardiac and renal functions in kidney transplant recipients. *Kidney360.* 2023;4(8):1130–8.
72. 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; ROX CONTROL HTN Investigators. Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial. *Lancet.* 2015 Apr 25;385(9978):1634–41.
73. Bertog SC, Kolmer C, Kleschnew S, Franke J, Wunderlich N, Kardos P, et al. Percutaneous femoral arteriovenous shunt creation for advanced chronic obstructive pulmonary disease: a single-center safety and efficacy study. *Circ Cardiovasc Interv.* 2012;5(1):118–26.
74. Lobo MD, Ott C, Sobotka PA, Saxena M, Stanton A, Cockcroft JR, et al. Central iliac arteriovenous anastomosis for uncontrolled hypertension: one-year results from the ROX CONTROL HTN trial. *Hypertension.* 2017;70(6):1099–105.
75. Triantafyllidi H, Arvaniti C, Schoinas A, Benas D, Vlachos S, Palaodimos L, et al. Bilateral sphenopalatine ganglion block reduces blood pressure in never treated patients with essential hypertension. A randomized controlled single-blinded study. *Int J Cardiol.* 2018;250:233–9.
76. Goadsby PJ, Uddman R, Edvinsson L. Cerebral vasodilatation in the cat involves nitric oxide from parasympathetic nerves. *Brain Res.* 1996;707(1):110–8.
77. Binfalah M, Alghawi E, Shosha E, Alhilly A, Bakhiet M. Sphenopalatine ganglion block for the treatment of acute migraine headache. *Pain Res Treat.* 2018;2018:2516953.
78. Triantafyllidi H, Arvaniti C, Benas D, Schoinas A, Voutsinos D, Ikonomidis I, et al. Bilateral sphenopalatine ganglion block reduces blood pressure and blood pressure variability in never treated patients with essential hypertension. *Eur Heart J.* 2020. <https://doi.org/10.1093/ehjci/ehaa946.2786>.
79. Jones DW, Ferdinand KC, Taler SJ, Johnson HM, Shimbo D, Abdalla M, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM guideline for the prevention, detection, evaluation and management of high blood pressure in adults: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Hypertension.* 2025;82(10):e212–316.
80. Bruno RM, Taddei S, Borghi C, Colivicchi F, Desideri G, Grassi G, et al. Italian society of arterial hypertension (SIIA) position paper on the role of renal denervation in the management of the difficult-to-treat hypertensive patient. *High Blood Press Cardiovasc Prev.* 2020;27(2):109–17.
81. Volpe M, Rosei EA, Ambrosioni E, Cottone S, Cuspidi C, Borghi C, et al. Renal artery denervation for treating resistant hypertension: definition of the disease, patient selection and description of the procedure. *High Blood Press Cardiovasc Prev.* 2012;19(4):237–44.

Authors and Affiliations

Yusuf Ziya Şener¹  · Costantino Mancusi²  · Alexandr Ceasovschi³  · Andrej Belančić⁴  · Ariadni Menti⁵  · Christina Antza⁶  · Diana Ferrao⁷  · Jelena Petrović⁸  · Justine Huart⁹  · Karel Lábr¹⁰  · Ilaria Fucile²  · Marijana Vučković¹¹  · Andrej Porcnik¹² · Petra Sinigoj^{13,14}  · Niki Katsiki^{15,16} 

✉ Costantino Mancusi
costantino.mancusi@unina.it

¹ Department of Cardiology, Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands

² Department of Advanced Biomedical Science, Federico II University of Naples, Naples, Italy

³ Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania

⁴ Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

⁵ Hypertension Center STRIDE-7, School of Medicine, Third Department of Medicine, Sotiria Hospital, National and Kapodistrian University of Athens, Athens, Greece

⁶ 3rd Department of Internal Medicine, Hypertension, Hypertension-24h Ambulatory Blood Pressure Monitoring Center, Papageorgiou Hospital, Aristotle University, Thessaloniki, Greece

⁷ Hypertension Clinic of the Internal Medicine Department, Unidade Local de Saúde de São João, Porto, Portugal

⁸ Clinic for Cardiology, University Clinical Center of Serbia, Belgrade, Serbia

⁹ Division of Nephrology, University of Liège Hospital (ULiège CHU), University of Liège, Liège, Belgium

¹⁰ First Department of Internal Medicine – Cardioangiopathy, St. Anne's University Hospital, Faculty of Medicine, Masaryk University, Brno, Czech Republic

¹¹ Department of Nephrology and Dialysis, University Hospital of Split, Spinčičeva 1, 21 000 Split, Croatia

¹² Department of Neurosurgery, University Medical Centre Ljubljana, Ljubljana, Slovenia

¹³ Department of Hypertension, University Medical Centre Ljubljana, Ljubljana, Slovenia

¹⁴ Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

¹⁵ Department of Nutritional Sciences and Dietetics, International Hellenic University, Thessaloniki, Greece

¹⁶ School of Medicine, European University Cyprus, Nicosia, Cyprus