Device-Based Therapy for Resistant Hypertension: An Up-to-Date Review

Oussama Jami1,2 · Youssef Tijani3 · Aziz Et-tahir1

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Abstract
Hypertension is the major risk factor for cardiovascular morbidity and mortality. Matter of fact, untreated hypertension can worsen the overall health, whereas pharmacotherapy can play an important role in lowering the risk of high blood pressure in hypertensive patients. However, persistent uncontrolled hypertension remains an unsolved condition characterized by non-adherence to medication and increased sympathetic activity. This paper will review the non-pharmacological treatments for resistant hypertension (RH) that have emerged in recent years. In addition, the technologies developed in device-based RH therapy, as well as the clinical trials that support their use, will be discussed. Indeed, the novel device-based approaches that target RH present a promising therapy which has been supported by several studies and clinical trials, whereas drug non-adherence and high sympathetic activity are known to be the main causes of RH. Nevertheless, some additional aspects of these RH systems need to be tested in the near future, with a particular focus on the device’s design and availability of randomized controlled trials.

Keywords Device-based therapy · Resistant hypertension · Sympathetic nerve activity · Non-invasiveness · Clinical trials

1 Introduction

The World Health Organization highlighted the global prevalence of untreated HTN that has increased over the years, with more than one billion individuals worldwide suffering from HTN, and the spread of this disease can lead to serious cardiovascular complications [1, 2]. As a result, this growing scourge will necessitate the development of new effective treatments and novel therapies, particularly for patients with RH.

Indeed, the American Heart Association and the American College of Cardiology (AHA/ACC) took concrete step forward by defining RH as failing to achieve the target blood pressure level despite taking three different classes of medication, including one diuretic [3, 4], to another extent, to consider taking more than four drugs to achieve the desired Blood Pressure (BP) level was also used as a definition of RH [5].

The prevalence of RH is greater than 10%, and this percentage depends on the control target, which could exceed 17% when considering the new ACC/AHA recommendations that make the control target less than 130 mmHg in systole and 80 mmHg in diastole, a recommendation that still needs future confirmation [6].

The percentage of RH is expected to increase for other reasons, in which aging population, rising obesity rates, and sedentary lifestyle present today the important causes of this growth. Furthermore, 50% of RH patients were not adequately treated to achieve the BP target but could have had better BP control with an optimal drug prescription [7].

Patients with RH can be truly identified by referring them to specialists, the majority of whom are capable of evaluating their condition by ruling out pseudo-hypertension and white-coat HTN using 24 h ambulatory blood pressure monitoring, whereas non-adherence to medications will be excluded by drug absorption monitoring. When the RH is diagnosed as true RH, after exclusion criteria, optimization of drug regimen as ESC and AHA recommend, lifestyle adjustment, and...
addition of second-line antihypertensive medication could result in a significant improvement [7] while a secondary hypertension diagnosis can be performed whenever HTN persists uncontrolled, hereafter, interventional procedures will be considered.

On the other hand, refractory hypertension was recently highlighted by the AHA referring to patients with severe uncontrolled HTN who are taking more than five antihypertensive medications from different classes, including a mineralocorticoid and a thiazide-like diuretic, typically a chlorthalidone [6].

Because of the need to better control HTN, along with the non-adherence to drugs, the progressive R&D setbacks in pharmacological antihypertensive therapies [8, 9], and the focus on the renin-angiotensin-aldosterone system’s inhibition, new approaches began to emerge in RH treatments this last decade, revitalizing the need for device-based therapy as an adjunctive strategy in which specialists and professionals devote more attention, for all these reasons, the ESH (European Society of Hypertension) works on device-based therapy in HTN from several perspectives, with the goal of (European Society of Hypertension) works on device-based therapy in HTN from several perspectives, with the goal of

Over the course of 18 years of development through experimental and clinical research a greater knowledge of the physiological processes accounts for blood pressure decrease with baroreflex activation therapy and RDN, but recommendations emphasize the prematurity of these therapies, which should not be used in routine treatment for RH conditions.

The purpose of this review is to:

- Discuss RH therapies critically, with a focus on the arsenal of devices available and their specifications, to help not only new adherents to RH and cardiovascular disciplines, but also specialists who want a device-oriented idea on RH therapy.
- Highlight the latest devices under investigation and give new perspectives, along with suggested improvements to the existing devices.

## 2 Baroreflex Amplification

Baroreflex activation therapy (BAT) is a part of baroreflex amplification that specifically targets the carotid sinus. BAT can be divided into two subcategories, one is electrical, and the other is mechanical. In this paper, we will refer to the electrical stimulation therapy as BAT.

BAT is one of the most advanced and promising device-based therapy for RH that involves the baroreceptor reflex system; this system can modulate the Autonomic Nervous System (ANS) activity and regulate the blood pressure [10]. Indeed, baroreceptor stimulation showed promising results in early studies but was abandoned for technology and safety concerns in the second half of the nineteenth century when BA was first performed on humans with severe HTN [11]. Development of a device has been done after promising results came out proving the BP lowering effect of electrical stimulation of the baroreceptor area in animals [12, 13] and in humans [14]. This device was revived two decades ago with the development era of new device-based therapies, and with the technological advancements held by CVRx [15], more information about the two generations of CVRx.

Having developed the two BAT generations, clinical evidence was provided in published clinical trials proving their efficacy and safety. Rheos Pivotal trial [16] was the first trial for the first-generation Rheos System CVRx Inc., that did not get Food and Drug Administration (FDA) approval and therefore was discontinued, and Barostim Neo Trial [17] was for the second-generation Barostim Neo System CVRx Inc., that has been approved by FDA recently for Heart Failure (HF). In total, until the day of writing this review, twelve clinical trials at the Clinical Trials database were registered for RH condition along with ten clinical trials for HF, most important is the meaningful efficacy response of BAT, even if the acute efficacy endpoint was not fully met in some studies [16], but in general, the BAT presents many advantages over the other devices, including a rapid conversion response after an On-Off switch that can distinguish between true responders and patients with less beneficial outcomes from the therapy. Moreover, a recent cohort with the Barostim Neo device provided long-term efficacy; 25 patients out of 50 had their office Systolic Blood Pressure (SBP) controlled (less than 140 mmHg) [18].

What makes the future of this therapy unclear is the need for more randomized controlled trials to confirm the Ambulatory Blood Pressure (ABP) effects of BAT whilst CVRx is now shifting its resources to HF trials, despite the ongoing trials (NCT02364310CT and NCT02572024CT: the estimated primary completion date is October 2021 and November 2022, respectively), a sign of a suspended development in BAT related to RH.

Accordingly, we want to address some of the limitations of this novel device by introducing a new approach to baroreflex stimulation that will reduce the invasiveness of the procedure, overcome the battery replacement issue, and since Baroreflex sensitivity is constantly destabilized in HTN where it decreases HR Instantaneously after acute BP increase, we aimed to include a feedback loop that may overcome this limitation and reduce some side effects (Syncope,
arrhythmias, unadjusted BP level, etc.) along with reducing stimulation-related side effects which can occur even with the last generation of BAT [19, 20]. The objective of this new approach is to create an external device that stimulates the baroreflex region with pinpoint accuracy using a wireless energy transmission module. This new approach of BAT will be of great benefit, as it will retain only the internal electrode around the carotid artery next to the carotid sinus. A proof-of-concept study will demonstrate the viability of this innovative BAT approach, whereas the prototyping results will be published within a few months.

Alternatively, Endovascular Baroreflex Amplification (EVBA) MobiusHD, a less invasive device developed by Vascular Dynamics, could be implanted inside the carotid sinus. Thus, it can mechanically modulate the baroreceptors by increasing the wall stretch, thereby increasing the sympathetic activity to finally lower the BP level. Vascular Dynamics also proposed a device that can be implanted extravascularly around the carotid sinus by a semi-invasive procedure.

Having demonstrated the efficacy in clinical trials with promising results in animals, experimental data from a comparison between a conventional self-expanding stent and the MobiusHD device shows an immediate and sustained BP lowering with an acceptable safety profile in the latter [21]. The first-in-man and proof of principle study, CALM-FIM was conducted in Europe and in USA centers in May 2013, and the primary endpoint was Serious Adverse Events (SAE), in which five patients had hypotension, worsening HTN, and infection that required immediate intervention [21]. Notably, a significant decrease in Office Blood Pressure (OBP) was measured at six months in both systolic and diastolic BP of 24 and 12 mmHg, respectively [21]. After 3 years of follow-up, the SBP has decreased by 30 mmHg, thus proving EVBA’s efficacy in reducing BP and having an acceptable safety profile [22]. Despite these promising results, several limitations were attributed to the trial’s design and the small number of patients enrolled in these studies, which need to be overcome by large randomized controlled trials meeting all safety and efficacy requirements. Unfortunately, a recent randomized, double-blind, sham-controlled, multi-center, post-market trial (CALM-START: NCT02804087)CT was cancelled due to the strict trial’s Measures and enrollment interruptions caused by COVID-19. The study enrolled only 3% of participants. As a result, this study was closed due to the enrollment shortage.

Indeed, ongoing trials are thoroughly evaluating EVBA with the MobiusHD device. The CALM-2 (NCT03179800)CT trial, a prospective, randomized, double-blind, sham-controlled pivotal study with the primary completion date in May 2025 aiming to enroll 300 participants with change in mean 24-h systolic ABP at 6 months as primary outcome. Therefore, results from this study will confirm the significant role of EVBA in the treatment of RH by providing a supportive efficacy and safety data for MobiusHD device.

In parallel, CALM-DIEM is an open-label, prospective, multicenter study that is still recruiting which the primary endpoint is change in systolic ABP at 3 months (NCT02827032)CT. Ten of the fourteen patients with MobiusHD were evaluated. Along with an improvement in Heart Rate Variability (HRV), the systolic OBP decreased by 14 mmHg [23]. Notably, this device-based therapy did not lower the muscle sympathetic nerve activity and did not alter the normal carotid-area function [23]. In general, more randomized sham-controlled trials are needed to confirm the long-term safety and efficacy of this therapy, with interventionists and clinicians working closely together will determine the success of the MobiusHD device [24].

3 Renal Denervation

In this chapter, we will not go through the details of RDN; however, we will briefly discuss the important milestones that marked the development of this therapy for three main reasons:

(1) RDN is the most developed therapy for RH and has already proved its feasibility through multiple trials and large RCTs. Furthermore, plenty of ink has been spilled in the literature, which has excessively reviewed this therapy with much more attention than the other therapies [15, 25–29], presenting an overall of more than 70% of RH therapy coverage.

(2) More than ten RDN systems are clinically approved and have been given the CE mark.

(3) Even if this therapy relies on device-based technology, it will not be permanently present in the human body, but it will only take a one-time surgery.

Having said that, and because renal nerves present one of the major responsible for kidney function and BP related regulatory function [30], they are well studied, especially the efferent nerves, which are believed to have a major role in renin release, NaCl retention, vasoconstriction, as well as blood pressure homeostasis in general [31]. In this respect, RDN has been tested on animals [32, 33] and humans [34–36] demonstrating its BP lowering efficacy. In addition, several techniques were developed in order to achieve optimal RDN therapy for better afferent and efferent nerve activity suppression [37, 38].

Since 2009, clinical trials have been conducted to test the efficacy and safety of this new catheter-based RDN approach, and similar trials are still being performed until this day. The first proof-of-principle open-label trials,
SYMPPLICITY HTN-1 and SYMPPLICITY HTN-2 [37, 39], show promising results that encourage researchers to further investigate the unexpected BP lowering outcomes from the first generation mono-electrode Radiofrequency (RF) catheter (Symplicity). On the contrary, the sham RCT SYMPPLICITY HTN-3 yielded less promising results, with no superiority of the RDN group over the sham group [40], which calls into question the future of this new therapy. Some experts attribute the trial’s disappointing results to a number of variables [41, 42], and based on these disappointing outcomes, recommendations were provided for optimal trial design [42, 43].

Fortunately, this therapy was revived after positive results from DENERHTN [44], a multicenter randomized controlled trial using the same Symplicity radiofrequency electrode. This trial highlights the importance of patient selection and procedure execution, which were suggested to be the main reasons for SYMPPLICITY HTN-3 failure [41].

A new generation of catheter-based RDN electrodes was introduced to the RDN device arsenal, which includes multi-electrode RF denervation and UltraSound (US) denervation. Both were investigated in several RCTs, in particular, SPYRAL HTN [45, 46] and RADIANCE-HTN [47–49]. All trials have shown the superiority of RDN group over sham group. In addition, alcohol-mediated denervation and Cryo-RDN are undergoing research to demonstrate their short-term efficacy and safety, and the preliminary results indicate a promising future for both systems [38, 50–52], whereas the high-frequency non-focused ultrasound was investigated in both RDN and PADN (Pulmonary Artery Denervation) with the TIVUS system which received FDA Investigational Device Exemption (IDE) approval, showing good safety and efficacy results [53, 54].

In spite of the promising results of the two previously mentioned new generations, there are a number of limitations in this regard, such as the large in-between patients’ variabilities, the average achievement of RDN extent to the artery branches [15], or even methodological shortcomings, remarkably, the small differences between the RDN group and the sham group were apparent in more than one trial, including the randomized, sham-controlled, double-blind trial (ReSET) that produced results similar to the SYMPPLICITY HTN3 trial [55]. Furthermore, the multicenter, randomized, sham-controlled trial RADIANCE-HTN SOLO also shows an average difference between groups in ABP after 2 months (−6.3 mmHg) [47], but even smaller after 12 months (−2.3 mmHg) [56]. It is also worth noting that the majority of patients in both groups required the addition of antihypertensive drugs after six months of procedure [57], implying that the drug’s need after procedure did not diminish significantly. Similarly, the Vessix system developed by Boston Scientific shows, in the primary follow-up, a decrease in ABP of −5.3 and −8.5 mmHg for the RDN group and Sham group, respectively, after 8 weeks of procedure, bringing the enrollment process in the off medications, randomized, sham-controlled multicenter trial (REDUCE HTN:REINFORCE) to an end, while the secondary follow-up shows a decrease in ABP of −18.2 and −14.3 mmHg for the RDN group and Sham group, respectively, 12 months post-procedure while medications were being introduced after 8 weeks post-procedure, but authors provide two main reasons for these results: delayed treatment effects and positive impact of medications along with RDN [58]. Last but not least, the recently published results of the South Korean randomized, controlled REQUIRE trial, which used the paradise RDN system, show that the RDN and sham groups had similar reductions in systolic ABP [59]. In this respect, further experimental research and clinical trials designed in a sham-controlled manner must be conducted with much more patients’ in-depth selection and good therapy assessment, within and after the procedure.

### 3.1 Ultrasound RDN (Between Endovascular and External Denervation)

Recently, a completely non-invasive RDN therapy was introduced, presenting an attractive method for ablating renal nerves with externally focused US energy and with a diagnostic doppler device for targeting and tracking. This device-based therapy (Surround Sound system) was developed by Kona Medical Inc. Campbell, California, and six trials investigated the feasibility of this novel non-invasive solution, in which evidence approved the BP lowering efficacy in humans [60] and a sham-controlled trial confirmed the preliminary results [61]. Unfortunately, a recent sham-controlled, double-blind study (NCT02029885) CT was published in 2018 which doesn’t succeed to show the superiority of external US denervated group over sham group, but a greater ABP change was observed in the RDN group due to stabilization of BP at baseline [62] and attenuation of splanchnic auto-transfusion was demonstrated in the same study [63]. Further RCTs are needed to scrutinize the feasibility of this new device-based therapy. Endovascular US RDN and externally US RDN differ in terms of invasiveness, clinical trials, and efficacy and safety profiles.

To sum up, RDN remains the most advanced RH device-based therapy in which clinical professionals, biomedical industry, and research community have given much consideration thanks to its relevant results and promising future, moreover the ESH declare in the ‘2021 position paper on RDN’ that a process that ensures the appropriate performance of the endovascular RDN procedure and adequate selection of hypertensive patients could make the RDN implementation as an innovative third option in the armamentarium of HTN treatment possible [64]. Despite these advantages and the European approval for RDN, the 2018 ESC/ESH joint guidelines
Neuromodulation Therapy (CNT) was recently introduced to pacemaker patients (approximately 70%) [71]. Cardiac Due to the high prevalence of HTN in clinically indicated pacemaker patients, CNT is considered a promising therapy for resistant hypertension (RH) which sets it apart from other therapies that modulate the sympathetic nervous system. The AVF is generally a 4 mm diameter anastomosis between the iliac vein and the iliac artery, performed with a catheter-based device under fluoroscopy imaging guidance. For the time being, Rox Medical company is the exclusive investigator of this new device-based therapy with their ROX coupler device, clinically approved to lower BP immediately after the AVF procedure [66].

This novel nitinol stent-like coupler was first introduced in: Chronic Obstructive Pulmonary Disease (COPD) condition to improve exercise capacity and oxygen delivery [67, 68]. Unexpectedly, the procedure outcomes showed a significant BP drop [68] suggesting a possible benefit in HTN treatment. Later on, the ROX CONTROL HTN trial, the first randomized controlled trial investigates the efficacy of AVF in human HTN [69] that showed after one year, systolic OBP and ABP decreased of 27 and 14 mmHg, respectively. Despite its efficacy in lowering BP and the manageable venous stenosis events that account for 30% of patients, the multicenter sham-controlled trial CONTROL HTN-2 was terminated at an early stage due to HF concerns [70], putting the final nail in the coffin of this novel therapy.

Because the major concerns are venous stenosis and HF, the first of which is manageable, this promising therapy could be revitalized if we could improve the safety profile by developing a new design and an adapted clinical procedure based on the same direct BP lowering principle. This therapy could also be made safer by applying a device concept-oriented safety that modulates the hemodynamic circulation while preserving the heart variabilities as normal without any impairment.

5 Pacemaker-Based Cardiac Neuromodulation

Due to the high prevalence of HTN in clinically indicated pacemaker patients (approximately 70%) [71], Cardiac Neuromodulation Therapy (CNT) was recently introduced in HTN disease. In this respect, the Moderato system was developed in a dual-chamber design aiming to reduce the left ventricular ejection volume by altering the atrioventricular intervals (a sequential short and long intervals). These repeated sequences obtained from the pacing algorithm can reduce the left ventricular filling and thereby lower the BP level [72].

Clinical evidence suggests that the CNT could be an effective and safe device for hypertensive patients who are resistant to other treatments. Hence, many experts expect a bright future for this therapy, which offers several advantages compared with other device-based therapies. Four trials will be completed in the upcoming months of 2022 to provide more evidence on the efficacy and safety of the pacemaker-based Programmable Hypertension Control (PHC) Moderato system in the long term and in a larger set of patients.

The MODERATO-I study (NCT02282033) is a clinical evaluation of the BackBeat Moderato system that included thirty-five patients with SBP of more than 140 mmHg. Changes in SBP were observed shortly after the device activation, indicating a significant acute response to this therapy. Furthermore, the SBP was maintained lower, reaching a 24 mmHg decrease in office SBP at three months [72]. However, some adverse events were documented in PHC therapy at about the same time as the procedure and while applying the pacing sequences, such as atrial remodeling and symptoms of heart failure [72].

Nevertheless, early indications show that PHC therapy has an acceptable safety profile as well as a promising outlet for indicated pacemaker patients with RH [72] and recent results from a double-blind randomized study MODERATO-II (NCT02837445) that is evaluating the safety and efficacy of the Moderato System confirmed the significant reduction in SBP in 47 patients who met the trial criteria, 23 patients with isolated systolic HTN having their device ON while 15 patients with the same criteria with the device inactivated. The drop was of 11 mmHg in systolic ABP compared to the control group with only 3 mmHg [73], the same study showed no significant adverse events with CNT in the short-term results.

Additional advantages put the CNT one step ahead of the other RH devices, especially in patients with indicated pacemakers. The device’s adjustable BP reduction, for example, can be tailored to each patient’s condition profile. In addition, research showed that PHC can target the left ventricular ejection and the baroreflex at the same time, potentially making this therapy a cornerstone in the future of RH device-based therapy, particularly for the management of isolated systolic hypertension [72]. However, there are some limitations with regard to long-term safety concerns and possible pacemaker implantation in

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patients without heart’s rhythm abnormality. If that’s the case, would the cost-effectiveness ratio be acceptable [74]?

6 Deep Brain Stimulation

Green Alexander Laurence published the first evidence of Deep Brain Stimulation (DBS) in humans for HTN purpose in 2007. He reported that the Central Nervous System (CNS) reduces BP by 25/8.4 mmHg with a stimulation profile of 2v and 30Hz frequency [75]. Another case was reported in a 55-year old patient with severe pain syndrome, in whom the blood pressure dropped by 33/13 mmHg after 27 months of subsequent ON-switching [76]. Even though the decrease in BP is significant, DBS remains a difficult technology to incorporate into CNS regulations. Nonetheless, the FDA has approved this device for other conditions (i.e. Parkinson’s disease, dystonia, and essential tremor) that have shown good safety records [77]. Moreover, recent research has also revealed the causes of neurogenic HTN in the CNS as well as its triggers that amplify the SNA within these territories, notably the periaqueductal gray matter, rostral subcallosal neocortex, and insular cortex [76, 78]. Despite DBS’s high cost-effectiveness ratio [79], patients with RH could benefit from this therapy if continuous stimulation of those specific CNS regions produced a sustained drop in BP using less expensive devices and more sophisticated algorithms by including artificial intelligence, which can play an important role in understanding brain device-based stimulation.

7 Electro-acupuncture

Peripheral nerve stimulation using electro-acupuncture is a safe and effective therapy for the treatment of various types of pain, anxiety, stroke, and other conditions, as evidenced by several clinical studies approving its beneficial effect [80]. Electro-acupuncture has also been found to be effective in HTN cases, where stimulation of the median nerve results in BP reduction through Sympathetic Nervous System (SNS) modulation [81, 82].

A number of clinical trials have studied the effect of electro-acupuncture stimulation on BP, and a recent randomized sham-controlled trial (NCT02926495)CT is focusing on RH using the eCoin device, which is a relatively new device, lead-less and minimally invasive, that bilaterally stimulates the median nerve by delivering a low-frequency stimulation of 30 minutes per week, based on unpublished results from Valencia Technologies showing a significant decrease in BP of more than 10 mmHg at 6 months [83]. Unfortunately, this study was halted due to funding shortage, but by and large, eCoin system got FDA approval in March 2022 for the treatment of urinary urge incontinence [84].

8 Carotid Body Modulation

Carotid body ablation was first used in COPD and bronchial asthma, which fortuitously shows a good BP control benefit for hypertensive patients [85, 86], but Carotid Body (CB) resection could not be performed in humans with RH until 2016 in a proof-of-principal trial providing promising safety and average efficacy results [87, 88].

In spite of several complications that a CB open resection procedure can cause, they can be avoided with a less invasive endovascular carotid body ablation, typically using a bipolar catheter based RF ablation CIBIEM system, where two non-randomized clinical trials have been tested (NCT02099851, NCT03314012)CT and were expected to be completed in 2016 and 2020, respectively. The results of the first study have not been published, whereas the second study has shown a decrease in BP at six months of 9.1±13.5/6.7±8.7 mmHg along with 6 patients reported to have SAEs [89]. Therefore, CB ablation therapy still needs more RCTs to confirm a sustained efficacy and a guaranteed safety results.

9 Conclusion

It is undeniable that device-based therapy will play a significant role in improving the medical care of RH patients by the end of the first quarter of the twenty-first century. Multiple approaches have been introduced and thoroughly investigated since the beginnings of this novel non-pharmacological therapy era. In our review, we have focused on the RH medical devices with a projection into the near future, in which the latest technologies and clinical trials for device-based therapy in RH conditions. Moreover, we observed the need for a few improvements, as we discussed the limitations of some therapies and some suggestions to overcome some of these challenges. We will lay out our opinions from three different perspectives.

The first part is about clinical trials in which a massive recruitment strategy needs to be implemented in order to gather more data and to build enough evidence in an effort to relay on these novel therapies in the future. Furthermore, we need a better understanding of the interaction between RH therapy and the complex BP pathophysiology in order to widely use device-based therapy in hypertensive humans, which we cannot achieve without performing larger RCTs and a well-tailored clinical trial designs [42]. The second part is more about device design, in which procedure and mode of action should be adapted to several constraints, such as a less invasive device design with
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improved efficacy and safety, and a real-time feedback loop for some permanently and electrical implanted systems that can adjust the therapy aligned with the patient’s vital signs, typically the BP level. Of note, the BAT, which can be less invasive and stimulation can be adapted to the patient’s unique characteristics. The third part is about the economic aspect, particularly the cost-effectiveness for RH device-based therapy, which has not been studied for all RH therapy systems [79, 90–94], due to the importance of having a common ground to compare these systems for a future health economic evaluation, which can incentivize specialists and decision-makers to trust in device-based therapy.

In the future, we expect to see a rise in device-based therapy use, owing primarily to a higher prevalence of drug-resistance, a sedentary lifestyle, and bad behaviors. This rise will benefit from the industry 4.0 development, technological advancements whether in device miniaturization, high precision systems, artificial intelligence, or digitalization, all of which will play a significant role in personalized therapy. In fact, if these non-pharmacotherapies succeed in larger RCTs by providing consistent positive results and pinpoint accuracy in patient selection that defines eligible profiles to maximize the benefits from each therapy, the use of device-based therapy in RH could become a routine clinical treatment in a few years. As a matter of fact, RDN is on the verge of doing so following the publication of new results from pivotal RCTs inciting ESH to issue updated recommendations in the favor of a structured pathway for clinical use [64].

In a nutshell, some limitations in efficacy and safety should be addressed as well as the design of both trials and devices. Only four RH therapy devices have received FDA approval, including the Barostim Neo for HF, the eCoin system for the treatment of urinary urge incontinence, and the PARADISE and TIVUS systems for RH with the breakthrough device designation.

9.1 Limitation

Some limitations are related to this research in terms of the short time frame in the detailed information gathering and limited access to data, especially for clinical trials as well as COVID-19 pandemic hurdles, which are the principal limitations of this review.

Declarations

Conflict of interest All authors have no conflicts of interest and no human participants or animals were involved in this regards.

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