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REVIEW

Hypertension: history and development of established and novel treatments

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Abstract

Background This article summarizes the emerging field of hypertension over the last decades. It covers paradigm shifts on hypertension from an undefined cardiovascular condition to the most relevant cardiovascular modifiable risk factor and the developments of drug treatments and interventional treatments to improve cardiovascular outcomes.

Methods We performed a selective literature research in PubMed on trials published in the past until 2018 without time restrictions and covered unpublished trials disclosed in ClinicalTrials.org.

Results The development of treatments of hypertension is a success story covering many decades from the early attempts with drug treatments, development of tolerable and effective medications to interventional techniques involving renal denervation, AV fistulas, and autonomic devices. Novel guidelines define new definitions and treatment targets of hypertension, which are a matter of ongoing discussion.

Conclusion Despite the development of tolerable and effective drugs, new treatments in the field of neuroendocrine modulation by drugs and devices are still under development trying to further improve treatment of patients with hypertension and to further reduce cardiovascular events in those individuals.

Keywords Hypertension · History of hypertension · Guideline overview · Medical treatment · Interventional treatment

History of misconceptions and successes in the developments of hypertension treatments

High blood pressure is now recognized as one of the leading and most prevalent causes for cardiovascular death and cardiovascular hospitalizations [1]. It is regarded as a highly relevant risk factor rather than a risk mediator, because it has been shown that blood pressure reduction reduces cardiovascular outcomes like stroke, myocardial infarction, and cardiovascular death dependent on blood pressure levels at baseline, accompanying cardiovascular risk and achieved blood pressure reduction [2, 3]. Organ perfusion, as early recognized by William Harvey, has been suggested to be dependent on blood pressure [4]. The development of blood pressure measurement, which was first performed in a horse in 1733 and later further developed by Riva-Rocci [5] and Korotkoff [6], paved the way to recognize that blood pressure levels beyond the requirement of organ perfusion are associated with cardiovascular outcomes and death [7]. However, there was a longstanding uncertainty of whether it might be useful to reduce blood pressure. John Hay wrote, in 1931, that "High blood pressure is often the penalty of success…" [8]. He stated in his conclusion section: "The greatest danger to a man with high blood pressure lies in its discovery, because then some fool is certain to try and reduce it" [8]. The connotation that hypertension is essential to success and certain life styles founded or at least influenced the term "essential hypertension" still used today. However, the strong association of elevated blood pressure with outcomes, in particular of malignant blood pressure (diastolic blood pressure above 110 mmHg), resulted in death rates of 80% after 1 year (Fig. 1a) [9]. The potential use of blood pressure-reducing drugs was scrutinized by studies after the development and implementation of diuretics showing that, in a similar population of patients, death rate was markedly reduced (Fig. 1a) [10].

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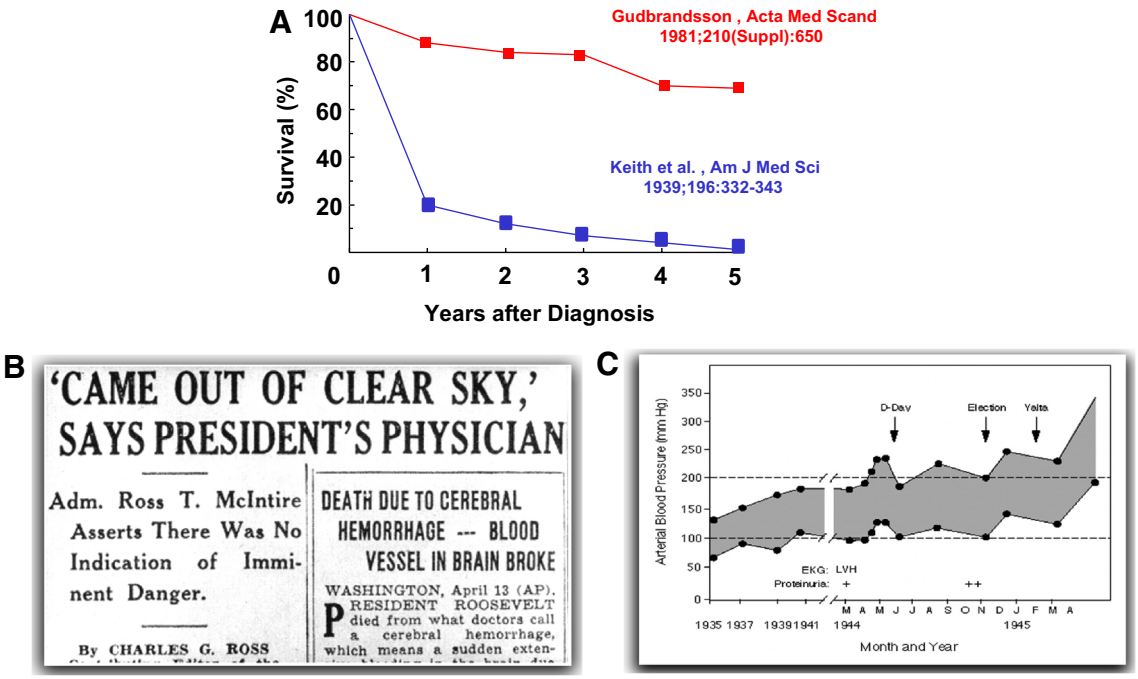

Fig. 1 Survival of patients with resistant hypertension who were untreated in 1939 and treated with diuretics 1981 (**a**). Press note on the death of President Roosevelt 1946 according to a cerebral hemorrhage after longstanding hypertension (**b**). Blood pressure values over 10 years of President Roosevelt in association with different historical events (**c**). President Roosevelt died finally due to a cerebral hemorrhage

One famous case of untreated hypertension was that of Franklin D. Roosevelt, who was diagnosed with elevated blood pressure in 1937. The blood pressure rose progressively from 160/90 mmHg to levels of 220/150 mmHg, which was strongly dependent on historical events in the following 7–8 years (Fig. 1b, c) [11, 12]. President Roosevelt died of an intracerebral hemorrhage on April 12th, 1945 aged 63 years after having developed renal failure and heart failure before. From the 1940–1950s, there was still a misbelief in the necessity of treating hypertension, because it was assumed that blood pressure reduction could lead to inadequate perfusion pressure and could damage organs.

The first controlled studies, which marked the paradigm changes into the future, were performed by the Veterans Administration Cooperative Study Group on antihypertensive agents funded by the National Institute of Health [13]. The first controlled, randomized study in hypertension investigated the effects of treatment on mortality and morbidity in hypertensive patients with a diastolic blood pressure averaging 115–129 mmHg [13]. This study was based on 143 male hypertensive patients (no women!) showing in a randomized study against placebo that hydrochlorothiazide or reserpine plus hydralazine significantly reduced blood pressure and resulted in a reduction of outcome events with 27 events in the placebo group and 2 events in the actively treated group (with 4 versus 0 death). Among those events, there were typical deaths for hypertensive complications like intracerebral bleeding, ruptured abdominal aortic aneurysm, sudden cardiac death, and stroke, as well as myocardial infarction [13]. This was later extended to patients with a lower diastolic blood pressure of 90–114 mmHg with a similar outcome reduction [14]. These studies paved the way for future outcome trials and started extensive efforts to develop novel, effective drug treatments drug treatments, with acceptable tolerability.

Development of treatments

Nutrition

The first experience with a blood pressure lowering diet was generated by Kempner who introduced a nutrition regimen consisting of fruit, fruit juice, and rice containing only 20 g of proteins, 5 g of fat, and less than 200 mg of sodium per day. He observed that beyond a strong body weight reduction, heart failure decompensations were reduced and papilledema was cleared in 322 out of 500 patients after this diet [15]. In hypertensive crises, there were heroic attempts to produce vasodilatation by pyrogens [16], or other toxic vasodilatory drugs [17, 18]. One of the most exciting topics in blood pressure research is salt. Increased salt intake

leads to inhibition of endothelial sodium pumps in vessels, increasing intercellular sodium and calcium. This ultimately induces vascular smooth muscles contraction and increases peripheral vascular resistance [19]. A general reduction of the absorbed salt is a cost-effective and safe method to prevent high blood pressure and other cardiovascular diseases. However, since most of the consumed salt comes from industrially processed food [20], salt depletion is not possible without governmental help. The UK salt reduction program could diminish salt intake from 2003 to 2011 by 1.4 g/day resulting in a decrease of blood pressure by 3/1.2 mmHg (Sys/Dia) and 41 and 22% reduction in stroke and ischemic heart disease, respectively [21]. Although not everything can be explained by the cut in salt intake, the previous studies could already demonstrate the advantages of a lower salt consumption [22, 23]. Nevertheless, it should be noted that the 24-h urine collection method used in these trials cannot reflect the exact salt concentration [24]. Furthermore, an individual salt reduction seems to be difficult and might easier be achieved by diuretics.

Sympathetic nervous system

The first demonstration of the role of the sympathetic nervous system in circulatory regulation, in particular the role of the kidney, was provided by Carl Ludwig [25]. His ideas were further developed by J. Rose Bradford, showing that stimulation of renal nerves elevated blood pressure [26]. This led to first surgical attempts to reduce blood pressure by surgical interventions to interrupt the sympathetic innervation. One of them was decapsulation of the kidneys in 1936 with a subsequent reduction in blood pressure [27]. Resection of renal nerves was done for pain relief in hydronephrosis [28]. Furthermore, sympathetic splanchnicectomy resulted in a significant blood pressure reduction with a remarkable reduction of death rate depending on cardiovascular comorbidities [29, 30]. This treatment was performed in more than 1200 cases in the United States until 1953 [31]. However, these procedures were accompanied by a high mortality and severe side effects and rehospitalizations due to orthostatic hypotension, syncopes, erectile dysfunction, and incontinence [32]. Nevertheless, the clarification of mechanisms how the sympathetic nervous activation stimulates blood pressure elevation [33] led to the development of more selective interventional techniques to reduce blood pressure like renal sympathetic denervation decades later [34].

Development of drugs

The medical student Albert Vogl observed that the medication merbaphen (Novasurol®) for the treatment of syphilis increased diuresis. Medical student applied this drug 1919 in Wenckebach Clinic in Vienna undercover and provided an illustrative documentation about their surprising observation of a unexpectedly "torrential" [35] urine excretion. This finding was further developed to another mercury-containing diuretic Mersalyl (Salyrgan®) by the company Hoechst in Germany, which remained a standard diuretic for more than 30 years. Starting from an antibacterial chemotherapeutic, the first sulfure containing diuretics was discovered in 1949. This led to the development of the carboxy anhydrase inhibitor acetazolamide (Diamox®). Chlorothiazide was first introduced 1958 as a first orally effective agent [36]. Furosemide was developed 1973 by Hoechst (Germany) [37]. Potassium-sparing diuretics like amiloride and spironolactone were following some years later.

Rauwolfia drugs

Stimulated by the findings of blood pressure reduction by splanchnicectomy to reduce sympathetic activity, rauwolfia alkaloids were introduced first in the United States in 1940 and 1950 [38]. These drugs were based on an old traditional medication from India. It was isolated from the Indian root Apocynacee rauwolfia serpentina-bentham, a plant which was named after the German physician Leonard Rauwolf, practicing in Augsburg in 1560. Modification of the reserpine molecule did not lead to better compounds. However, this discovery was followed by the development of guanethidine and alpha-methyldopa. Alpha-methyldopa was shown to inhibit dopamine decarboxylase to deplete sympathetic neurotransmitter stores due to the inhibition of noradrenaline formation and leading to a less active neurotransmitter reference as the concept of "false transmitter" [39]. Neurosympathetic inhibition was further developed by the development of clonidine by Boehringer-Ingelheim (Germany) activating presynaptic α2-adrenergic receptors [40]. Alpha-adrenoceptor blockers phentolamine, phenoxibenzalin, and prazosin were developed later. Some of these agents are still in use for pheochromocytoma.

Beta-blockers

The first beta-blocker for clinical use was developed in 1958 (dichloriso-proteronol). It was not used clinically. Further compounds like pronenalol were developed in England and followed later by propanolol, which was introduced 1965. This was the first step in the development of more specific blockers of the beta1-adrenoceptor-subtype.

Renin–angiotensin system inhibitors

It has been known since 1898 that extracts of harvested kidneys from rabbits reinjected into rabbits increased blood pressure. This first observation was made by Tigerstedt and

Bergman [41, Fig. 2]. Already in 1958, Franz Gross (President of the German Society of Cardiology and founding president of the German Hypertension League) first suggested an association between the renin–angiotensin system and hypertension. The first angiotensin-converting enzyme inhibitor was teprotide isolated from the venom of the snake Bothrops jararaca. Captopril was the first orally available ACE inhibitor (1977) followed by the development of losartan, the first angiotensin AT1-receptor antagonist introduced in 1995.

Calcium antagonists

The first calcium antagonist was developed by Lindner in Germany (Segontin propylamin), which was developed to produce dilation of the coronary arteries [42]. Verapamil, a combination hybrid molecule from veratrin and papaverine, was discovered later. Cardiac effects of calcium antagonism were discovered by Albrecht Fleckenstein [43]. The novel calcium antagonists binding to the dihydropyridine site of Ca^{2+} channels are now in widespread use for hypertension and are discovered later (nifedipin, nisoldipine, amlodipine, and others).

Epidemiology and cardiovascular risk

Hypertension remains the most prevalent risk factor worldwide and is closely associated with cardiovascular outcomes [2]. Blood pressure increases with age and older people have higher a prevalence of hypertension. It was estimated that 31% of the world's adults had hypertension in 2010, and 75% of those with hypertension lived in low- and middle-income countries. Of those, only 7.7% of patients with hypertension had their blood pressure (BP) controlled to less than 140/90 mmHg [44]. The number of patients with hypertension is projected to increase by 60%, bringing a total number of hypertensives to 1.6 billion in 2025 [45]. A continuous log-linear association between blood pressure and vascular events has been reported to a BP of 115/75 mmHg, with no apparent threshold [3]. The association between BP and events has been documented for men and women, with and without established vascular disease, individuals aged 40–89 years, and from different ethnicities [46, 47]. In 2013, the leading causes of death worldwide were ischemic heart disease and stroke, accounting for 1 in 4 deaths globally [44], both of them

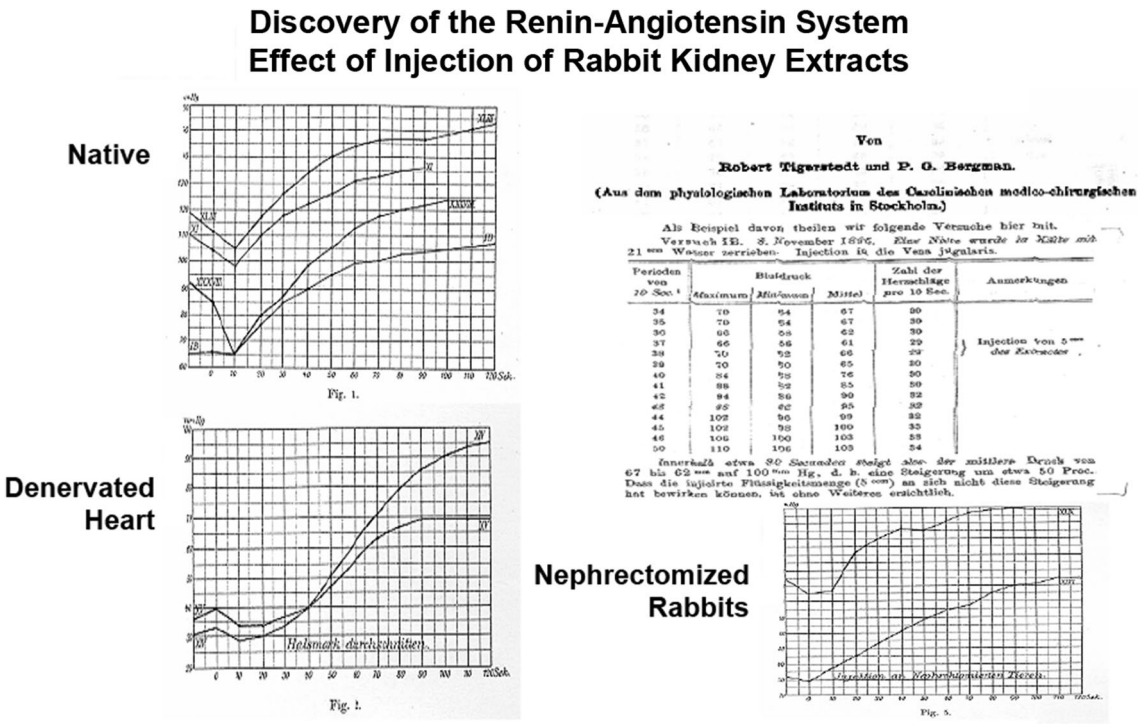

Fig. 2 Discovery of the renin–angiotensin system. Rabbit kidney extracts were injected into rabbits. After a short drop in blood pressure, there was a longstanding increase in blood pressure. After denervating the heart (below), the initial drop in blood pressure was not present, which was associated with the abolished reduction in heart rate which might have been potentially due to lost baroreceptor effects after denervation. Hemodynamic data in nephrectomized rabbits show blood pressure increases without direct effects on the kidney rather than on the peripheral circulation [35]

closely related to hypertension. It has been shown that every 10 mmHg reduction in SBP, the risk of major cardiovascular disease events is lowered by 20%, coronary heart disease by 17%, stroke by 27%, heart failure by 28%, and all-cause mortality by 13% [2]. Treatment and control of hypertension are not only important for the prevention of cardiovascular and renal events but also to reduce costs to societies.

Diagnosis

Thresholds for the definition of hypertension are provided in Table 1. The most frequently used blood pressure measurement modality is office-based or clinic BP measurement. International guidelines have endorsed a standard approach for clinic BP measurement, which involves the patient being seated and relaxed for 5 min before BP is recorded in the nondominant arm with an appropriately sized cuff and a validated device, with readings taken 3 times, at least 1 min apart, with the average of the last two readings [48]. However, in clinical practice, very often less rigor is paid in obtaining clinic BP, which may significantly affect the documented values [49]. To reduce variability and improve standardization, automated devices have been developed that record a series of seated unobserved BP. When SBP is measured this way it may be 5–10 mmHg lower than when measured with manually or even when patients are being observed or talking. Of note, this BP measurement modality was utilized in the SPRINT trial, which has led to a controversial discussion about the generalizability of the observed results [50].

Ambulatory blood pressure monitoring (ABPM) has become frequently used in Europe and other geographies as it provides a more comprehensive assessment of blood pressure of the day and night. It also allows identifying patients with distinct BP profiles such as patients with normal office BP and high ABP (masked hypertension) and those with high office but normal ABP (white-coat hypertension). ABP data have further been suggested to predict outcome better than office-based BP measurements [51]. A recently published analysis from the large Spanish ABPM registry ($n = 63{,}910$) [52], elegantly documented that 24-h, day-time, and night-time ambulatory systolic BP were indeed all better predictors of all-cause and cardiovascular mortality than clinic BP, which was consistent across subgroups of age, sex, and status with respect to obesity, diabetes, cardiovascular disease, and antihypertensive treatment. Interestingly white-coat hypertension and masked hypertension were both associated with an increased risk of death with the strongest association being observed with masked hypertensive patients.

Table 1 Blood pressure thresholds for definition of hypertension with different types of blood pressure measurement

Category	Systolic BP (mmHg)		Diastolic (mmHg)
Office BP	≥ 140	and/or	≥ 90
Ambulatory BP			
Day-time (or awake)	≥ 135	and/or	≥ 85
Night-time (or asleep)	≥ 120	and/or	≥ 70
24 h	≥ 130	and/or	≥ 80
Home BP	≥ 135	and/or	≥ 85

Treatment goals

Controversy exists currently on BP treatment goals. Following publication of the 2013 ESC/ESH guidelines on hypertension, there appeared to be consensus regarding a goal BP of < 140/90 mmHg for most hypertensive with few exceptions: (i) elderly patients (> 80 years) with the initial SBP ≥ 160 mmHg were recommended to be lowered to SBPs between 150 and 140 mmHg, (ii) patients with severe chronic kidney disease and proteinuria to SBP < 130 mmHg, and (iii) a DBP target of < 85 mmHg was recommended in diabetics. The publication of several studies has recently revived the discussion on lower treatment goals in hypertension [2, 53–55]. The prospective, randomized, controlled SPRINT [53] trial documented in patients at high risk for cardiovascular events but without diabetes or prior stroke, that an intensive BP control (SBP target of < 120 mmHg) when compared with standard control (SBP target of < 140 mmHg), resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause. It should be noted that the intensified study attained blood pressure values of 121 mmHg, while the standard group reached 136 mmHg. Two more well-conducted meta-analyses [2, 54] in more than 610,000 and 247,000 patients confirmed that SBP lowering to < 130 mmHg was associated with significantly reduced cardiovascular risk. It is important to mention, that the new guidelines will be published soon [56].

An important aspect of treatment of goals is the association of lower BP values and increase in risk, which has been described as the J-curve phenomenon. A recently published analysis of the ONTARGET/TRANSCEND study [55] suggested that lowering SBP < 120 mmHg during treatment was associated with increased risk of cardiovascular outcomes except for myocardial infarction and stroke. Similar patterns were observed for DBP < 70 mmHg, plus increased risk for myocardial infarction and hospital admission for heart failure (Fig. 3). Very low blood pressure achieved on treatment was associated with increased risks of several cardiovascular disease events. This association is supported by data from the CLARIFY registry [57] in patient with coronary artery

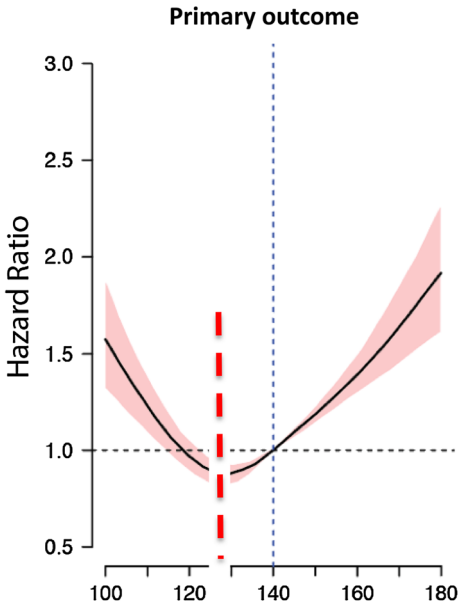

Fig. 3 Risk of the primary endpoint (cardiovascular death, myocardial infarction, stroke, and hospital admission for heart failure) according to mean achieved systolic blood pressure of 30,937 patients at high cardiovascular risk [49]

disease, in which BP values of < 120/< 70 mmHg were each associated with adverse cardiovascular outcomes, including mortality (Fig. 4). These two studies support the concept of the existence of a J-curve phenomenon and suggest that the lowest BP possible is not necessarily the optimal target for high-risk patients. Special attention has to be paid to lower BP not too intensively. In light of the available evidence, the optimal target blood pressure target appears to be between 120 and 130 mmHg for SBP and between 70 and 80 mmHg for DBP in patients with hypertension [58].

Medical treatment of hypertension

Beside lifestyle changes, medical treatment represents a cornerstone in the treatment of hypertension. While lifestyle changes may modify cardiovascular risk in many ways, the main benefits of antihypertensive treatment are due to lowering of BP per se. Diuretics, calcium antagonists, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers are all suitable for the initiation of antihypertensive therapy as they have been shown to reduce morbidity and mortality in large, randomized-controlled studies [59–62]. The European guidelines of 2013 and the latest US guidelines favor a combination therapy over a monotherapy in case of moderate or severe elevation of blood pressure and, if patients are at high risk [63, 64]. Which drug should be considered is dependent of the respective cardiovascular risk profile and cardiovascular as noncardiovascular comorbidities.

Drug treatment

Diuretics, calcium antagonists (CCBs), angiotensin-converting enzyme inhibitors (ACE-Is), and angiotensin-II receptor blockers (ARBs) have a class IA recommendation as monotherapy for the initial antihypertensive therapy. Their different application should be considered depending on concomitant diseases [63, 64]. Diuretics are superior in preventing heart failure, CCBs are superior in the prevention of stroke but inferior in the reduction of new-onset heart failure, and ACE-Is and ARBs are, if compared to CCBs, inferior in prevention of stroke but superior in prevention of chronic kidney disease [2, 65, 66]. Beta-blockers are controversial as they are inferior in the reduction of cardiovascular events, total mortality

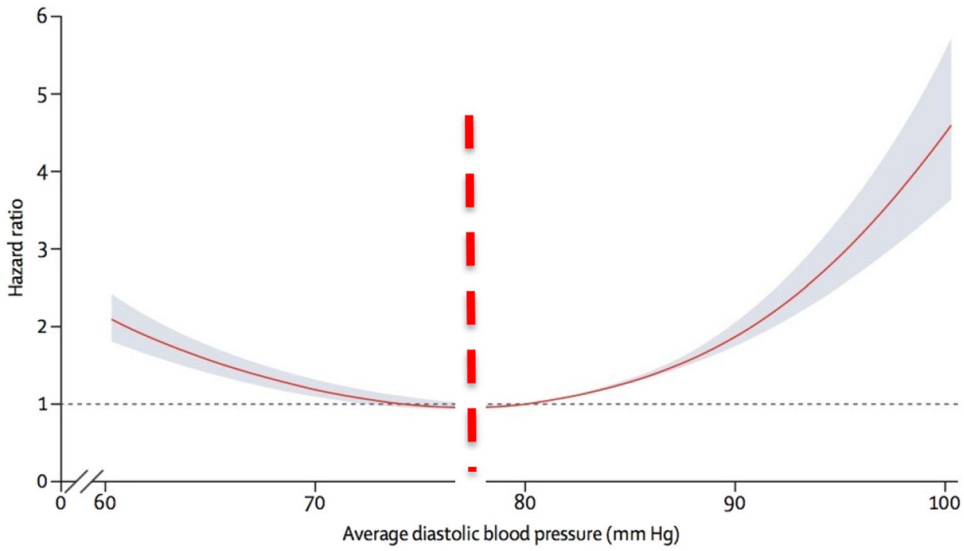

Fig. 4 Risk of cardiovascular death, myocardial infarction, or stroke according to baseline diastolic blood pressure in 22,672 patients with hypertension and coronary artery disease [51]

and especially inferior in preventing stroke, compared to ARBs [2, 67] (Table 2). Furthermore, they also appear to have more side effects [68].

The different substance classes can be combined as they have different synergistic effects on blood pressure reduction (Fig. 5).

Resistant arterial hypertension

Resistant hypertension is defined as high blood pressure that is insufficiently controlled according to the current guidelines. Around 5–15% of all patients with hypertension have apparent resistant hypertension [69–71], the exact prevalence being unknown. The standard regimen for the treatment of resistant hypertension contains of ACE-I/ARB, diuretic, and CCB. According to recently published data, spironolactone appears

Table 2 Recommended drugs in the treatment of hypertension depending on contra-indications and preferred conditions

Class of drugs	Contra-indications	Preferred conditions
Diuretics	Gout Metabolic syndrome Glucose intolerance Pregnancy Hypercalcaemia Hypokalaemia	Heart failure ISH (in elderly) Blacks
Calcium antagonists	A-V block (verapamil, diltiazem) Severe LV dysfunction (verapamil, diltiazem) Heart failure (verapamil, diltiazem) Tachyarrhythmia (dihydropyridines) Heart failure (dihydropyridines)	LVH Asymptomatic atherosclerosis Angina pectoris Peripheral artery disease ISH (in elderly) Metabolic syndrome Pregnancy Blacks
ACE-Inhibitors	Pregnancy Angioneurotic oedema Hyperkalaemia Bilateral renal artery stenosis Women with children bearing potential	LVH Asymptomatic atherosclerosis Microalbuminuria Renal dysfunction Previous myocardial infarction Heart failure Atrial fibrillation (prevention) End-stage kidney disease Peripheral artery disease Metabolic syndrome Diabetes mellitus
Angiotensin receptor blockers	Pregnancy Hyperkalaemia Bilateral renal artery stenosis Women with children bearing potential	LVH Microalbuminuria Renal dysfunction Previous myocardial infarction Heart failure Atrial fibrillation (prevention) End-stage kidney disease Metabolic syndrome Diabetes mellitus
Mineralocorticoid receptor blockers	eGFR <30ml/min Hyperkaliaemia	Resistant arterial Hypertension Heart failure Atrial fibrillation (prevention)
Beta-blocker	Asthma A-V block (2° or 3°) Metabolic syndrome Glucose intolerance Athletes Chronic obstructive pulmonary disease	Previous myocardial infarction Angina pectoris Heart failure Aortic aneurysm Atrial fibrillation Pregnancy

Dark red font: Compelling contra-indication. Orange font: possible contra-indication. Green font: Preferred conditions. Green background: recommended in monotherapy. Light red background: not recommended in monotherapy

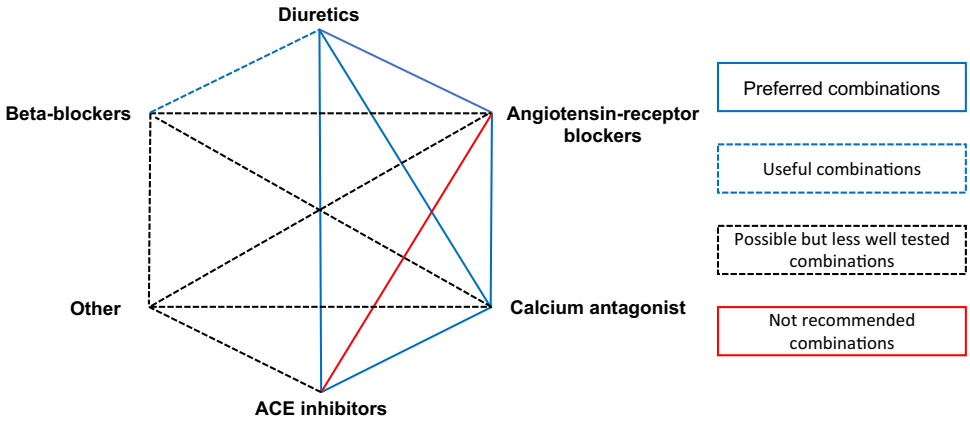

Fig. 5 Combinations of different classes of antihypertensive drugs. *ACE* angiotensin-converting enzyme

to be the most effective fourth-line agent for the treatment of resistant hypertension [71–73], when compared with bisoprolol and doxazosin.

Adherence and combination therapy

Crucial for the success of every medical treatment is the adherence and persistence to the prescribed regimen. In a study of 255.000 patients, only 56.3% were still adherent after a 2-year period to their prescribed medication plan [74]. In a recent meta-analyses, nonadherence in hypertension appears to range from 23 to 66%, respectively [75]. Important risk factors for nonadherence are younger age, male sex, prescription of diuretics, a higher number of daily doses, and different drugs [76]. These finding suggest that, especially in patients with uncontrolled hypertension, fixed-dose combinations may help to improve adherence and persistence. Further work has shown that the combination therapy is superior to a doubling of monotherapy by 4–5 times [77]. Interestingly, a recent published cross-over study has shown that the initial treatment with a pill containing four different drugs with a quarter of the normal concentration is resulting in significantly more potent blood pressure reduction compared to monotherapy [78]. Other strategies like SMS-Text Adherence Support (StAR), Refill and Medication Scale (ARMS), and urine/plasma toxicological analysis may help to improve adherence [79–81]. In summary, several antihypertensive drugs can reduce blood pressure sufficiently, however mainly due to nonadherence and prescription of suboptimal drug combination, control rates remain unsatisfactorily low. Close collaboration between physicians and patients is crucial for treatment success.

Interventional treatment of hypertension

Renal denervation

Catheter-based renal denervation (RDN) is a safe and minimally invasive treatment option for patients with uncontrolled hypertension, and has been shown to reduce renal and central sympathetic activity [82, 83]. Several observational studies [84, 85], as well as national and international registries [86–88], have validated the outcomes of the pivotal Symplicity HTN-1 and HTN-2 trials. However, after 6 months, the randomized, blinded, sham-controlled Symplicity HTN-3 trial [89] could not prove the superiority of RDN in reducing blood pressure (BP) compared with a sham procedure. The neutral results of the Symplicity HTN-3 trial have been extensively discussed and attributed to several possible confounding factors, including inadequate patient selection, low operator experience, and inadequate procedural performance [90]. In contrast, the multicenter, randomized-controlled DENER-HTN study established the superiority of RDN and antihypertensive medication over pharmacotherapy alone [91]. The study enrolled 121 patients who received a standardized triple antihypertensive treatment during a 4-week run-in period; the remaining 106 patients with resistant hypertension (verified by the day-time ambulatory BP) were randomly allocated to undergo RDN or served control procedures. After randomization, if home BP was $\geq$ 135/85 mmHg, patients in both groups underwent stepped-care antihypertensive drug treatment from months 2–5. The primary

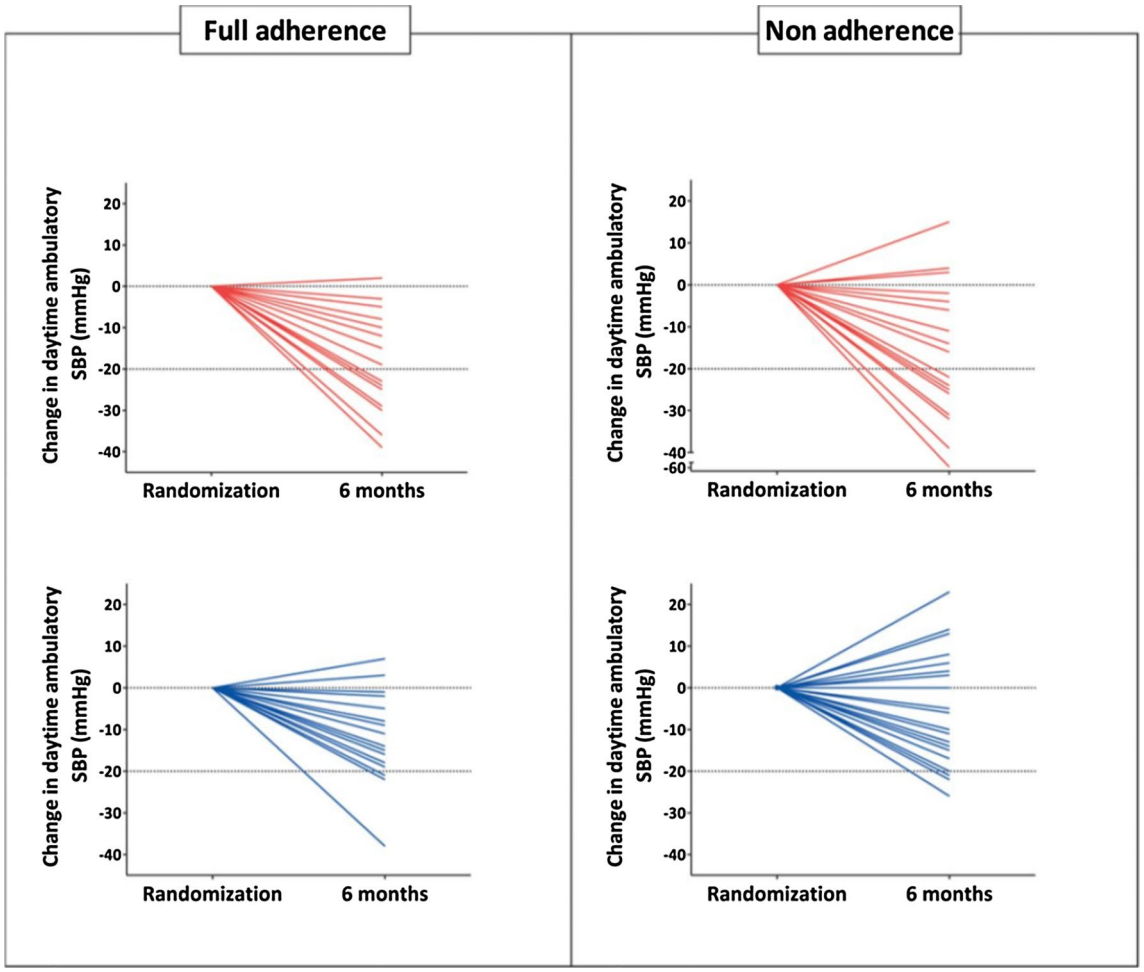

Fig. 6 Fan plots of individual changes in day-time ambulatory systolic blood pressure (SBP) between baseline and 6 months in the renal denervation group (red lines) and control group (blue lines) in patients who were fully adherent and nonadherent (partially nonadherent plus completely nonadherent) to SSAHT. SSAHT indicates standardized stepped antihypertensive treatment. Modified from Azizi et al. [87]

efficacy endpoint at 6 months was met in the RDN group with a reduction in the mean ambulatory day-time systolic BP of 16 mmHg following RDN compared with a decreased systolic BP of 10 mmHg in the control group [91]. However, even this comprehensive and well-conducted investigation reported a substantial variation of interindividual 24-h ambulatory BP response because of various explanations after the detection of the procedure including nonadherence (Fig. 6) [92, 93].

A series of new studies have been designed after judiciously considering the limitations and learnings of the previous studies to address open questions and to elucidate the role of RDN in the armamentarium of antihypertensive treatments [85]. The prospective, randomized, double-blind, sham-controlled SPYRAL HTN studies were conducted to ascertain the effect of RDN in patients with uncontrolled BP without concomitant medication (OFF-MED) and in patients with concomitant medication (ON-MED) [94]. The studies enrolled patients with combined hypertension having an office systolic BP of 150–180 mmHg, office diastolic BP of >90 mmHg, and 24-h systolic BP of 140–170 mmHg at 21 centers in the United States (US), Europe, Japan, and Australia [95, 96]. Compared with the SYMPLICITY HTN protocols, the study design of SPYRAL HTN comprises several critical modifications: (i) a multi-electrode catheter designed to facilitate reliable circumferential four-quadrant ablation; (ii) the main distal renal artery and all branches and accessory arteries will be treated, which has reportedly exhibited the highest change in the renal norepinephrine and axon density in pig [97]; (iii) the procedure was performed in advanced centers, with all involved in the study having experienced RDN, and has been conducted by one proceduralist per center only. The SPYRAL HTN OFF-MED trial obtained the primary outcomes from the interim analysis of 80 patients (the intervention group, $n=38$; the sham-control group, $n=42$), demonstrating a significant difference in the

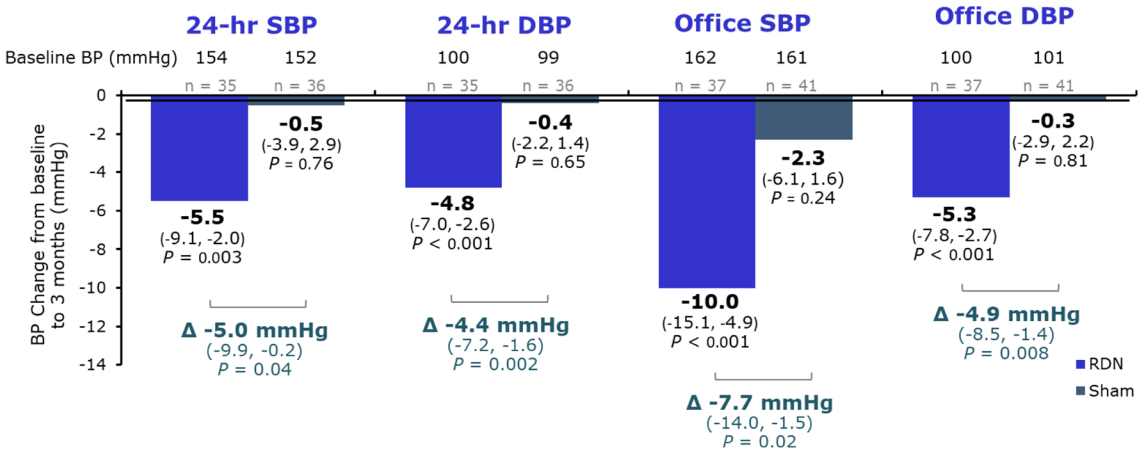

Fig. 7 Changes at 3 months in office and ambulatory SBP and DBP for renal denervation and sham-controlled groups 95% CIs and unadjusted *p* values shown. *SBP* systolic blood pressure, *DBP* diastolic blood pressure. Modified from Townsend et al. [92]

primary endpoint 24-h ambulatory BP and office BP in favor of RDN at 3 months (Fig. 7) [98]. In addition, no relevant adverse event was reported in the RDN and sham-controlled groups [98]. Notably, this trial provides the biological proof-of-principle for the efficacy of catheter-based RDN to reduce BP in patients with uncontrolled BP not treated with antihypertensive medications. Particular attention should be paid to two recently published renal denervation studies. The SPYRAL HTN-ON-MED [99] trial investigated the effect of RDN in the presence of blood pressure medication. The RADIANCE-HTN SOLO ([100]) trial used a balloon-based ultrasound ablation catheter. Both studies could de novo confirm the efficacy of renal denervation and show a significant reduction in blood pressure.

Carotid baroreceptor stimulation

The first human feasibility study with the implantation of the Rheos system (CVRx, Minneapolis, MN) was the non-randomized DEBuT-HT open-label trial, which enrolled 45 patients with resistant hypertension. After 2-year follow-up, a significant decline in mean office BP by 33/22 mmHg was reported [101]. Recently, the 6-year long-term safety and efficacy results of three baroreflex activation therapy (BAT) studies (patients enrolled initially, $n = 383$; patients after 6 years, $n = 48$), namely the US Rheos Feasibility Trial (prospective, nonrandomized), the DEBuT-HT Trial (prospective, nonrandomized), and the Rheos Pivotal Trial (randomized, sham-controlled) [102]. Of note, all three trials used the first-generation Rheos system (CVRx), which was implanted in patients with resistant hypertension. The findings provided crucial information, suggesting that BAT exerted a sustained effect on BP over the entire follow-up period without major safety issues. However, some limitations, which now seem prerequisites for device-based hypertension trials, warrant consideration while interpreting the study results; these limitations comprise the lack of 24-h ambulatory BP data, the absence of a control group, and the lack of adherence testing to antihypertensive medication [103].

Central iliac arteriovenous anastomosis

The ROX Medical arteriovenous coupler (ROX Medical, San Clemente, CA, USA) is a stent-like device made of nitinol that displays preformed shape memory, thereby sustaining the constant pressure gradient and flow. Under fluoroscopic guidance, the device is percutaneously deployed between the external iliac vein and artery at the femoral head level, causing an arteriovenous shunt of approximately 800–1200 mL/min [104]. Immediately after the dilatation of the coupler using a 4-mm noncompliant balloon, the invasively measured BP declines with an elevation in the cardiac output, stroke volume, and ejection fraction and a reduction in the end-diastolic pressure [105]. The multicenter, open-label, randomized, controlled trial (ROX CONTROL HTN trial) investigated the effects of anastomosis and standard care (medication continuation), or standard care alone in patients with confirmed office and ambulatory resistant hypertension [104]. After 12 months, the intention-to-treat analysis ($n = 39$) revealed that the office BP and 24-h ambulatory BP were decreased by 25/21 and 13/15 mmHg, respectively [106]. The 1-year follow-up revealed that 14 patients (33%) developed ipsilateral venous stenosis after coupler therapy

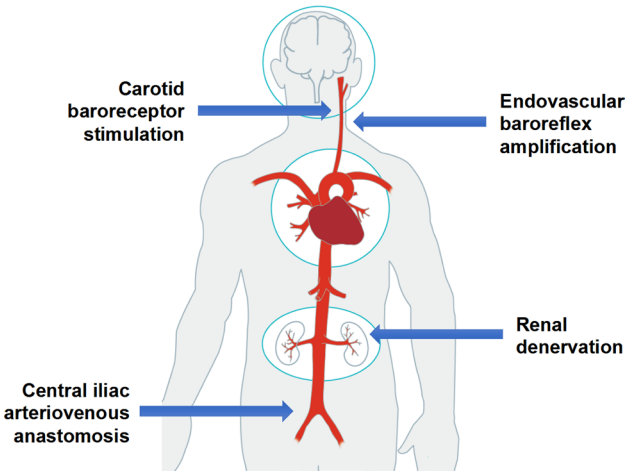

Fig. 8 Representation of different devices for interventional blood pressure reduction. Modified from Mahfoud F, presented at EuroPCR 2018

[106]. Remarkably, in contrast to RDN [95, 96], the BP decline was comparable in patients with either combined (office SBP, > 140 mmHg; DBP, > 90 mmHg) or isolated systolic BP (office SBP, > 140 mmHg; DBP, < 90 mmHg) [25]. Notably, the ROX coupler device is currently undergoing evaluation in the pivotal sham-controlled ROX CONTROL Hypertension (HTN)-2 (NCT02895386) study that started enrollment in 2017 in the US and Europe.

Endovascular baroreflex amplification

The CALM (Controlling and Lowering Blood Pressure with the MobiusHD) trial was the first-in-man, multicenter, open-label, and nonrandomized study that enrolled patients ($n = 31$) with resistant hypertension in the US and Europe with an objective to investigate the safety and efficacy of the MobiusHD implant (Vascular Dynamics, Inc.), a dedicated carotid stent developed to passively augment the pulsatile strain and reduce BP by increasing the carotid sinus baroreceptor activation and enhanced sympatho-inhibition. The carotid stent was percutaneously delivered to the carotid sinus using a rapid exchange catheter through a conventional 8-F guide catheter or a 6-F sheath. In the study, the average inclusion office-cuff BP and average inclusion 24-h ambulatory BP were 182/106 and 164/96 mmHg, respectively. Of note, 14 patients reached the 180-day safety endpoint, with an average variation in the office BP and 24-h ambulatory BP monitoring of −23/−10 and −14/−8 mmHg, respectively. Furthermore, nine patients with a 1-year follow-up exhibited a sustained lowering in the office BP of 26/16 mmHg [107]. Figure 8 depicts a summary of the different interventional treatments mentioned in this review.

Perspectives

Defining treatment goals (in particular lower boundaries of optimal blood pressure targets to achieve) as well as implementing innovative treatments providing the best tolerability and efficacy to patients is still a challenge in hypertension. New treatment options from the interventional field are on the horizon, which requires a close interdisciplinary collaboration between cardiologists, nephrologists, and hypertension specialists to achieve the optimal goals for patients with hypertension and to provide the best benefit concerning endpoint reduction and quality of life. Further research is needed to improve our understanding of pathophysiological backgrounds and novel treatment approaches; the majority of them need to be further studied in prospective randomized clinical trials.

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