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Views and Reviews

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- Hypertension: History and Development of Established and Novel Treatments

  High blood pressure is now recognized as one of the leading and most prevalent causes for cardiovascular death and cardiovascular hospitalizations. 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.

Therapeutic Updates

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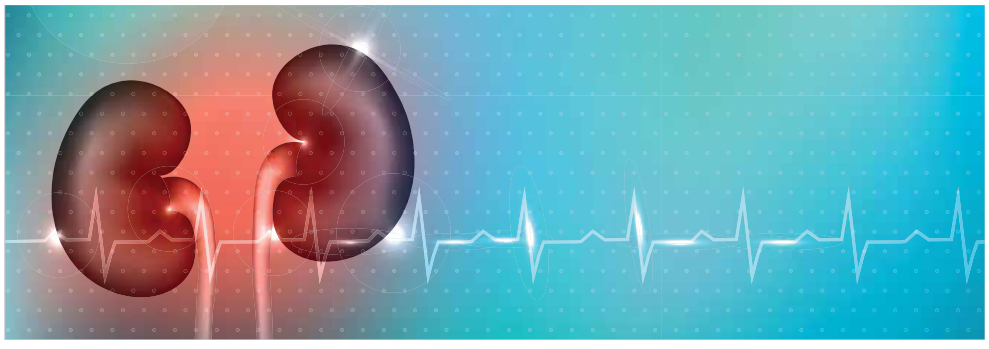
- Treatment of Hypertension in Chronic Kidney Disease

  Although kidney disease is characterized by progressive scarring that ultimately affects all structures of the kidney regardless of the underlying cause, however, the presence of hypertension may accelerate further kidney injury; therefore, hypertension treatment is important for the prevention of further kidney damage in an apparent vicious circle that leads to a functional decline.



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- Heart Failure and Stroke

  Heart failure (HF) is a frequent condition associated with diverse comorbidities such as cardiac arrhythmias, thromboembolism, impaired renal function, and an increased mortality as a result. An increased stroke risk in HF patients has been described in several studies.

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- Treatment of Hypertension in Light of the New Guidelines: Pharmacologic Approaches Using Combination Therapies

  Resistant hypertension (RH) is very common in patients with chronic kidney disease (CKD), with a prevalence of 20–35%, according to various studies. Most antihypertensive agents available for the general population can also be used in CKD patients, after consideration of their metabolism and dosing adjustments according to the level of renal function.

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Hypertension: History and Development of Established and Novel Treatments

Milan Wolf, Sebastian Ewen, Felix Mahfoud, Michael Böhm

High blood pressure is now recognized as one of the leading and most prevalent causes for cardiovascular death and cardiovascular hospitalizations. 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.

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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].

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.

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.

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

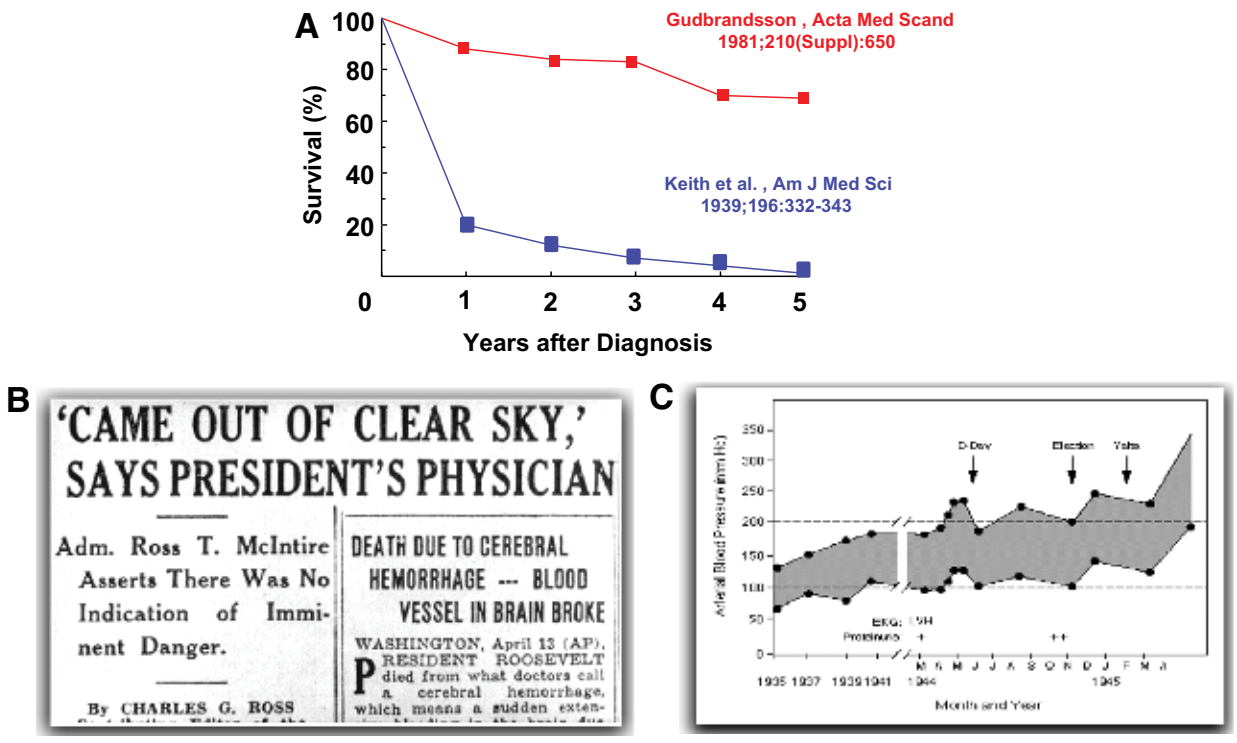

Fig. 1: Survival of patients with resistant hypertension who were untreated in 1939 and treated with diuretics 1981 (**A**). Press note on the death of President Roosevelt 1946 according to a cerebral hemorrhage after longstanding hypertension (**B**). Blood pressure values over 10 years of President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

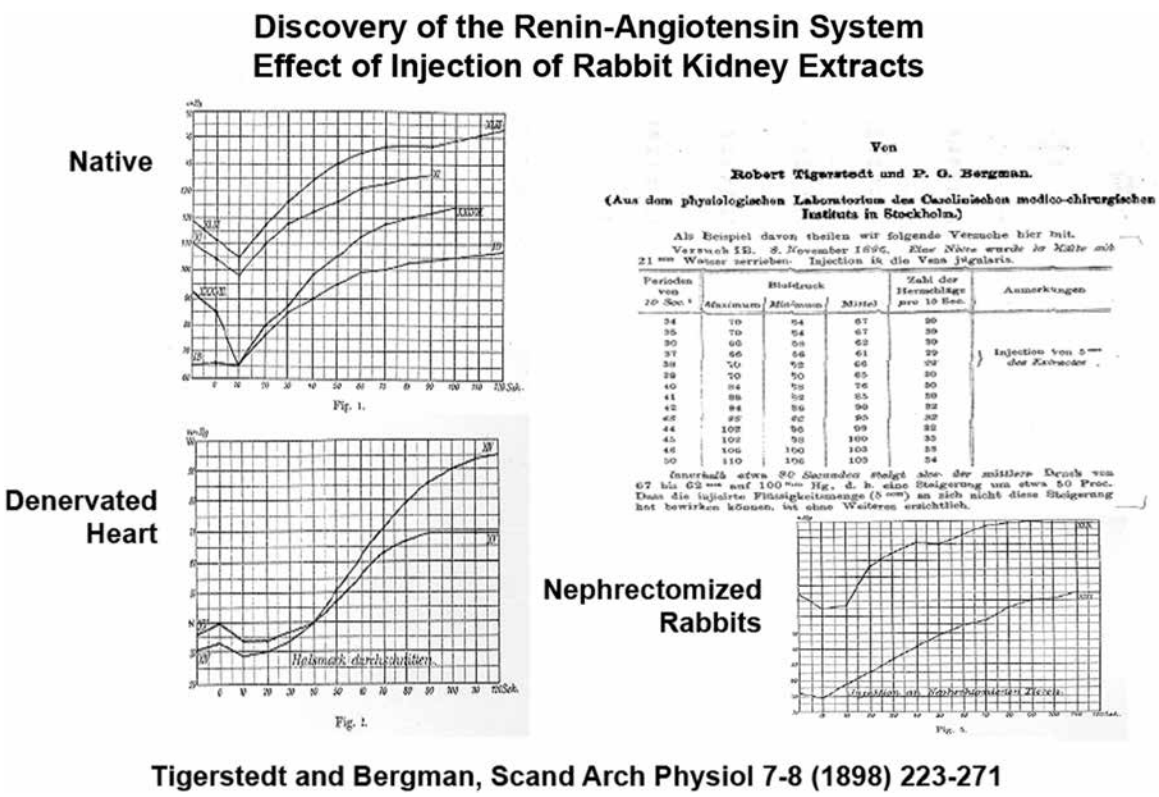

Fig. 2: Discovery of the renin–angiotensin system. Rabbit kidney extracts were injected into rabbits. After a short drop in blood pressure, there was a longstanding increase in blood pressure. After denervating the heart (*below*), the initial drop in blood pressure was not present, which was associated 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].

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 sulphur 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

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

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 (dichloroisoproterenol). 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 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.

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.

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

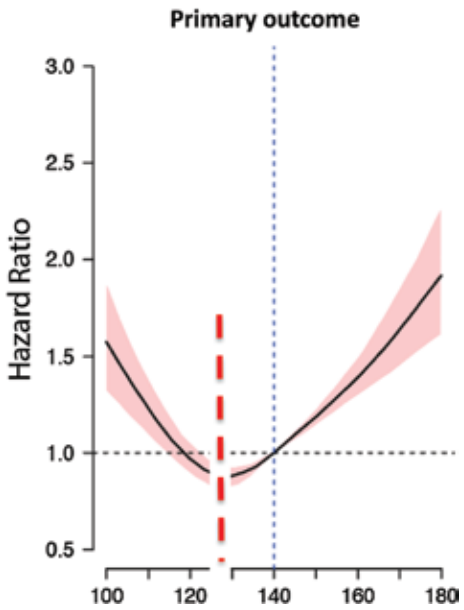

Fig. 3: Risk of the primary endpoint (cardiovascular death, myocardial infarction, stroke, and hospital admission for heart failure) according to mean achieved systolic blood pressure of 30,937 patients at high cardiovascular risk [49].

hypertensive patients.

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 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].

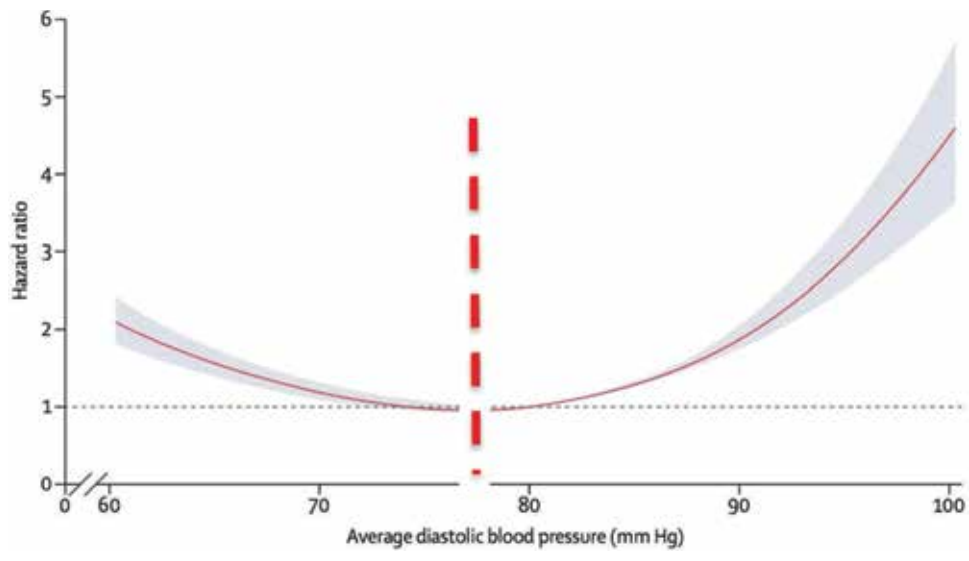

Fig. 4: Risk of cardiovascular death, myocardial infarction, or stroke according to baseline diastolic blood pressure in 22,672 patients with hypertension and coronary artery disease [51].

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 and especially inferior

Table 2: Recommended drugs in the treatment of hypertension depending on contraindications and preferred conditions.

Class of drugs	Contraindications	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

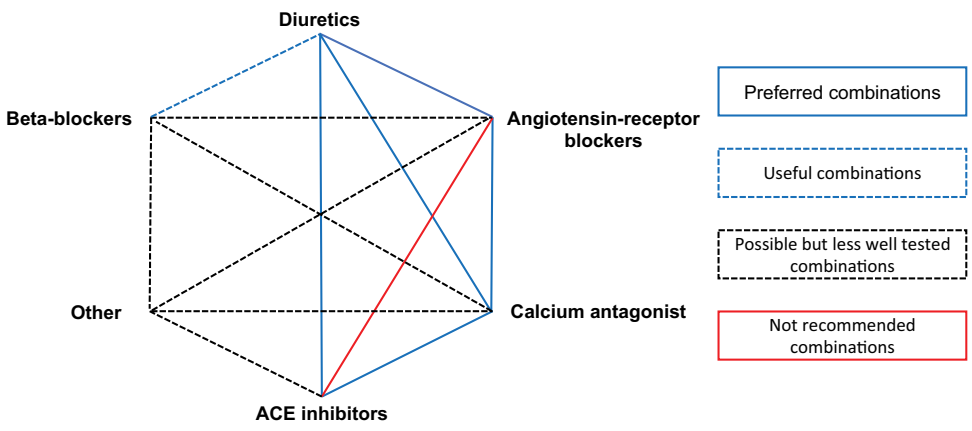

Fig. 5: Combinations of different classes of antihypertensive drugs. *ACE* angiotensin-converting enzyme

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).

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 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

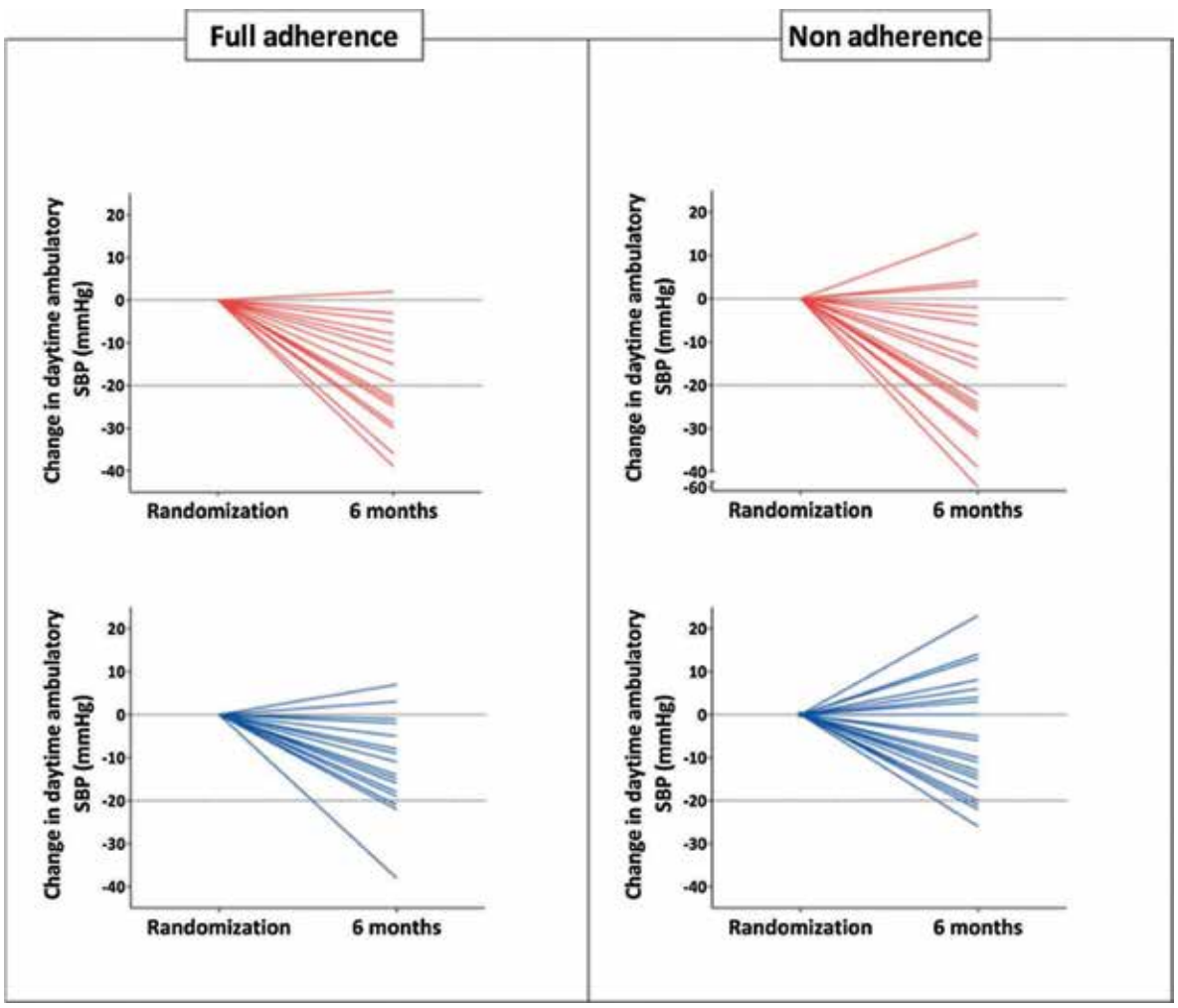

Fig. 6: Fan plots of individual changes in day-time ambulatory systolic blood pressure (SBP) between baseline and 6 months in the renal denervation group (*red lines*) and control group (*blue lines*) in patients who were fully adherent and nonadherent (partially nonadherent plus completely nonadherent)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

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 nonrandomized 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

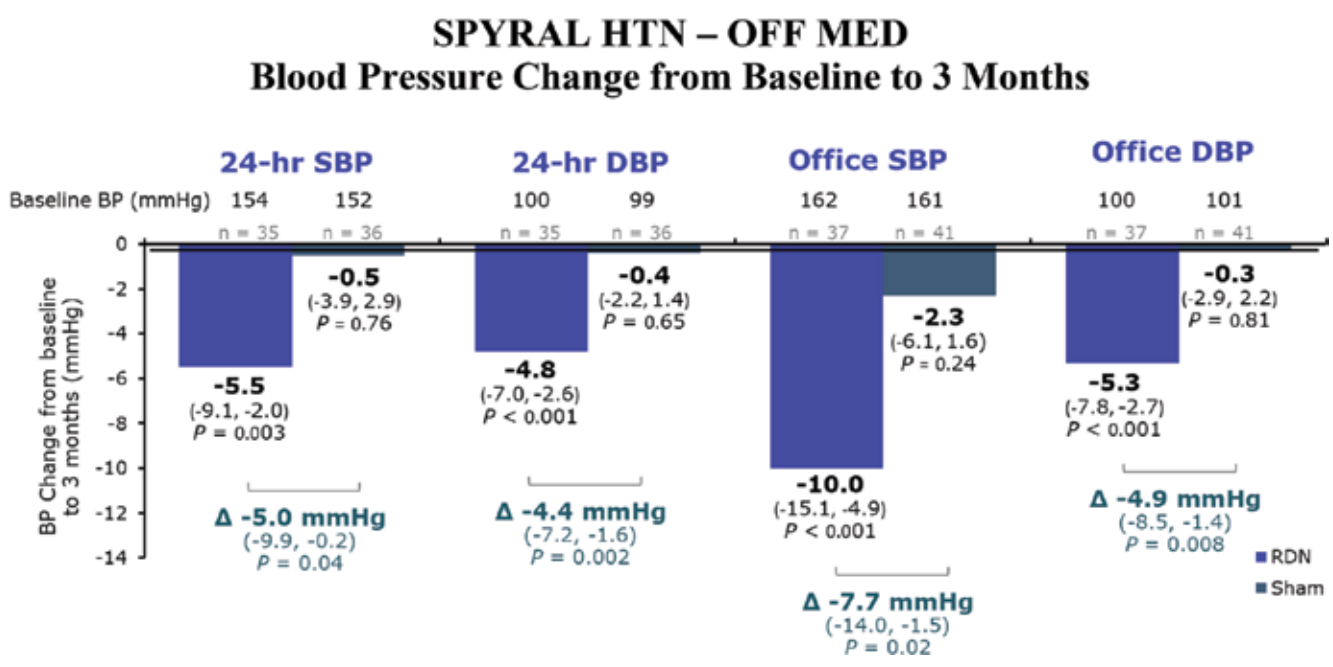

Fig. 7: Changes at 3 months in office and ambulatory SBP and DBP for renal denervation and sham-controlled groups 95% CIs and unadjusted *p* values shown. *SBP* systolic blood pressure, *DBP* diastolic blood pressure. Modified from Townsend *et al.* [92].

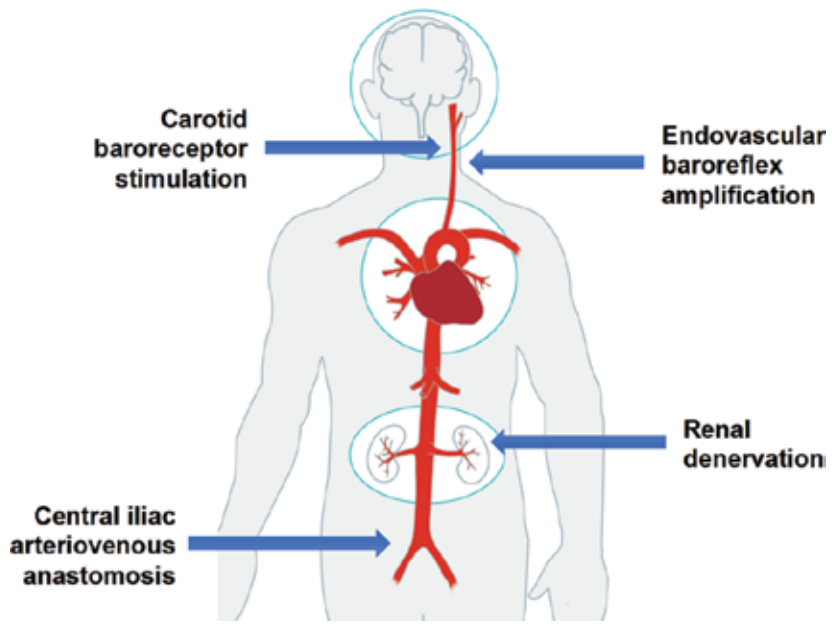

Fig. 8: Representation of different devices for interventional blood pressure reduction. Modified from Mahfoud F, presented at EuroPCR 2018.

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 [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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Treatment of Hypertension in Light of the New Guidelines: Pharmacologic Approaches Using Combination Therapies

Liviu Segall

Resistant hypertension (RH) is very common in patients with chronic kidney disease (CKD), with a prevalence of 20–35%, according to various studies. Most antihypertensive agents available for the general population can also be used in CKD patients, after consideration of their metabolism and dosing adjustments according to the level of renal function.

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Introduction

Resistant hypertension (RH) is very common in patients with chronic kidney disease (CKD), with a prevalence of 20–35%, according to various studies [1].

Unfortunately, since individuals with advanced CKD and end-stage renal disease (ESRD) have usually been excluded from randomized controlled trials (RCTs), there is very little evidence to guide the pharmacological therapy of hypertension, and particularly RH, in these patients [2].

Nevertheless, it is widely thought that the multifactorial pathogenesis of RH in CKD requires multiple drug therapy, to simultaneously target factors like the intravascular volume expansion and the hyperactivity of the renin-angiotensin system (RAS) and the sympathetic nervous system [3]. Combined therapy, however, has to be individualized, depending on the patient's pathophysiologic profile, comorbidities, and contraindications. Moreover, the optimal combination should be well tolerated, to ensure long-term adherence [3]. Most antihypertensive agents available for the general population can also be used in CKD patients, after consideration of their metabolism and dosing adjustments according to the level of renal function [4]. The pharmacological armamentarium includes diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers (BBs), alpha-blockers, centrally acting drugs, and other vasodilators [3] (Table 1).

Table 1: Indications, additional benefits, caution, and combined use of the different antihypertensive drug groups in CKD patients [5].

Type of drug	Other indications besides hypertension	Additional benefits	Caution	Combined use
RAS blockers				
ACEIs and ARBs	Proteinuria Heart failure Post-AMI	Reduction of intraglomerular pressure, reduction of proteinuria, and CKD progression Reduction of fibrosis and cardiovascular remodeling	Hyperkalemia Monitor kidney function and K^+ after starting treatment Use of NSAIDs Use of COX-2 inhibitors Combined use with other RAS blockers Bilateral renal artery stenosis Volume depletion	Diuretics CCBs BBs
MR antagonists	Heart failure Post-AMI	Reduction of albuminuria or proteinuria	Hyperkalemia Monitor kidney function and K+ after starting treatment Use of NSAIDs Use of COX-2 inhibitors	ACEIs ARBs
DRIs		Reduction of albuminuria or proteinuria	As above Increased risk of complications in diabetic or CKD patients when combined with ACEIs or ARBs	Diuretics CCBs
Diuretics				
Thiazides		Reduced risk of hyperkalemia	May aggravate hyperglycemia Replace with or add loop diuretic if GFR <30 ml/min/1.73 m^2	ACEIs ARBs
Loop diuretics	Edema	Reduced risk of hyperkalemia		
CCBs				
DHP	Angina			ACEIs ARBs BBs Diuretics
Non-DHP	Angina Supraventricular tachycardia	Reduction of intraglomerular pressure Reduction of heart rate	They increase the levels of CNIs and mTOR inhibitors Do not associate with BBs	ACEIs ARBs Diuretics
BBs				
	Heart failure (bisoprolol, carvedilol, and metoprolol) Angina Post-AMI	Reduction of heart rate	Risk of bradycardia Do not use with non-DHP CCBs	ACEIs ARBs Diuretics DHP CCBs
Others				
Centrally acting alpha-agonists			Reduce moxonidine dose if GFR <30 ml/min/1.73 m^2	Diuretics
Alpha-blockers	Prostatic hypertrophy		Orthostatic hypotension	BBs Diuretics
Direct vasodilators			Salt and water retention Tachycardia	BBs Diuretics

NSAIDs nonsteroidal anti-inflammatory drugs, *ARBs* angiotensin receptor blockers, *COX2* cyclooxygenase 2, *DHP* dihydropyridines, *CKD* chronic kidney disease, *AMI* acute myocardial infarction, *ACEIs* angiotensin-converting enzyme inhibitors, *RAS* renin-angiotensin system

Treatment of Resistant Hypertension in the General Population

Triple Therapy

For hypertensive patients requiring a triple therapy, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) recommendation of 2013 indicates that the choice should be made between four classes of antihypertensive drugs: RAS inhibitors (ACEIs and ARBs), BBs, CCBs, and thiazide diuretics [6]. However, in the past decade, BBs have been slightly "downgraded," after the publication of a meta-analysis [7] which revealed the association of these drugs with a 16% higher stroke rate, as compared to the other agents [8]. Therefore, other expert societies, including the British Hypertension Society [9], American Heart Association [10], and French Society of Arterial Hypertension [11], suggest that the triple combination should consist of ACEI/ARB + CCB + diuretic (the "ACD regimen"), although there are no RCTs to support this suggestion.

Definition of RH

Resistant hypertension is defined as uncontrolled hypertension (i.e., office BP ≥140/90 mmHg in a patient <80 years or systolic blood pressure [BP] ≥150 mmHg in a patient ≥80 years, confirmed by home self-measurement or ambulatory monitoring of BP), despite antihypertensive treatment consisting of appropriate lifestyle changes and triple drug therapy for at least 4 weeks, in optimal doses, including a diuretic [11]. However, before making the diagnosis of RH, adherence to prescribed

therapy should be confirmed (e.g., by using specific questionnaires or serum drug-level measurements), and possible interference of pro-hypertensive factors, such as high salt intake, excess alcohol consumption, or use of vasopressor drugs (like cyclosporine, steroids, erythropoietin, or oral contraceptives), should be searched for [11]. If true RH is established, causes of secondary hypertension including primary aldosteronism, pheochromocytoma, hypercorticism, renal artery stenosis, or sleep apnea syndrome should also be considered and investigated [11].

Treatment of RH

In patients with RH for which no curable cause can be identified, the addition of a fourth antihypertensive agent is indicated. This should preferably be an MR antagonist (spironolactone or eplerenone), in the absence of contraindications [11].

Mineralocorticoid receptor (MR) antagonists are weak diuretics, but they play a special role in the management of RH, for several reasons. Patients with RH often have secondary hyperaldosteronism and may also exhibit the so-called aldosterone escape or breakthrough. This phenomenon is defined as an increase in aldosterone levels after initiation of ACEIs or ARBs, most likely by non-ACE pathways of angiotensin II activation [12]. However, MR antagonists were shown to improve BP control in patients with RH, regardless of circulating aldosterone levels [13]. The RCT Addition of Spironolactone in Patients with Resistant Arterial Hypertension (ASPIRANT) [14] evaluated the antihypertensive effects of spironolactone 25 mg/day in 117 patients with RH after treatment for 8 weeks. Existing antihypertensive treatment was continued during this period. The study showed that systolic BP was reduced significantly in treated patients, with no adverse effects. More recently, the Prevention and Treatment of resistant Hypertension With Algorithm-Guided Therapy (PATHWAY-2) study [15] demonstrated the superior BP-lowering effect (and similarly good tolerance) of spironolactone 25–50 mg/day, as compared to each of bisoprolol, doxazosin, and placebo, in patients with RH already on ACD regimen.

In cases with contraindications, resistance, or intolerance to spironolactone, the use of a BB, an alpha-blocker, or a centrally acting agent is recommended [11].

Another important therapeutic measure, given the role of volume overload in the pathogenesis of RH, is to reinforce diuretic medication, together with the low-salt diet [11]. This involves a dose increase or a change in diuretic therapy.

Recently, there has been much debate about which diuretic is better: hydrochlorothiazide (HCTZ), chlorthalidone, or indapamide? Chlorthalidone is often thought to be superior to HCTZ in terms of efficacy and reduction of cardiovascular events, as it has been shown by two meta-analyses [16, 17]; however, in these meta-analyses there was no head-to-head comparison, and also, in the Multiple Risk Factor Intervention Trial (MRFIT), chlorthalidone was used in higher doses than HCTZ [13]. Indapamide is considered a good alternative to chlorthalidone. If the BP target is still not reached, a sequential blockade of tubular sodium reabsorption, using both thiazides and loop diuretics, is suggested [8].

In patients with RH for which no curable cause can be identified, the addition of a fourth antihypertensive agent is indicated. This should preferably be an MR antagonist (spironolactone or eplerenone), in the absence of contraindications.

With thiazides and/or loop diuretics, the risk of hypokalemia should be considered and avoided. In contrast, with aldosterone antagonists, hyperkalemia may occur, in particular in cases of CKD or if combined with an RAS inhibitor, a BB or a nonsteroidal anti-inflammatory drug (NSAID). Therefore, during treatment with any of these drugs, monitoring of serum potassium and creatinine is indicated [8].

Some authors have proposed the guidance of antihypertensive therapy in RH by plasma renin activity (the Cambridge αβΔ-guideline) [8]. This method can be applied in patients without concomitant diseases, taking into consideration the results of plasma renin testing. According to this strategy, inadequately controlled patients should receive (in addition to the ACD regimen) a BB in case of high renin levels, an alpha-blocker in case of normal renin levels, and diuretic reinforcement in case of low renin levels [8]. In the PATHWAY-2 study, the BP response to spironolactone was superior to bisoprolol and doxazosin across most of the plasma renin distribution; however, the magnitude of spironolactone superiority was much higher at the low-renin pole of the distribution [15].

Other drugs, including centrally acting antihypertensive agents (e.g., clonidine) and direct vasodilators (e.g., minoxidil, hydralazine), are often indicated as drugs of last resort, when previously recommended treatments have failed. However, their use is not supported by evidence from large interventional studies [8]. Clonidine is a potent antihypertensive drug, and patients with RH seem to respond well to this medication [8]. Minoxidil is a strong vasodilator and has been successfully used for many years, as well as clonidine, in patients with RH, including those with advanced CKD. Its use is limited, however, because of numerous side effects, like tachycardia, salt retention, pericardial effusion, and hirsutism [8]. Hydralazine is less effective than minoxidil but may be used in cases with contraindications or intolerance to the latter. Due to its short duration of action, hydralazine has to be administered three or four times daily. It can also induce tachycardia, requiring the association of BBs [8].

Treatment of Resistant Hypertension in Pre-Dialysis CKD Patients

Definition of RH and Target BP According to Guidelines

The general definition of RH is largely applicable to the CKD population. Most of the current guidelines, including those from the ESH/ESC 2013 [6], American Society of Hypertension/International Society of Hypertension (ASH/ISH) 2014 [18], Eighth Joint National Committee (JNC 8) 2014 [19], American Heart Association/American College of Cardiology/Centers for Disease Control and Prevention (AHA/ACC/CDC) 2014 [20], Caring for Australasians with Renal Impairment (CARI) 2013 [21], and Canadian Hypertension Education Program (CHEP) 2014 [22], recommend a BP goal for these patients <140/90 mmHg, but some suggest a lower target (<130/80 mmHg) for the subgroup with proteinuria [6, 18, 21].

Triple Therapy

The triple regimen ACD seems to be a reasonable choice for patients with CKD and difficult-to-treat hypertension.

The efficacy/safety of the ARB olmesartan (OM) 40 mg, the CCB amlodipine 10 mg (AML), and the diuretic hydrochlorothiazide 25 mg (HCTZ) versus the component dual combinations (OM/AML, OM/HCTZ, and AML/HCTZ) was evaluated in participants with diabetes, CKD, or cardiovascular diseases in the Triple Therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in Hypertensive Patients Study (TRINITY) [23]. At 12 weeks, OM/AML/HCTZ resulted in significantly greater systolic BP reductions in participants with CKD. The BP goal achievement was greater for participants receiving triple-combination treatment compared with the dual-combination treatments. At week 52, there was sustained BP lowering with the OM/AML/HCTZ regimen. Overall, the triple combination was well tolerated.

Although RCTs comparing it with other triple therapies have never been performed, the ACD combination is thought to be scientifically sound, effective, and well tolerated, and it is widely used in everyday clinical practice. It should be tried in optimum doses as the first therapeutic step in patients with CKD and RH, in the absence of contraindications and after all forms of pseudo-resistance have been excluded. This regimen might be applied in terms of switching previous therapy or of treatment intensification in patients already using this combination in lower doses [3].

Table 2: Strategies to minimize risk of hyperkalemia caused by RAS inhibitors in patients with CKD [25].

Wherever possible, discontinue drugs that can impair renal potassium excretion (e.g., NSAIDs, including selective COX-2 inhibitors)
Prescribe a low-potassium diet; advise patients to avoid use of salt substitutes that contain potassium
Prescribe thiazide diuretics (and/or loop diuretics if estimated GFR is <30 mL/min/1.73 m^2) Prescribe sodium bicarbonate to correct metabolic acidosis; decrease dose of ACEI or ARB
Measure serum potassium level 1 week after initiating ACEI or ARB therapy or after increasing the dose
If patient is taking some combination of an ACEI, an ARB, and a MR antagonist, discontinue one and recheck serum potassium level
Do not exceed a 25-mg daily dose of spironolactone when used in combination with an ACEI or an ARB

ACEIs and ARBs

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are RAS blockers, with both cardioprotective and renoprotective effects. They reduce cardiac and vascular remodeling and myocardial fibrosis, as well as intraglomerular pressure and proteinuria [4, 5]. Therefore, they are not only very effective antihypertensive agents, but they are also beneficial in patients with heart failure, post-myocardial infarction, and proteinuric CKD [5], in whom they can prevent cardiovascular mortality and CKD progression, respectively.

Adverse effects of ACEIs and ARBs include hypotension, acute kidney injury, and hyperkalemia. Caution is required when using these drugs in patients with bilateral renal artery stenosis, volume depletion, and concurrent use of NSAIDs or other RAS inhibitors. Monitoring of serum creatinine and potassium is indicated after starting treatment, especially in such high-risk cases [5]. The use of these drugs in women of child-bearing age should be balanced with the risk of pregnancy, since they are potentially teratogenic [24].

Most available ACEIs have active moieties that are largely excreted in the urine. Fosinopril and trandolapril are partially (approximately 50%) excreted by the liver, such that the blood levels are less influenced by kidney failure than levels of other ACEIs which are predominantly excreted by the kidneys. Since ACEIs are generally titrated to achieve optimal clinical effect, the mode of excretion is not regarded as a major factor in dosing. If hyperkalemia occurs in CKD patients taking a renal-excreted ACEI, possible interventions include dietary advice, reducing the dose, or adding a potassium-losing diuretic [24]. If strategies to minimize hyperkalemia (Table 2) fail to maintain serum potassium concentrations below 5.6 mEq/L, the RAS inhibitor should be discontinued, and another class of antihypertensive drugs should be used instead [25].

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are RAS blockers, with both cardioprotective and renoprotective effects. They reduce cardiac and vascular remodeling and myocardial fibrosis, as well as intraglomerular pressure and proteinuria.

Virtually all guidelines recommend ACEIs/ARBs as first-line therapeutic agents in hypertensive CKD patients, regardless of proteinuria levels and diabetic status [5, 6, 18–24]. However, some guidelines suggest that these drugs are particularly preferable in CKD patients with micro- or macroalbuminuria [24, 26], in which they are associated with better kidney and cardiovascular outcomes [24]. ACEIs and ARBs are probably equivalent with respect to renal outcomes [26]. They should be considered for use particularly in patients with CKD who also have heart failure, recent myocardial infarction, a history of stroke, or a high cardiovascular risk, although this KDIGO recommendation is largely based on data from studies in non-CKD patients [24].

The support for the recommendation of ACEIs/ARBs as first-line therapeutic agents in hypertensive CKD patients is provided by several studies. The KDIGO recommendations cite five relevant trials: reanalyses of the Heart Outcomes Prevention Evaluation (HOPE) trial [27], the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial [28], the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) [29], as well as the Investigation on Type 2 Diabetic Nephropathy (INNOVATION) study [30] and the Irbesartan in Development of Nephropathy in Patients with Type 2 Diabetes (IDNT) trial [31]. A meta-analysis of 11 RCTs [32] included studies of patients with nondiabetic CKD treated with BP-lowering regimens containing ACEIs to those not containing ACEIs. All trials included in the analysis targeted a BP <140/90 mmHg, and nearly all patients were hypertensive at baseline. In this analysis, the use of an ACEI was associated with a significant reduction in the risk of progression of kidney disease as defined by doubling of serum creatinine or the need for dialysis. This effect was independent of other important covariates, including baseline BP and urinary protein excretion. Of relevance, there was no significant interaction between current urinary protein excretion and treatment allocation. In other words, there was no evidence that the degree of protein excretion

modified the relationship between the use of ACEIs and the progression of kidney disease. The results of the meta-analysis suggest that ACEIs should be the antihypertensive drugs of choice in individuals with CKD. However, another analysis of the same data set [33] suggested that baseline urinary protein excretion was an important effect modifier, in that those with baseline urine protein excretion ≥500 mg/day seemed to have greater benefits with ACEI therapy. Those with proteinuria <500 mg/day at baseline appeared to receive little if any benefit compared to other antihypertensive regimens. TRANSCEND [34] randomized patients at high vascular risk to telmisartan or placebo. No difference was observed between groups in the primary cardiovascular endpoint or the secondary renal endpoint of dialysis, doubling of serum creatinine, or death. In a reanalysis of TRANSCEND, individuals without microalbuminuria had an increased risk of the renal endpoint, while there was no significant difference in those with urinary albumin excretion ≥30 mg/day, although the trend favored telmisartan.

There are also some other significant controversies between guidelines regarding ACEIs and ARBs. First, according to the ERBP guideline [35], it is unclear if the renoprotective superiority of ACEIs and ARBs is truly a BP-independent effect or simply a reflection of better BP control. Second, in contrast with the KDIGO guidelines, the authors of ERBP recommend that, due to increased risk of side effects, consideration should be given to stopping ACEIs/ARBs in patients with advanced CKD (stages 4 and 5) when there are no other compelling indications for these agents (such as heart failure), especially in those with renovascular disease, or when discontinuation of the drug may enable the start of renal replacement therapy to be postponed or avoided [35].

Diuretics

Diuretics are the cornerstones of hypertension treatment in CKD and, by definition, a component of any antihypertensive drug combination for RH. Most patients with CKD should receive a diuretic as their first or second agent to manage volume and sodium retention, with the possible exception of those with autosomal dominant polycystic kidney disease, in which there is concern that diuretic therapy can stimulate the RAS and subsequent cyst growth [4]. However, the efficacy of diuretics is limited in CKD, because both the tubular secretion of these drugs and the fractional reabsorption of sodium are reduced. Therefore, CKD patients often require large doses of diuretics, which are achieved in practice by sequentially doubling the dose until a response is seen or a ceiling dose is reached [12].

Verdalles *et al.* [36] used bioimpedance spectroscopy (BIS) to assess fluid status and guide the use of diuretics to treat hypertension in CKD patients not on dialysis. They treated 30 patients with extracellular volume (ECV) expansion with a diuretic, which were compared to 20 patients without ECV expansion who instead received another additional antihypertensive medication. At 6 months of follow-up, systolic BP decreased by 21 mmHg in patients with ECV expansion versus 9 mmHg in patients without ECV expansion ($P < 0.01$). In addition, 9 of 30 patients with ECV expansion and 2 of 20 without ECV expansion achieved the target BP of <140/90 mmHg at 6 months. This novel approach to managing hypertensive CKD patients based on BIS assessment of volume status will need further study in larger cohorts before it can be considered for wider use.

Most clinicians choose to switch to a loop diuretic in patients with CKD stage 4, particularly if hypertension is becoming resistant to therapy or if edema is an issue.

Except for diuretics, most antihypertensive drugs induce sodium retention and ECV expansion. Diuretics counteract this by inhibiting sodium reabsorption. In addition, diuretics may also reduce the risk of hyperkalemia associated with RAS inhibitors. On the other hand, volume loss caused by diuretics activates neurohormonal pathways, particularly the RAS. Hence, the combination of diuretics with an ACEI or an ARB is synergistic and very effective [12].

Thiazide diuretics are less potent than loop diuretics when used alone in patients with moderate-to-severe CKD, because only 3% to 5% of filtered sodium is reabsorbed at the thiazide site of action and because the decrease in filtered sodium load in CKD causes a reduction in sodium reabsorption [12]. Most clinicians choose to switch to a loop diuretic in patients with CKD stage 4, particularly if hypertension is becoming resistant to therapy or if edema is an issue [24]. However, thiazides may still be useful for the treatment of high BP in CKD, as they have been shown to possess multiple nephron target sites and also to lower peripheral vascular resistance, by direct or indirect mechanisms [12]. By sequential tubular blockade, thiazide diuretics may augment the natriuretic effect of loop diuretics and improve BP control. However, when thiazides and loop diuretics are used together, the incidence of adverse effects is higher and requires close monitoring [12]. Knauf and Mutschler [37] showed that HCTZ alone or in combination with furosemide increased diuresis in patients with CKD even at a GFR <30 ml/min/1.73 m^2. Dussol *et al.* [38] conducted an RCT involving 23 patients with hypertension and stages 4 or 5 CKD, who received long-acting furosemide (60 mg) and HCTZ (25 mg) for 3 months, and then both diuretics for the next 3 months. The authors found no differences between furosemide and HCTZ with respect to natriuresis and BP control. Another trial [39] enrolled 60 CKD patients with a mean eGFR of 39 ml/min/1.73 m^2 and a systolic BP of 151 mmHg, under 1.8 antihypertensive drugs on average. After a run-in phase, all patients were treated with chlorthalidone, and at the end of the 8-week intervention, systolic BP was significantly reduced by 20 mmHg. Notably, the nine patients with eGFR <30 ml/min/1.73 m^2 had a similar reduction in BP.

Calcium Channel Blockers

The major subclasses of CCBs are the dihydropyridines (e.g., amlodipine, nifedipine, lercanidipine) and the non-dihydropyridines, including benzothiazepines (diltiazem) and phenylalkylamines (verapamil). Dihydropyridines tend to be more selective for the vascular smooth muscle (vasodilation) than for the myocardium. Accordingly, the side effects may include fluid retention and ankle edema, which can be problematic in patients with CKD. Dizziness, headache, and facial flush are also common. Non-dihydropyridines have direct effects on the myocardium, including the sinoatrial and atrioventricular nodes, causing reductions in heart rate and contractility [24].

Calcium channel blockers (CCBs) are widely used in the treatment of hypertension,

angina, and supraventricular tachycardia. Non-dihydropyridine CCBs have been shown to reduce proteinuria. In contrast, dihydropyridines completely abolish renal autoregulation, which is already impaired in CKD, and may thus aggravate proteinuria when used as monotherapy. Therefore, the use of dihydropyridines is not advisable without concomitant use of an ACEI or ARB [24, 35].

Most CCBs do not accumulate in patients with impaired kidney function, with the exception of nicardipine and nimodipine. Accumulation of these agents may also be due to reduced blood flow to the liver in the elderly. Caution is thus advised when using these two agents in elderly patients with CKD [24].

The combination of an RAS inhibitor with a dihydropyridine CCB attenuates the reflex vasoconstriction and tachycardia resulting from increased sympathetic nervous system activity in response to CCB-induced systemic vasodilation [25]. Fluid retention, seen particularly with dihydropyridines, can be problematic in patients with CKD, such that avoiding other vasodilators may be sensible. The combination of non-dihydropyridines such as verapamil and diltiazem with BBs can lead to severe bradycardia, particularly in patients with advanced CKD and if drugs like atenolol and bisoprolol (which accumulate in CKD) are used. CCBs, particularly non-dihydropyridines, also interfere with the metabolism and excretion of calcineurin inhibitors (CNIs), as well as with the mammalian target of rapamycin (mTOR) inhibitors. In patients taking such combinations, careful monitoring of CNIs and mTOR inhibitor blood levels is required if drugs or dosages are changed [24].

Dual Blockade of the RAS

Although dual blockade of the RAS with ACEI + ARB or ACEI/ARB + direct renin inhibitor (DRI) combinations may seem like a rational strategy for improving renal and cardiovascular outcomes, there is no conclusive evidence of the long-term renal and cardiovascular benefit of such combinations in hypertensive CKD patients [25].

In Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) [40], investigators randomized patients ≥55 years of age with cardiovascular disease or diabetes with end-organ damage to ramipril, telmisartan, or the combination of both drugs. The primary outcome of interest was the combined endpoint of dialysis, doubling of serum creatinine, or death. There was no significant difference in this outcome between ramipril and telmisartan alone, whereas combination therapy actually increased the risk. In addition, the ONTARGET trial found no benefit of combination therapy over ramipril monotherapy in reducing the cardiovascular risk. The Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial [41] enrolled 1448 patients with diabetic nephropathy, with or without hypertension. Subjects were randomized to losartan + lisinopril versus losartan + placebo for prevention of a primary composite endpoint of renal events or death. The trial was halted early because of lack of efficacy, as well as because of increased risk of hyperkalemia and acute kidney injury in the dual therapy group. Notably, BP was not different between groups.

Diuretics are the cornerstones of hypertension treatment in CKD and, by definition, a component of any antihypertensive drug combination for RH.

The Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial [42] studied the DRI aliskiren in combination with the ARB losartan versus losartan alone in 599 patients with type 2 diabetes and diabetic nephropathy. Combination therapy reduced the urinary albumin/creatinine ratio by 20%, as compared with losartan alone. There were only small differences in BP between the two groups and no differences between the rates of adverse events. In contrast, the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE) [43], involving the same combination of aliskiren + losartan in patients with diabetes and CKD, has been terminated early due to an increased risk of adverse events and no evidence of benefit in the dual therapy group. Consequently, the US Food and Drug Administration (FDA) [44] and the ERBP guideline [35] have counseled against the use of this combination.

Mineralocorticoid Receptor Antagonists

Aldosterone may mediate CKD progression, independently of its BP-increasing effect. Animal studies suggest that MR antagonists reduce proteinuria in diabetic nephropathy. MR antagonists may also ameliorate early renal injury and prevent renal fibrosis, presumably via the inhibition of macrophage infiltration, reduction in local oxidative stress, and the decreased expression of fibronectin, plasminogen activator inhibitor-1, and transforming growth factor-β1 [12].

In CKD, MR antagonists have been tried for anti-proteinuric and renoprotective purposes, as well as for the treatment of RH. In the largest relevant RCT [45] involving CKD patients with proteinuria and type 2 diabetes, the addition of eplerenone to enalapril resulted in a significant decrease in albuminuria, as compared to placebo, without an increase in the risk of hyperkalemia. The PATHWAY-2 study [15] unfortunately excluded patients with eGFR <45 ml/min. Based on current data, the long-term effects of MR antagonists on renal and cardiovascular outcomes, mortality, and safety in patients with CKD are unknown [24].

Because of the risk of hyperkalemia and acute kidney injury, MR antagonists should be used with caution in CKD patients. Plasma potassium levels and kidney function should be monitored closely during the introduction of these agents and during intercurrent illnesses, such as dehydration. Great care should be taken when MR antagonists are combined with ACEIs, ARBs, or NSAIDs. Caution is also advised when used together with other cytochrome P450-metabolized agents, such as verapamil [24]. Predictors of hyperkalemia include baseline renal function, serum potassium levels, the dose of MR antagonists, and the use of other RAS blockers or drugs that interfere with renal potassium handling [12]. MR antagonists are usually combined with thiazide or loop diuretics, which enhance potassium loss in the urine.

The ESH/ESC guidelines [6] suggest the addition of a MR antagonist as fourth-line therapy for RH (12.5–25 mg/day spironolactone or 25–50 mg/day eplerenone, to be adapted according to eGFR level) in patients with GFR ≥30 ml/min and plasma potassium concentrations ≤4–5 mmol/L or in patients with other indications, such as heart failure. However, the ESH guidelines do not recommend the routine use of MR antagonists in patients with CKD, especially in combination with RAS blockers, because of the risk of further renal impairment and hyperkalemia. The KDIGO [24] and ERBP

[35] guidelines only state that the place of MR antagonists as an add-on therapy in hypertensive patients with CKD needs to be explored in further studies.

Beta-Blockers

Beta-blockers (BBs) are one of the most extensively investigated drug classes, having been used to treat hypertension, as well as coronary artery disease, heart failure, and cardiac arrhythmias, for over 40 years. Although all BBs are effective for reducing BP, other issues may influence their indication in a given patient and which specific drug is chosen, since BBs vary widely in their pharmacological profile [24]. A recent systematic review and meta-analysis [46] endorsed the use of BBs in CKD patients with heart failure, but did not provide any definitive specific advice on their efficacy in preventing mortality, cardiovascular outcomes, or renal disease progression in CKD patients without heart failure [24].

Notable adverse effects associated with BBs include bradycardia, erectile dysfunction, fatigue, and lipid and glucose abnormalities [47]. In patients with CKD, the accumulation of BBs or active metabolites could exacerbate side effects like bradycardia. Such accumulation occurs with atenolol and bisoprolol, but not with carvedilol, propranolol, or metoprolol [24].

Beta-blockers (BBs) have often been combined with diuretics in RCTs and clinical practice. They can also be combined with ACEIs or ARBs. On the other hand, the combination of atenolol or bisoprolol with bradycardia-inducing drugs such as nondihydropyridine CCBs is not recommended. The association of lipophilic BBs (e.g., propranolol and metoprolol), which cross the blood-brain barrier, with other centrally acting drugs such as clonidine may lead to drowsiness or confusion, particularly in the elderly [24].

Centrally Acting Alpha-Adrenergic Agonists

Centrally acting alpha-agonists cause vasodilatation by reducing sympathetic outflow from the brain. The main agents in use are methyldopa, clonidine, and moxonidine. The use of centrally acting alpha-antagonists is limited by side effects, but since they interact minimally with other antihypertensives, they are valuable as adjunct therapy for RH in CKD patients [24].

Doses of methyldopa or clonidine are not generally reduced in patients with impaired kidney function. Moxonidine is largely excreted by the kidney, and accordingly it has been recommended that the dosage should be decreased in the presence of a low GFR [24].

Combination of alpha-agonists with thiazides may be particularly advantageous to reduce vasodilatation-induced fluid retention. Because of the side-effect profile, however, caution is advised when using alpha-agonists in the elderly, in patients with advanced CKD, and in those taking sedating drugs. Since clonidine can slow the heart rate, it should be avoided if bradycardia or heart block is present [24].

The KDOQI guidelines suggest RAS inhibitors to be the preferred antihypertensive agents in dialysis patients, particularly in those with diabetes or a history of heart failure.

Alpha-Blockers

Alpha-adrenergic blockers (e.g., prazosin, doxazosin, and terazosin) selectively act to reduce BP by causing peripheral vasodilatation. In general, they are not considered a preferred choice, because of common side effects like postural hypotension, tachycardia, and headache. These drugs should be started at a low dosage to avoid a first-dose hypotensive reaction. They are useful in CKD patients with RH, as well as in those with symptoms of prostatic hypertrophy. Vasodilatation can lead to peripheral edema, so they are commonly combined with diuretics. Alpha-blockers do not require dose modification in CKD, since they are excreted via the liver [24].

Direct Vasodilators

Hydralazine and minoxidil both act by directly causing vascular smooth-muscle relaxation and vasodilatation. Hydralazine is rarely used in CKD. Minoxidil is sometimes indicated in patients with RH; however, its side effects limit its use to the most resistant cases. Because of fluid retention and tachycardia, these drugs (especially minoxidil) are usually combined with a BB and a loop diuretic. Hydralazine and minoxidil do not require dose adjustment in patients with impaired kidney function [24].

Treatment of RH in Dialysis-Dependent (CKD-5D) Patients

In patients who are receiving renal replacement therapy, specific BP targets derived from RCTs are lacking. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggest that pre-hemodialysis (HD) and post-HD BP should be 140/90 mmHg and 130/80 mmHg, respectively, but these targets are mainly based on the expert judgment of the working group, applying weak evidence [48, 49].

ACEIs and ARBs

The KDOQI guidelines suggest RAS inhibitors to be the preferred antihypertensive agents in dialysis patients, particularly in those with diabetes or a history of heart failure [49].

Several studies demonstrated a 5–12 mmHg reduction in systolic BP with ACEIs [50, 51]. Retrospective analyses and small clinical trials also suggest that ACEIs may help preserve residual renal function [52], decrease arterial stiffness [50] and left ventricular hypertrophy [53], reduce mortality after acute coronary syndromes [54], and improve overall survival [55, 56] in HD patients. In the Fosinopril in Dialysis (FOSIDIAL) trial [51], 397 HD patients with left ventricular (LV) hypertrophy were randomized to fosinopril or placebo and followed for 2 years. The primary outcome was a combined endpoint of cardiovascular death, nonfatal myocardial infarction, unstable angina, stroke, cardiovascular revascularization, hospitalization for heart failure, and resuscitated cardiac arrest. At the end of the study, there was a nonsignificant reduction in the primary endpoint with fosinopril.

Some studies found ACEIs to be relatively safe in dialysis patients, with no significant effect on serum potassium, while others suggested that ACEIs may increase the risk of hyperkalemia in these patients, potentially by inhibiting extrarenal potassium loss. Therefore, monitoring of serum potassium after initiation of RAS inhibitors is recommended [47]. ACEIs have also been associated with higher dose requirements for erythropoietin-stimulating agents in HD [47].

Most ACEIs (with the exception of fosinopril) are removed by HD. This is not problematic in most hypertensive patients and may help avoid intradialytic hypotension. However, in those who experience intradialytic hypertension, dialyzable ACEIs should be switched to either fosinopril or an ARB [47].

The effects of ARBs on BP were variable in different studies. Some trials have shown an association of ARBs with a reduction of cardiovascular events and mortality in dialysis patients [57, 58], while others did not confirm this benefit [59].

Angiotensin receptor blockers (ARBs) can be administered once daily, they are not removed by HD, and they are well tolerated in dialysis patients [47]. In two trials, the use of an ARB was not associated with hyperkalemia or with higher erythropoietin requirements [57, 58].

Diuretics

In 16,420 HD patients from the Dialysis Outcomes and Practice Patterns Study (DOPPS) diuretic use was associated with lower interdialytic weight gain, lower risk of hyperkalemia (>6.0 mmol/L), and higher odds of retaining residual renal function after 1 year, as compared to patients not on diuretic therapy. Patients on diuretics also had a 7% lower all-cause mortality risk ($P = 0.12$) and 14% lower cardiac mortality risk ($P = 0.03$) than patients without diuretics [60].

Calcium Channel Blockers

Calcium channel blockers (CCBs) can effectively lower BP in dialysis patients. They are not removed by HD and, thus, do not require additional post-dialysis dosing [47]. A recent RCT found that amlodipine lowered systolic BP by 10 mmHg more than placebo, without an increased risk of intradialytic hypotension [61]. In an RCT comparing amlodipine to placebo in 251 hypertensive HD patients, Tepel *et al*. [62] found no difference in all-cause mortality at 30 months; however, amlodipine significantly reduced the secondary combined endpoint of all-cause mortality and cardiovascular events.

Dual Blockade of the RAS

A small study [63] randomized 33 incident diabetic HD patients to an ACEI versus ARB versus combination of ACEI + ARB and achieved good BP control and regression of LV mass index (LVMI) at 1 year in all groups. However, the patients treated with the ACEI + ARB combination exhibited an additional 28% reduction in LVMI when compared with those treated with monotherapy. Larger studies are required to determine whether this therapeutic combination can improve cardiovascular outcomes in HD patients.

A multicenter RCT [64] investigated the antihypertensive effect of the DRI aliskiren in comparison with the CCB amlodipine in 83 HD patients with difficult-to-treat or resistant hypertension. The baseline medications were dual therapy in 60% and therapy with ≥3 drugs in 40% of cases. Most patients (77%) were on ARBs or ACEIs. A significant decrease in BP was found only in the amlodipine group, but not in the aliskiren group.

The effects of ARBs on BP were variable in different studies. Some trials have shown an association of ARBs with a reduction of cardiovascular events and mortality in dialysis patients, while others did not confirm this benefit.

Mineralocorticoid Receptor Antagonists

The use of these agents in HD patients has not been thoroughly investigated, but it may be limited because of fear of the risk of hyperkalemia, particularly in anuric patients [47]. In two small open-label studies of low-dose (25 mg) spironolactone [65, 66], there was no significant increase in serum potassium with thrice weekly administration, but 7% of patients with daily dosage of the drug were withdrawn because of severe hyperkalemia. In a larger study of spironolactone 25 mg/day in 61 oligoanuric HD patients, potassium levels increased overall (from 4.6 to 5.0 mEq/l) with treatment; however, no patients had a potassium >6.8 mEq/l or required ion exchange resin therapy [67]. While these studies suggest that MR antagonists may be relatively safe, further research is required prior to their use in dialysis patients.

Beta-Blockers

Beta-blockers (BBs) are important antihypertensive agents for HD patients and are particularly indicated in those with coronary artery disease and heart failure [47]. In a secondary analysis of 11,142 prevalent HD patients from the United States Renal Database Systems (USRDS) Wave 3 and 4 Study, Foley *et al.* [68] found that the use of BBs was associated with a 16% lower adjusted risk of death. Two small RCTs by Cice *et al.* [69, 70] showed that carvedilol therapy, as compared to placebo, improved cardiac structure and function, as well as survival, in HD patients with heart failure.

Atenolol and metoprolol are dialyzable and require supplementation after dialysis, while combined α- and β-blockers (e.g., carvedilol) are not significantly cleared by HD. Metoprolol is mainly metabolized by the liver and therefore does not require dose adjustment, while atenolol is excreted mainly by the kidneys, and, thus, its half-life is prolonged in HD patients. Carvedilol is a nonselective inhibitor of β-adrenergic receptors and, theoretically, may increase the risk of hyperkalemia [47].

Other Agents

Alpha-blockers are seldom used in dialysis patients. However, in those requiring multiple antihypertensive agents, they can be safely prescribed and do not require additional dosing after HD. Nocturnal administration is preferred, in order to prevent postural hypotension. These agents should be avoided in patients with intradialytic hypotension [47].

Centrally acting alpha-adrenergic agonists are also rarely used, because of their high rate of adverse side effects. However, they may still be useful in dialysis patients, particularly those with RH [47].

Hydralazine and minoxidil are potent vasodilators and can be effective in dialysis patients with RH. These drugs are not removed by HD. Because of reflex stimulation of the sympathetic nervous system, they should be administered together with a BB. Fluid retention, including pleural and pericardial effusions, may occur during therapy and may require drug discontinuation [47].

New Antihypertensive Agents for CKD Patients

Phosphodiesterase Type 5 (PDE5) Inhibitors

In CKD, relative deficiency of circulating nitric oxide (NO) may contribute to

hypertension and atherosclerosis, whereas NO deficiency within the kidneys may promote a sharper decline in renal function. Abundant PDE5 expression has been identified in the kidney, and, therefore, it has been proposed that, through its inhibition, the function of the renal NO-cGMP pathway in the kidney can be enhanced, improving the NO deficit associated with CKD. The benefits of PDE5 inhibitors may extend from BP-lowering effects to renoprotective properties [71]. Experimental studies have demonstrated favorable effects of PDE5 inhibition on mesangial cell proliferation, extracellular matrix expansion, tubulointerstitial injury, renal cell apoptosis, oxidative stress, inflammation, and proteinuria in CKD models [71].

To date, only one clinical trial of PDE5 inhibition in CKD has been published [72]. In this study, 40 men with type 2 diabetes mellitus were treated for 1 month with either 50 mg sildenafil daily or placebo. The sildenafil-treated group had a 50% reduction in albuminuria and the drug was well tolerated. A randomized, placebo-controlled trial is currently investigating the impact of a long-acting PDE5 inhibitor on patients with diabetes mellitus and overt nephropathy [71].

Endothelin Antagonists

Endothelin-1 (ET-1) upregulation plays a pathogenic role in endothelial dysfunction and atherosclerosis and may also contribute to cardiovascular complications of CKD [71]. Selective endothelin type A (ETA) receptor antagonist darusentan, but not ETA/ETB receptor antagonist bosentan, prevented the aggravation of hypertension in renal failure rats treated with erythropoietin-stimulating agents [73]. Administration of a selective ETA receptor antagonist to hypertensive patients with CKD produced a substantial reduction in BP (10 mmHg) and increased renal blood flow [74]. In addition, chronic treatment with the mixed ETA/ETB receptor antagonist, avosentan [75], and the selective ETA receptor antagonist, atrasentan [76], in addition to standard ACEI/ARB treatment, substantially decreased albumin excretion in patients with diabetic nephropathy.

While ET receptor antagonists are generally well tolerated in clinical trials, the major adverse effects are peripheral edema, a mild decrease in hemoglobin (thought to be related to hemodilution secondary to increased extracellular fluid), headache, and flushing. As these drugs are primarily metabolized and eliminated by the liver, one significant adverse effect is hepatic dysfunction, which is dose dependent and reversible upon discontinuation of the drug [47].

Conclusions and Recommendations

In patients requiring a triple therapy, this should consist of an ACEI or ARB + CCB + diuretic (ACD regimen) for most patients. This regimen is thought to be effective and well tolerated in CKD. It should be tried in optimum doses as the first therapeutic step in patients with CKD and RH, in the absence of contraindications.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are especially preferred in patients with CKD and heart failure, post-myocardial infarction, and proteinuria. Adverse effects include hypotension, acute kidney injury, and hyperkalemia. Monitoring of serum creatinine and potassium is indicated after starting treatment. If strategies to minimize hyperkalemia fail to maintain serum potassium concentrations <5.6 mEq/l, the RAS inhibitor should be discontinued, and another class of antihypertensive drugs should be used instead. In patients with advanced CKD (stages 4 and 5), consideration should be given to stopping ACEIs/ARBs when there are no other compelling indications for these agents and especially when there is high risk of hyperkalemia and/or acute kidney injury, which may precipitate dialysis initiation. Dual therapy ACEI + ARB or ACEI/ARB + DRI is not indicated, because of increased risk of adverse events and lack of proven benefits.

Diuretics are the cornerstones of hypertension treatment in CKD and, by definition, a component of any antihypertensive drug combination for RH. The combination of diuretics with RAS inhibitors, CCBs, and BBs is synergistic and very effective. In patients with CKD stage 4 (GFR <30 ml/min/1.73 m^2) or with significant edema, thiazide diuretics should be replaced or combined with loop diuretics.

Calcium channel blockers (CCBs) are particularly useful in hypertensive patients who also have angina and/or supraventricular tachycardia. Most CCBs do not accumulate in patients with impaired renal function. Dihydropyridines may induce fluid retention, which can be counteracted with diuretics. Non-dihydropyridines should not be associated with BBs, because of risks of bradycardia and depression of myocardial inotropism.

Mineralocorticoid receptor (MR) antagonists may be used as fourth-line therapy for RH in patients with GFR ≥30 ml/min and plasma potassium concentrations ≤4–5 mmol/L or in patients with other indications, such as heart failure. However, they should be used with caution in CKD patients, particularly in combination with ACEIs or ARBs, because of increased risk of hyperkalemia and acute kidney injury. Although, these drugs were shown to be very effective in patients with essential RH, the long-term effects of MR antagonists on renal and cardiovascular outcomes, mortality, and safety in patients with CKD are still to be determined.

Beta-blockers (BBs) have been widely used for decades to treat hypertension, as well as coronary artery disease, heart failure, and cardiac arrhythmias. Adverse effects associated with BBs include bradycardia, erectile dysfunction, fatigue, and lipid and glucose abnormalities. Agents like metoprolol and carvedilol should be preferred over atenolol, which may accumulate in patients with CKD.

Other fourth- or fifth-line antihypertensive agents include centrally acting alpha-agonists, alpha-blockers, and direct vasodilators. They are potent BP-lowering drugs and do not require dose adjustments in CKD (except for moxonidine). However, their use is limited by numerous side effects; among these, fluid retention usually requires the association with diuretics.

References available on request
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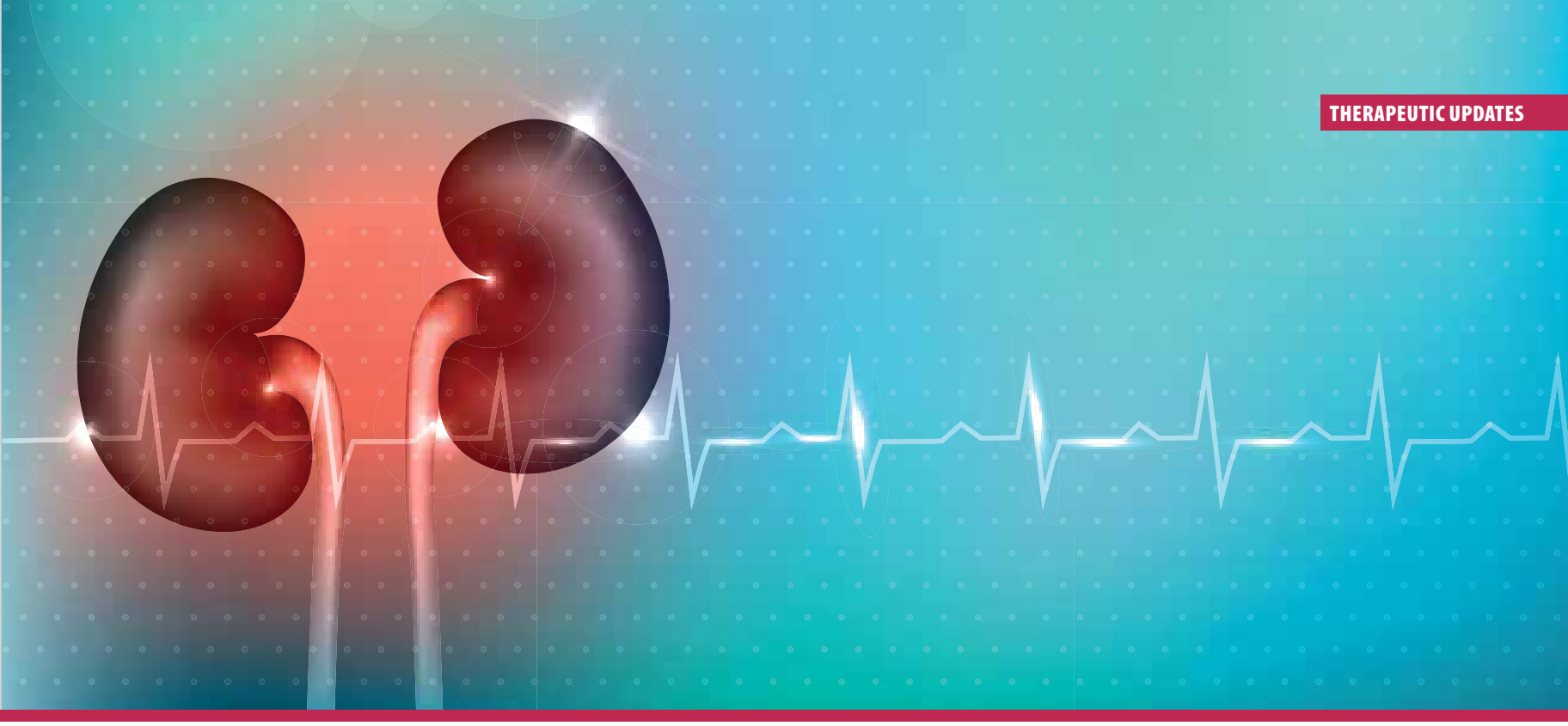

Treatment of Hypertension in Chronic Kidney Disease

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Although kidney disease is characterized by progressive scarring that ultimately affects all structures of the kidney regardless of the underlying cause, however, the presence of hypertension may accelerate further kidney injury; therefore, hypertension treatment is important for the prevention of further kidney damage in an apparent vicious circle that leads to a functional decline.

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Introduction

Hypertension and chronic kidney disease (CKD) are two leading risk factors for cardiovascular (CV) disease. In the United States (U.S.), hypertension affects 80 million people [1] while the overall prevalence of CKD in the adult population was 14.8% in 2011–2014 [2]. Furthermore, in people older than 65 years, the annual incidence of CKD is more than 1200 individuals per million [3]. Thus, CKD was recognized as a worldwide epidemic. Since individuals with kidney failure treated by hemodialysis or peritoneal dialysis and transplantation continue to increase, it seems that by the year 2030, CKD patients with end-stage renal disease (ESRD) requiring dialysis should be more than 2.2 million [4].

Hypertension coexists in approximately 80–85% with CKD. In hypertensive patients about 15.8% have CKD [5]. On the other hand, in the Chronic Renal Insufficiency Cohort (CRIC) study, hypertension has been reported in 67 to 92% of patients [6]. Additionally, hypertension prevalence is progressively increasing as kidney function declines [7].

The coexistence of hypertension and CKD results in increased difficulties to control BP levels. In the U.S., about 52% of Americans adults had their BP levels controlled in 2011–2014 [1]. In CKD patients, hypertension control is suboptimal and control rates are very low (13.2%) [8]. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study resistant, hypertension was noticed in 28.1% of adults with concomitant hypertension and CKD [9]. These proportions increased with advancing stage of kidney disease and elevated systolic BP mainly accounted for the inadequate control [8]. However, the proportion of CKD individuals who were

aware, treated, and disease-controlled rose steadily from approximately 8% in the early cohorts 1999–2002, to 28% in 2011–2014 [2].

Although kidney disease is characterized by progressive scarring that ultimately affects all structures of the kidney regardless of the underlying cause, however, the presence of hypertension may accelerate further kidney injury; therefore, hypertension treatment is important for the prevention of further kidney damage in an apparent vicious circle that leads to a functional decline [7, 10]. In CKD patients, the level of BP may predict the development of ESRD. In the Kidney Early Evaluation Program (KEEP), database included 88,559 participants, baseline systolic BP independently was associated with the presence of kidney disease [11]. In the Multiple Risk Factor Intervention Trial (MRFIT), in more than 330,000 middle-aged men who participated in the over a 16-year period study, a strong, graded relation between both systolic and diastolic BP and ESRD was identified [12].Therefore, BP control in CKD patients has become one of the greatest challenges to improve kidney functional decline and consequently patients survival.

Blood Pressure Target in CKD Patients

The newly updated hypertension guidelines developed by the American Heart Association (AHA) and the American College of Cardiology [13] support an intensive BP control in patients with established CKD and the threshold for high BP has lowered to 130/80 mmHg. The guidelines suggest that antihypertensive treatment should be based on overall Atherosclerotic Cardiovascular Disease (ASCVD) risk assessment combined with BP levels [13]. The consensus report further supports a systolic BP goal between 125 and 130 mmHg for those who can tolerate this level [7, 13]. This strategy may prevent more CVD events compared with the treatment based on BP levels alone. The intensive BP goals are not in agreement with the former guidelines in the past, which recommended a BP goal < 140/80 mmHg for patients with CKD and/or diabetes, including those from the Eighth Report of the Joint National Committee (JNC-8) and the European Society of Hypertension–European Society of Cardiology committee, as well as the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Working Group on CKD [7, 14, 15]. The ADA recommendations suggest that in diabetic individuals at high risk of CV disease, a lower systolic and diastolic BP target (< 130/80 mmHg) may be appropriate, if it can be achieved without burden undue treatment [16••]. Intensification of antihypertensive therapy to target BP lower than < 130/80 mmHg may be beneficial for selected patients with diabetes such as those with a high risk of CV disease (Table 1) [16••].

This is best exemplified In The Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial were intensive BP control among people with type 2 diabetes to a target systolic BP < 120 mmHg did reduce the risk of stroke, at the expense of increased adverse events and may be reasonable in selected patients who have been educated about added treatment burden [17].

The newly updated hypertension guidelines developed by the American Heart Association (AHA) and the American College of Cardiology support an intensive BP control in patients with established CKD and the threshold for high BP has lowered to 130/80 mmHg.

These data are also supported by The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation–Blood Pressure (ADVANCE BP) trial, where the active BP intervention arm, a fixed-dose combination of perindopril and indapamide, was compared with the placebo group [18]. Lower systolic BP levels during follow-up, even to < 110 mmHg, was associated with progressively lower rates of renal events without any BP threshold below which renal benefit was lost [19].

In non-diabetic patients, the available evidence was inconclusive for the CKD group as a whole because the existed appropriately randomized trials, including The Modification of Diet in Renal Disease (MDRD) trial [20], the African American Study of Kidney Disease [21], and the renoprotection in patients with non-diabetic chronic renal disease (REIN 2) study, failed to show any benefit with BP reduction < 130/80 mmHg. The MDRD trial examined whether two levels of BP (mean arterial pressure (MAP) < 92 vs. 102–107 mmHg would result in a slower decline in CKD and reduce the risk for renal replacement therapy with mean baseline glomerular filtration rate (GFR) 39 mL/min, and proteinuria more than 500 mg per day. The AASK study included over a 1000 African-American patients with a GFR between 20 and 65 mL/min/1.73m^2 and albuminuria in two BP levels, i.e., 140/82 vs. 128/77 mmHg. The REIN-2 trial included patients with proteinuria greater than 1000 mg/d randomly assigned in either conventional (diastolic < 90 mmHg) or intensified (systolic/diastolic < 130/80 mmHg) BP control [22]. These studies did not prove that a BP target of less than 130/80 mmHg improves clinical outcomes more than a target of less than 140/90 mmHg in adults with CKD [23]. Those with higher levels of proteinuria > 1000 mg might benefit from the intensive BP lowering [23]. The recent guidelines [13] were influenced by the Systolic Blood Pressure Intervention Trial (SPRINT) [24] published 3 years ago. The SPRINT trial was designed to test the benefits of a systolic BP target below 120 mmHg compared with < 140 mmHg in non-diabetic patients older than 55 years of age, including a substantial subgroup with CKD. The study showed that intensive treatment of systolic BP < 120 mmHg reduced the combined rate of having a heart attack, acute coronary syndrome, heart failure, or stroke by nearly one third, and reduced deaths from any cause by nearly a one-quarter compared to reducing BP to less than 140 mmHg [24]. The results of the SPRINT provide evidence that the goal of systolic BP should be closer to 120 than 140 mmHg. The cardiovascular benefits were also seen in the 30% of SPRINT patients with CKD [24]. Indeed, in prespecified subgroup analyses of outcomes in participants with CKD, intensive BP control < 120 mmHg compared with < 140 mmHg resulted in a substantial decrease in major CV events and all-cause death. Interestingly, in CKD patients, the intensive BP control did not correlate with a slower decline in kidney function. The overall rate of serious adverse events did not differ between treatment groups, although some specific adverse events occurred more often in the intensive group [25••]. In a recent systematic review and meta-analysis including more than 8000 patients with CKD without diabetes during a follow-up of 3.3 years, intensive BP

Table 1: Major recommendations of treatment guidelines related to management of hypertension in patients with CKD and albuminuria.

	2017 ACC/AHA [13]	2013 ESH/ESC [14]	2018 ADA [16••]	2012 NKF KDOQI [3, 7]
Type of CKD considered	Albuminuria ≥ 300 mg/d or ≥ 300 mg/g creatinine	Overt proteinuria	Urinary albumin-to-creatinine ratio ≥ 300 mg/g creatinine or 30–299 mg/g creatinine	Urine albumin excretion of 30 to 300 mg or > 300 mg per 24 h
Recommended BP target (mm Hg)	Lowering < 130/80	Lowering SBP to < 140 Lowering < 130/80 mmHg in individuals with overt proteinuria	Lowering < 140/90 Lowering < 130/80 mmHg, for individuals at high risk of cardiovascular disease	Lowering ≤ 130/80
Recommended initial antihypertensive treatment	ACE inhibitor or ARB if ACE inhibitor is not tolerated	ACE inhibitor or ARB	ACE inhibitor or ARB If one class is not tolerated, the other should be substituted	ACE inhibitor or ARB
Other comments	A 10 to 25% increase in serum creatinine may occur in some patients with CKD as a result of RAAS therapy	RAS blockade is more effective in reducing albuminuria than other antihypertensive agents and is also effective in preventing incident microalbuminuria	Patients and clinicians should engage in a shared decision-making process to determine individual BP targets Bedtime dosing: moving at least one antihypertensive medication to bedtime	The antihypertensive and antialbuminuric effects ACE inhibitor or ARB are complemented by dietary sodium restriction or administration of diuretics

ACC/AHA American College of Cardiology/American Heart Association; ACE inhibitors, angiotensin-converting enzyme inhibitors; *ADA*, American Diabetes Association; *ARBs*, angiotensin II receptor blockers; *CKD*, chronic kidney disease; *ESH/ESC*, European Society of Hypertension/European Society of Cardiology; *RAS*, renin angiotensin system; *NKF*, National Kidney Foundation

control (< 130/80 mmHg) was compared with standard BP control (< 140/90 mmHg) on major renal outcomes. It was shown that targeting BP below the current standard did not provide additional benefit for renal outcomes compared with standard treatment. Even in this analysis, non-Black patients or those with higher levels of proteinuria might benefit from the intensive BP lowering and the risk of adverse events was mostly similar among different BP targets emphasizing the need for individualization of BP targets [26••].

BP Measurement in CKD Patients

Chronic kidney disease (CKD) has been shown to be linked to alterations in circadian BP profile, such as greater nocturnal hypertension, non-dipping (blunting of nocturnal BP fall) profile, or increased BP variability. Therefore, an increasing emphasis should be given on the preferred method for recording BP and the usefulness of the Home Blood Pressure Self-monitoring (HBPM) and 24-h Ambulatory Blood Pressure Monitoring (ABPM) [27]. In the office, the preferred method for recording BP is Automated Office Blood Pressure Measurement (AOBPM) which has been shown that closely predict cardiovascular events [28•]. Furthermore, ACCORD BP and SPRINT studies measured BP using AOBPM which yields values that are generally lower than typical office BP readings by approximately 5–10 mmHg [29]. HBPM and 24-h ABPM may provide evidence of white-coat hypertension, masked hypertension, BP variability, or other discrepancies between office and "true" blood pressure [28•] usually noticed in CKD patients. The importance of excluding white-coat hypertension before initiating pharmacological therapy in CKD patients may be achieved by HBPM or ABPM as appropriate. Masked hypertension may occur in up to 30% of patients with CKD and is considered to be associated with further kidney injury [27]. In CKD patients, BP variability is associated with poor outcome [30••]. HBPM also may improve patient medication adherence and thus help reduce cardiovascular risk [31].

The presence of albuminuria is associated with a faster progression to renal failure and with increased risk of CVD. The risk for adverse outcomes, including mortality and ESRD, increases with increasing albuminuria and decreasing GFR.

Lifestyle Modifications

Achievement of a BP target < 130/80 mmHg in CKD patients is difficult and requires lifestyle modifications and multiple antihypertensive medications. Individuals with nephropathy exhibit impaired salt excretion and sodium restriction may be appropriate, followed by smoking cessation and moderate alcohol consumption. Furthermore, weight loss if overweight or obese, regular exercise, and interventions for obstructive sleep apnea also should be part of a comprehensive strategy of effective treatment of hypertension in CKD [7]. Lifestyle modifications enhance the effectiveness of some antihypertensive medications and probably reduce the appearance of adverse effects.

The Spectrum of Abuminuria

If urinary albumin-to-creatinine ratio (ACR) is < 30 mg/g creatinine, 30–300 or > 300 mg/g, abuminuria is characterized as normal to mild increased, moderately increased formerly named microalbuminuria, and severely increased formerly named macroalbuminuria respectively. In the U.S. population, the prevalence of ACR 30–300 mg/g creatinine was 8.5% and of ACR > 300 mg/g was 1.4% in 2011–2014 [2]. Approximately 20% of individuals had urinary ACR below the threshold for albuminuria 10–29 mg/g creatinine [2].

The presence of albuminuria is associated with a faster progression to renal failure and with increased risk of CVD. The risk for adverse outcomes, including mortality and ESRD, increases with increasing albuminuria and decreasing GFR [32••, 33••]. Therefore, in CKD patients with albuminuria, the proper BP medications should be carefully titrated to reduce albuminuria. Indeed, it is now fairly well established that albuminuria reduction supports a better preservation of renal function and a lower CV mortality [34]. It is suggested that the risk of ESRD

in hypertensive patients with diabetic nephropathy is more likely related to the albuminuria reduction than to lowering BP [35]. Optimization of drug prescribing for hypertensive individuals with CKD and albumiuria remains a challenge and has become an important public-health issue worldwide. Incremental BP reduction may be appropriate with careful monitoring of kidney function.

The Renin Angiotensin-Aldosterone System Inhibitors

Chronic kidney disease (CKD) as an important risk factor for CVD [36] belongs to the certain co-morbidities that may affect clinical decision making in hypertension. The majority of adults with CKD are likely to have a 10-year risk of ASCVD that exceeds 10%. Furthermore, selection of medications for use in treating high BP in patients with CKD is guided by the existed compelling indications (e.g., albuminuria). Agents that block the renin angiotensin-aldosterone system (RAAS) should be the drugs of choice in CKD patients because the role of RAAS in the pathogenesis of cardiovascular and renal disease is well documented [18, 37–40]. Strategies targeting RAAS interruption have shown to improve CKD outcomes in patients with albuminuria whether diabetic or not [40, 41] and in preventing microalbuminuria [42, 43].

The new hypertension guidelines suggest that if albuminuria > 300 mg/g is present, the preferred drug should be an ACE inhibitor or in case of ACE inhibitor intolerance, an ARB [13] (Fig. 1). RAAS inhibitors consistently reduce proteinuria and slow the decline in kidney function [44, 45]. In CKD patients without albuminuria, there is no evidence that the use of an ACE inhibitor or an ARB is more effective compared with other antihypertensive first-line agents. RAAS blockers are often discontinued or are administered at suboptimal doses to large proportion of patients with proteinuric CKD because of the increases in serum creatinine or due to incident hyperkalemia (Table 2). It should be emphasized that to achieve BP goals as well as to lower albuminuria, moderate to high doses of these drugs are often required. Inarguably, the side-effect profile of these agents is not affected to a large extent by their dose [7]. Substantial evidence from outcome trials has demonstrated a great benefit with the use of RAAS blockers on

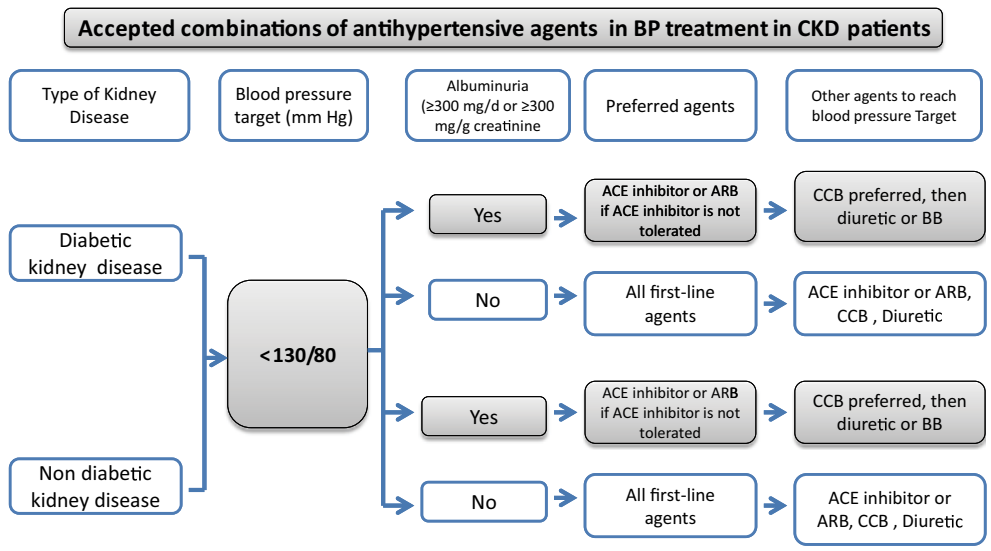

Fig. 1: Accepted combinations of antihypertensive agents for BP management in CKD patients. BP, blood pressure; CKD, chronic kidney disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BB, beta-blocker

slowing CKD progression in patients with an eGFR less than 50 mL/min/1.73 m^2 albeit these agents are generally avoided by most physicians in these patients [3, 45, 46••, 47]. On the basis of current evidence, the administration of RAAS blockers could prevent both CKD progression to ESRD and premature mortality [48•]. An increase in serum creatinine with concurrent reduction in GFR often occurs because these agents reduce intraglomerular pressure. It has been

CKD as an important risk factor for CVD belongs to the certain co-morbidities that may affect clinical decision making in hypertension. The majority of adults with CKD are likely to have a 10-year risk of ASCVD that exceeds 10%.

suggested that the rise in serum creatinine in these patients within a few weeks of starting a RAAS inhibitor is associated with better CKD outcomes especially in those with proteinuric nephropathy and leads to a better preservation of kidney function over a mean follow-up period of 3 or more years [49]. With an increase of serum creatinine up to 30%, other causes should be carefully considered, such as volume contraction, bilateral renal artery stenosis, unsuspected left ventricular dysfunction, the use of non-steroidal anti-inflammatory agents, and/or other drugs affecting renal hemodynamics [50]. When serum creatinine rises from baseline values more than 30% within the first 3 to 4 months of therapy or incident hyperkalemia occurs (serum potassium > 5.2 mEq/L), a dose adjustment or withdrawn of RAAS-blocking therapy should be considered [49].

The combination of an ACE inhibitor with an ARB should be avoided and it is not supported by all recent guidelines [13, 14] due to an increased concern regarding the adverse events such as renal dysfunction, hyperkalemia, and symptomatic hypotension in high-risk CKD patients. RAAS inhibitors are contraindicated for use in pregnancy due to their extremely teratogenic effect. In addition, these agents should not be used in patients with a history of angioedema [7] (Table 2).

Aldosterone Receptor Antagonists

In patients with proteinuric CKD, aldosterone receptor antagonists, such as spironolactone or eplerenone in low-doses, may be also indicated. Indeed, a combination of a RAAS blocker with an aldosterone receptor antagonist may be beneficial in patients with proteinuric nephropathy and results in a further reduction of urine protein excretion [51]. However, aldosterone receptor antagonists in low doses are preferred. In fact, a dose-dependent increase in serum potassium levels after aldosterone receptor antagonists administration is commonly observed. Thus, serum potassium levels should be closely monitored during their administration [51]. In such cases, a dose adjustment of aldosterone receptor antagonist or a concomitant use of a loop diuretic therapy should be used.

Table 2: Antihypertensive drugs and common side effects.

Antihypertensive drugs	Common side effects
Thiazides and thiazide-like diuretics (e.g., hydroclorothiazide, indapamide chlorthalidone)	Hypovolemia Hypokalemia Hypomagnesemia Hypercalcemia Hyperuricemia Dyslipidemia Carbohydrate intolerance Sexual dysfunction
Loop diuretics (e.g., furosemide, torsemide)	Hypovolemia Ototoxicity (high doses) Hypokalemia Hypomagnesemia
Potassium-sparing diuretics (e.g., spironolactone, eplerenone amiloride, triamterene)	Hyperkalemia Hypotension Gynecomastia Impotence (in case of spirolactone)
B-blockers (e.g., metoprolol, atenolol, carvedilol, nebivolol)	Bradycardia Hypotension Tiredness Sexual function Hyperkalemia Dyslipidemia Bronchospasm Reduced exercise tolerance Cold hands and feet Carbohydrate intolerance (with all except nebivolol and carvedilol)
ACE inhibitors	Cough Hyperkalemia Angioedema Acute renal failure (in case of renal artery stenosis)
ARBs	Hyperkalemia Acute renal failure (in case of renal artery stenosis
Calcium channel blockers Diltiazem/Verapamil	Hypotension Sinus bradycardia
Dihydropyridines (e.g., amlodipine, nifedipine)	Hypotension Sinus tachycardia
Alpha(1)-blockers (doxazosin, terazosin)	Orthostatic symptoms
Central alpha-2 agonists (moxonidine, clonidine, alpha methyldopa)	Nausea Allergic skin reactions Dry mouth
Direct vasodilators such as minoxidil, hydralazine	Hirsutism Hypotension Reflex tachycardia

ACE inhibitors angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers

Consideration should be given with the use of spironolactone because the drug is associated with a greater risk of gynecomastia and impotence as compared with eplerenone, while eplerenone often requires twice–daily administration for adequate BP control [13] (Table 2).

Potassium-sparing diuretics are minimally effective antihypertensive agents and should be avoided in CKD patients with GFR < 45 mL/min [13]. Furthermore, spironolactone or eplerenone as well as amiloride and triamterene should be avoided if serum potassium concentration is > 5.2 mmol/L. On the contrary, in patients with CKD and hypokalemia, supposing that dietary causes have been excluded, combination therapy of an ACE inhibitor or an ARB, with low dose of potassium-sparing diuretic, can be considered in terms of correction of hypokalemia as well as proteinuria reduction [51].

New pharmacologic therapy for hyperkalemia management represents two novel agents for potassium lowering in patients with nephropathy. These agents, patiromer and sodium zirconium cyclosilicate, are ion exchange with promising results in treating hyperkalemia in patients with CKD without exhibiting serious adverse effects [52•].

Diuretics

Volume overload is often the hallmark in patients with kidney function deterioration. Thus, diuretics are the linchpin in the management of CKD. Thiazides and especially thiazide-like diuretics, such as chlorthalidone and indapamide, are preferred on the basis of their prolonged half-life. Thiazide diuretics may stimulate the RAAS system and a combination with ACE inhibitors or ARBs may be appropriate leading to an additive effect. These agents become less effective when GFR falls below 30 mL/min/1.73 m^2 [13]. On the other hand, loop diuretics exhibit a higher intrinsic efficacy compared to thiazides in patients with severe renal insufficiency. Furthermore, these agents are preferred in CKD patients with concomitant symptomatic heart failure. Thiazides should not be used in patients with a history of acute gout [13].

Calcium Channel Blockers

Calcium channel blockers (CCBs) are very effective antihypertensive drugs in patients with nephropathy. Different effects on proteinuria within the class of CCBs have been observed beyond their BP-lowering effects because of different effects on glomerular permeability. Non-dihydropyridine CCBs, verapamil and diltiazem, consistently reduce proteinuria and also slow the decline in kidney function among proteinuric CKD patients [42, 45]. Dihydropyridine CCBs, only when used in combination with a RAAS blocker, can reduce proteinuria among patients with advanced proteinuric nephropathy [3, 44]. Interestingly, manidipine, compared to amlodipine despite similar BP reductions [53], reduce intraglomerular pressure and thereby reduce albuminuria to a greater extent as compared to amlodipine [54].

In patients with CKD stage 3 to 5D, CCBs has similar effects on long-term BP reduction, mortality, heart failure, stroke or cerebrovascular events, and renal function to RAAS blocker agents [55•]. Moreover, as mentioned, dihydropyridine CCBs should not be used as monotherapy in proteinuric CKD patients but always in combination with a RAAS blocker (Fig. 1). Amlodipine or felodipine may be used if required in treating angina pectoris and heart failure in CKD patients with preserved ejection fraction [13]. It should be mentioned that

non-dihydropyridine CCBs should not be used in CKD patients with heart failure with systolic dysfunction. These agents also increase the risk of bradycardia and heart block (Table 2), thus should not be used with beta-blockers [13]. According to the results of the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, a calcium antagonist, amlodipine, rather than a thiazide diuretic, should be considered as an add-on therapy to an ACE inhibitor, benazepril, because this combination is more effective in preventing the doubling of serum creatinine and ESRD, though less effective in preventing proteinuria [56]. These potential advantages should be kept in mind when selecting among possible agents to add to an antihypertensive treatment.

Agents Blocking the Sympathetic Nervous System

Beta-blockers

Beta-blockers are not first-line drugs in the treatment of hypertension particularly in patients over 60 years of age unless the patient has ischemic heart disease or heart failure. These agents have been shown to reduce cardiovascular mortality in high-risk patients, whereas their renoprotective effects have not been well established [57]. Beta-blockers with vasodilating properties such as nebivolol and carvedilol exhibit a better metabolic profile including lipid metabolism and insulin sensitivity compared to the traditional beta-blockers. Additionally, nebivolol induces nitric oxide-induced vasodilation [58]. Certain members of this class such as bisoprolol and metoprolol succinate are preferred in patients with heart failure with reduced ejection fraction [13]. Beta-blockers are not recommended in patients with bradycardia or with second- or third-degree heart block and should not be combined with a non-dihydropyridine CCB. In addition, it is important to point out that an abrupt cessation of these agents should be avoided [13].

Central Alpha-Adrenergic Agonists

Central alpha-adrenergic agonists reserve as last lines of therapy due to their adverse effects especially in older people. These agents exhibit a dose-dependent side effects profile and their tolerability is poor. The most obvious explanation of their use is to mitigate the increase in sympathetic activity observed in patients with nephropathy. The most commonly used is clonidine [59]. An abrupt discontinuation of clonidine may induce rebound hypertension thus clonidine must be carefully tapered to avoid hypertensive crisis [13]. Other members of this class include guanfacine and methyldopa, which are used primarily in pregnancy [60]. It is worth mentioning that moxonidine is an effective adjunctive therapy in combination with other antihypertensive agents. In fact, an improvement in the metabolic profile in hypertensive patients with diabetes mellitus or impaired glucose tolerance has been shown after moxonidine administration [61]. However, a central alpha-adrenergic agonist and a β-blocker in combination can induce bradycardia and should be avoided [62].

Alpha 1-Adrenergic Blockers

Certain members of this class (doxazosin, prazosin, terazosin) are reserved as fifth-line agents in CKD patients. Since hypertension and benign prostatic hyperplasia often coexist in approximately 30% of adult men, alpha blockers might be used as add on therapy in hypertensive patients with benign prostatic hyperplasia [63]. These agents failed to slow renal disease progression or improve proteinuria in diabetic patients. Furthermore, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [64], a twofold higher incidence of congestive heart failure was noticed in the doxazosin arm compared with individuals receiving chlorthalidone [64].

Direct Vasodilators

Direct vasodilators, minoxidil or hydralazine, are used when treatment with the other primary agents has failed. Hydralazine is sometimes prescribed for acute BP lowering in hospitalized patients [65]. Some of the adverse effects related to hydralazine reported in the literature, include reflex tachycardia, hemolytic anemia, vasculitis, glomerulonephritis, and a lupus-like syndrome [66]. Minoxidil as a reserve antihypertensive agent still has a niche indication in a particular subgroup of CKD patients [67•]. It is associated with hirsutism and can induce pericardial effusion. Because these agents are associated with sodium and water retention, a combination with a beta-adrenergic blocker and/or a diuretic should be recommended and patients should always be closely monitor their body weight [13]. Antihypertensive therapy with direct vasodilators has not been shown to improve kidney outcomes.

Conclusions

Hypertension prevalence is progressively increasing as kidney function declines. In patients with CKD, an intensive BP goal < 130/80 mmHg has been recommended. The use of the HBPM and 24-h-ABPM may provide evidence of white-coat hypertension, masked hypertension, and BP variability that closely predict CV events. In patients with CKD and albuminuria > 300 mg/g, ACE inhibitors should be the drugs of first choice while ARBs should be used if the ACE inhibitor is not well tolerated. A CCB should be considered as an add-on therapy to the RAAS blocker. Non-dihydropyridines and manidipine can reduce intraglomerular pressure and thereby reduce albuminuria. Chlorthalidone and indapamide are preferred on the basis of their prolonged half-life, while a loop diuretic should be considered when GFR falls below 30 mL/min/1.73 m^2. Beta-blockers should be used preferably in patients with ischemic heart disease or heart failure. Central alpha-adrenergic agonists, alpha-adrenergic blockers, and direct vasodilators reserve as antihypertensive drugs in a particular subgroup of CKD patients when the primary agents are contraindicated and BP is not adequately controlled.

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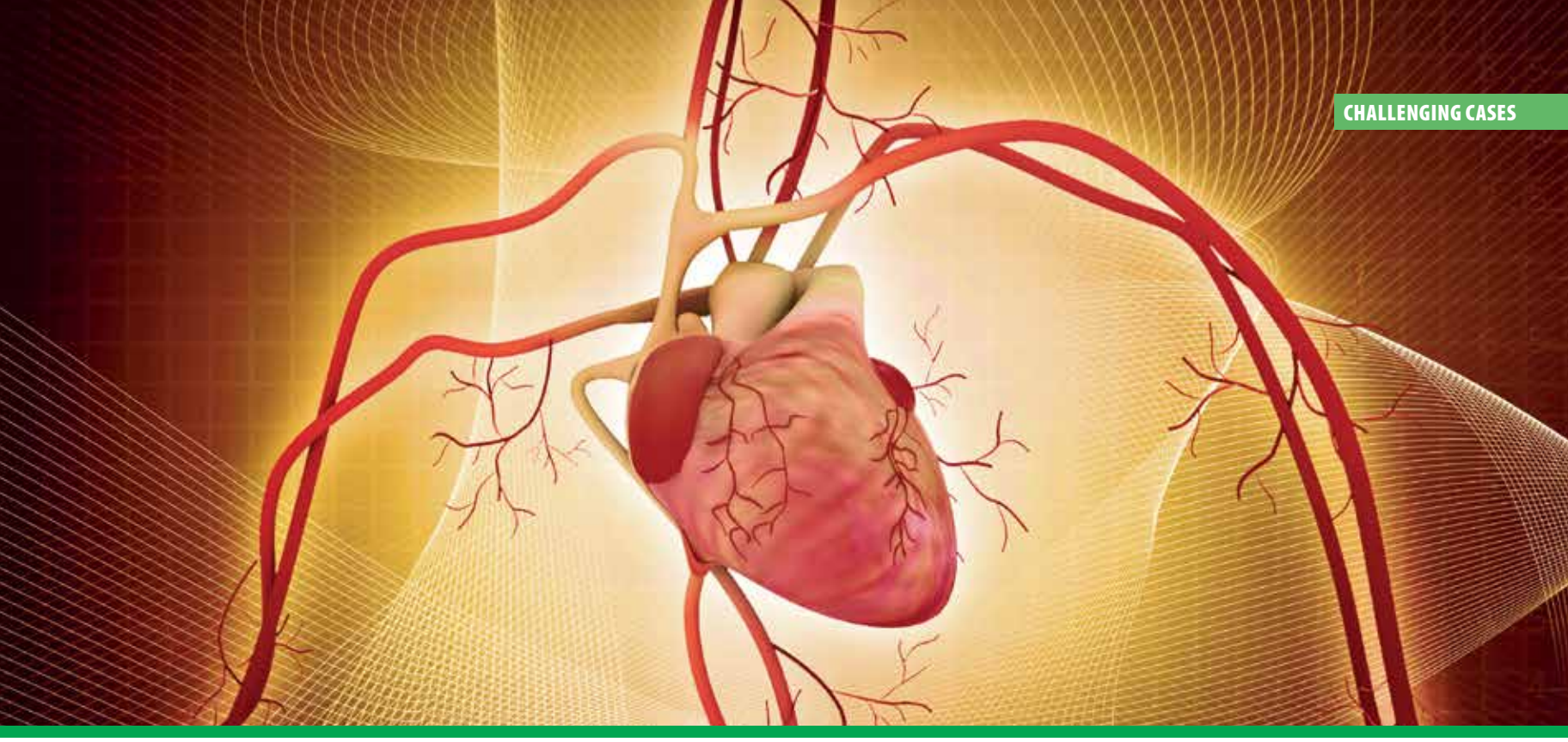

Heart Failure and Stroke

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Heart failure (HF) is a frequent condition associated with diverse comorbidities such as cardiac arrhythmias, thromboembolism, impaired renal function, and an increased mortality as a result. An increased stroke risk in HF patients has been described in several studies.

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Introduction

Heart failure (HF) is a frequent condition associated with diverse comorbidities such as cardiac arrhythmias, thromboembolism, impaired renal function, and an increased mortality as a result [1]. The prevalence of HF is approximately 1–2% of the adult population in developed countries with a higher percentage (> 10%) in the population age > 70 years [1].

An increased stroke risk in HF patients has been described in several studies [2]. Pathophysiologically, a predisposition to thromboembolism is caused by abnormal blood flow, abnormal vessel/chamber lining, and abnormal blood particles, also referred to as Virchow's triad [3]. Abnormal blood flow is evident in patients with HF because of left ventricular systolic dysfunction (LVSD) associated with left ventricular dilatation and abnormal (slowed) blood flow [4]. Given the fact that HF patients with preserved EF (HFpEF) also have an increased stroke risk [5, 6], such patients also exhibit flow abnormalities—apart from vessel wall changes (e.g., endothelial dysfunction) [7, 8] and abnormal blood constituents (e.g., platelet function) [9].

Atrial fibrillation (AF) is the strongest independent risk factor for stroke, followed closely by HF [10]. Of note, HF and AF frequently coexist and exacerbate each other: while AF occurs in more than half (57%) individuals with HF, HF is present in over one third (37%) of AF patients. These results had been shown in 1737 individuals with new AF and 1166 individuals with new HF from Framingham Heart Study [11]. Particularly, paroxysmal AF is mostly associated with stroke in comparison to persistent AF [12]. Problematically, patients are often unaware of these (often asymptomatic) paroxysmal AF attacks and remain underdiagnosed. Indeed, episodes of silent AF are present in approximately one third of the total population of patients with AF [13].

Given the high rates of hospitalization and lethality due to stroke in HF patients, there is a major clinical interest in stroke

prediction. Several risk factors associated with an increased stroke risk (e.g., advanced age, prior stroke, diabetes mellitus) [14] have already been identified and were included into different risk models [15•]. The predictive value of the CHA_2DS_2-VASc score, originally designed for stroke prediction in AF patients, has also been shown in the HF population [16••, 17].

While oral anticoagulation in AF is recommended dependent on the CHA_2DS_2-VASc score, current HF guidelines do not recommend oral anticoagulation for HF patients without documented AF. Indeed, there is an explicit recommendation for an oral anticoagulation only in patients with both HF and AF.

In this review, we discuss the risk of stroke in HF patients, distinguishing between HF with and without coexisting AF. Second, we debate the role of silent AF in these patients and, third, give an overview of risk stratification and therapy approaches.

Search Strategy

Electronic searches of English literature were performed in the PubMed database for relevant publications from 2000 to 2018 evaluating the risk of stroke in HF patients with and without AF as well as the role of silent AF, possibilities of risk stratification, and therapeutic implications. The following search terms were used in this review: "heart failure" AND/OR "stroke" AND/OR "atrial fibrillation" AND/OR "AF" AND/OR "silent atrial fibrillation" AND/OR "epidemiology" AND/OR "risk stratification" AND/OR "NOAC" AND/OR "warfarin." Articles were used when studies investigated abovementioned aspects or reviewed the current state of research of stroke in HF. Two authors (K.S. and J.K.) screened all the studies for qualification by abstract screening and full-text reviewing.

HF Epidemiology

Over 40 million individuals have HF, which is considered as the second most important risk factor for stroke after AF [10, 18]. Of note, 10–24% of patients with stroke have HF, while HF per se (without AF) appears to be the cause of stroke in 9% in comparison to 15% for AF per se and 2% for both HF and AF [19]. As mentioned above, analysis of Framingham Heart Study patients (participants with new-onset AF ($n = 1737$) and/or HF ($n = 1166$)) showed that AF occurs in more than half (57%) of the individuals with HF; HF is presented in over one third (37%) of AF patients [11]. Nevertheless, data reporting the incidence of stroke in HF patients vary among studies with designs and populations [20].

Several clinical trials—*W*arfarin/*A*spirin *S*tudy in *H*eart failure (WASH), *HE*art failure *L*ong-term *A*ntithrombotic *S*tudy (HELAS), *W*arfarin and *A*ntiplatelet *T*herapy in *C*hronic *H*eart failure trial (WATCH), and *W*arfarin versus *A*spirin in *R*educed *C*ardiac *E*jection *F*raction trial (WARCEF)—investigating HF patients in sinus rhythm have reported a low incidence of stroke in their populations [21, 22, 23]. In the WATCH trial, the incidence of stroke ranged from 0.4% in the warfarin group to 2.3% in the aspirin plus clopidogrel group. In a community-based cohort of 630 patients, Witt *et al.* found that 16% of the HF patients (where 41% had AF) experienced an ischemic stroke [2]. Their stroke risk was 17.4-fold increased within first 30 days after the initial diagnosis and remained elevated during follow-up of 5 years [2]. In another study, Mujib reported an approximately 1% annual rate of stroke in HF patients with sinus rhythm, which was higher than in general population (0.3%) [24] but lower than in those with both HF and AF. The presence of HF is associated with high mortality and hospitalization rates. Indeed, stroke patients with HF have longer hospitalization periods and a 2.0–2.5-fold higher mortality than patients without HF [2]. Stroke risk in HF patients seems to depend on HF severity: mild to moderate HF is associated with an annual stroke risk of 1.5% [25, 26], while stroke risk in severe HF approaches 4% [27].

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As mentioned, concomitant HF and AF are the cause of 2% of all strokes. The overall rate of stroke in HF without AF (1.6% per year) is about one third of that seen in AF without HF (5%) [19]. Of note, AF type could play an important role for the stroke occurrence in HF patients. However, the literature is controversial. On the one hand, persistent AF is described to not increase stroke risk in contrast to paroxysmal AF [12]. On the other hand, several studies reported an equal risk of stroke for paroxysmal and persistent AF [28] or even opposite results [29]. A meta-analysis including 18 papers with 134,847 AF patients [30] showed that the stroke risk was higher in patients with persistent AF with ORs of 0.75 (95% confidence interval (CI) 0.61–0.93) in studies with no oral anticoagulants and 0.77 (95% CI 0.68–0.88) in studies with oral anticoagulants in all patients. Nevertheless, it remains unclear if AF type is an independent predictor of stroke or predicated on a different patient profile regarding risk factors and comorbidities [31]. Patients with paroxysmal AF are likely to be younger, with a lower prevalence of structural heart disease, major comorbidities, and also have lower estimated thromboembolic and bleeding risks [32]. Based on this knowledge, it seems more reasonable that persistent AF has the higher stroke risk. But paroxysmal AF remains often asymptomatic as well as undiagnosed and consequently untreated leading to a possible increased risk of cardioembolic events [33].

Four randomized clinical trials investigating the effect of non-vitamin K antagonist oral anticoagulants (NOACs) anticoagulants (NOACs) in AF patients have presented different data on the effect of concomitant HF and AF. Whereas the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study [34] and the Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) study [35] could not find a significant difference in risk rates for stroke in AF patients with and without HF, the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF TIMI 48) trial found an increased risk for patients with both AF and HF present [36]. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, there was a numerically higher incidence of stroke in patients with AF and HF compared to AF without HF, but this was non-significant after multivariable adjustment [37].

While both HF and AF are independent risk factors for stroke, the coexistence of both diseases increased the risk even more. Kang *et al.* reported a 3.5-fold increased

risk for stroke in HF-only patients, while patients with HF + AF had a fivefold risk in stroke [38]. A more recent study did not find any significant difference in stroke risk between HF patients with or without AF (incidence = 2.6% patients with AF vs 2.8% without AF) [39]. The presence of AF had been also attributed to play a role in stroke etiology, as patients with both HF and AF mostly experienced cardioembolic strokes regardless of the HF etiology. Of note, patients with HF but without AF have different stroke causes according to the HF etiology: for example, patients with dilated cardiomyopathy or valvular heart disease had more frequent cardioembolic strokes while those with coronary artery disease/hypertension tended to experience atherosclerotic and lacunar strokes [40].

Heart Failure with Preserved Ejection Fraction

Most of prior studies investigated the stroke risk in patients with HF and reduced ejection fraction (HFrEF); however, HF with preserved EF (HFpEF) had an increased risk for strokes as well [5, 6]. Studies investigating the stroke risk in patients with HFpEF in comparison to HFrEF have generally found a similar stroke risk [41–45]. In contrast to HFpEF, the patients with HFrEF have a higher mortality [44, 45]. Cogswell *et al*. hypothesized a possible influence of undiagnosed (silent) paroxysmal AF on stroke risk in HFpEF patients, given that stroke risk in patients with HFpEF without AF and HFpEF with AF as well as AF-only was similar [5].

Silent Atrial fibrillation in HF

Atrial fibrillation is the most common cardiac arrhythmia [46] and the strongest risk factor for the thromboembolic stroke [10]. Because of a high prevalence of paroxysmal AF in patients with acute stroke [12], more extensive diagnostic approaches to reveal paroxysmal AF episodes are needed [47]. This is aggravated by the fact that one third of patients with AF are not aware of its presence; hence, the term "silent AF" has been introduced.

Silent AF is often discovered after serious cerebro- and cardiovascular complications such as ischemic stroke and HF via routine self-monitoring of the pulse, 12-lead electrocardiogram (ECG), 24-h Holter ECG [13], implanted pacemakers, and defibrillators. In this context, attention has been directed towards AF burden, defined by time spent in AF per unit of time [48]. Several studies analyzing implanted devices showed that 20–42% of HF patients have silent AF episodes [49, 50, 51]. Silent AF was also common (10%) at the acute phase of ischemic stroke or transient ischemic attacks (TIAs) [52]; 46% of patients suffering a cryptogenic stroke had silent AF on continuous electrocardiographic monitoring [33]. Of note, stroke incidence in silent AF is significantly higher in patients with multiple risk factors, especially hypertension, advanced age, obesity, diabetes mellitus, smoking, and previous cardiac disease [53, 54, 55] and in those with higher CHA_2DS_2-VASc score [56].

The presence of silent AF had been also described in patients with coronary artery disease and myocardial infarction [57]. Turakhia *et al*. found a threefold higher rate of cardiovascular death and a fivefold higher rate of hospitalization for HF in patients with silent AF [58]. In this context, silent AF was also common after coronary artery bypass grafting (a third had recorded AF episodes) [59]. The fact that silent AF is a common finding in different populations leads to the assumption that it could also play a role in stroke development in HF patients.

Risk Stratification of Stroke in HF

Because of the high prevalence of HF in the population and the associated stroke risk, there is interest in stroke prediction and evaluation of the possible need of antithrombotic therapy (Fig. 1).

The CHA_2DS_2-VASc score is widely used to estimate the risk of stroke in AF patients and to help in decision-making regarding oral anticoagulation [60]. In a nationwide prospective cohort of 42.987 patients with HF, Melgaard *et al*. demonstrated that CHA_2DS_2-VASc score has also predictive power for stroke, regardless of AF presence [16••]. Similar results have been found by Wolsk and colleagues in the Danish registry of 136,545 HF patients (with or without AF) [17] and in the WARCEF cohort [61]. The studies support consideration of the CHA_2DS_2-VASc score for prediction of the risk of stroke in HF irrespective of AF presence. Indeed, several studies examined the components of the CHA_2DS_2-VASc score and demonstrated their individual association with stroke in HF: congestive HF represented by a decreased ejection fraction (hazard ratio [HR] 0.98–2.15) [15•, 34, 62, 63], hypertension (HR 1.18) [15•, 62, 64, 65], age (HR 1.34–1.35) [14, 15•, 62–64], diabetes mellitus (HR 1.114–1.87) [14, 15•, 16••, 62,

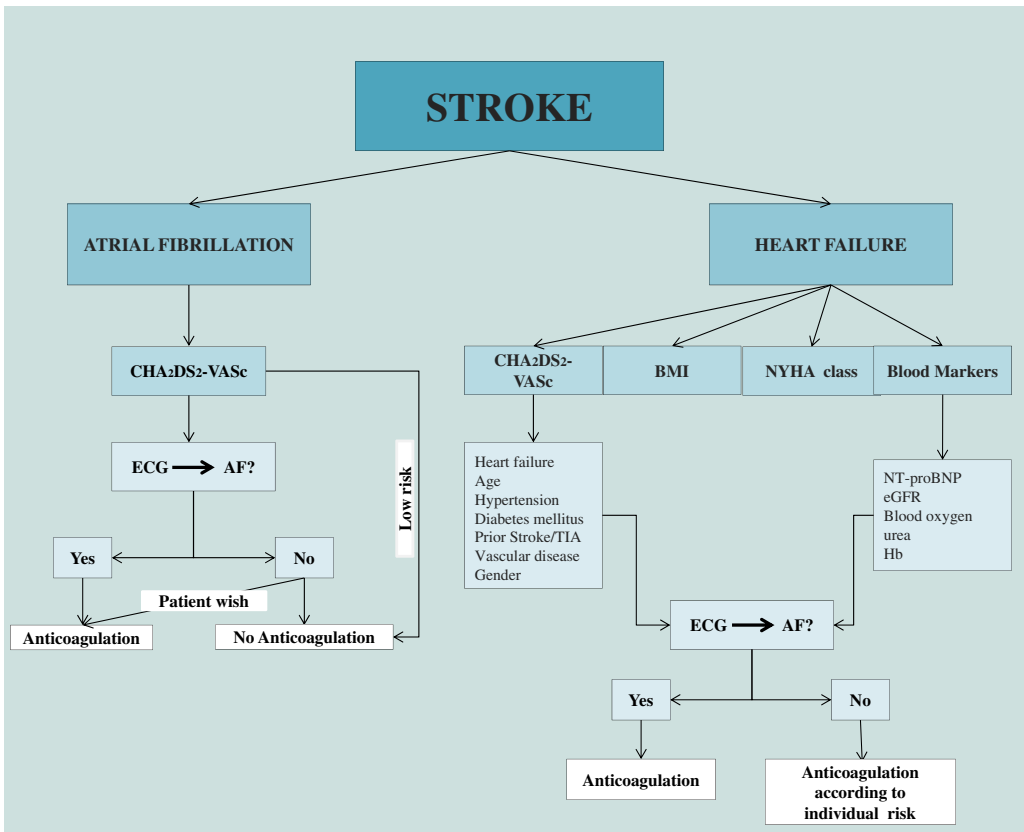


Fig. 1: Risk factors for stroke in patients with heart failure. Abbreviations: AF, atrial fibrillation; BMI, body mass index; NYHA class, New York Heart Association class; TIA, transient ischemic attack; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; eGFR, estimated glomerular filtration rate; Hb, hemoglobin

63, 65], prior stroke/TIA (HR 1.81–2.68) [14, 15•, 39, 63, 64], vascular disease (HR 1.34) [66], and gender (HR 0.569) [15•, 62, 63]. In WARCEF sub-study with patients with sinus rhythm, the ejection fraction was associated with stroke only if its baseline values were less than 15% [62, 63].

However, the data are inconsistent. For example, McMurray *et al.* did not find a correlation between ejection fraction and stroke risk despite numerically higher rate of stroke and systemic embolism in patients with left ventricular systolic dysfunction [34]. Prior stroke [14, 15•, 39, 62, 64], gender [15•], and also peripheral artery disease [66] are associated with stroke risk in HF patients. Nevertheless, the correlation between stroke risk and age [14, 15•, 64] in HF patients as well as those with diabetes mellitus [15•, 16••, 65] and hypertension are conflicting [62].

Although there are many different scores predicting the mortality in HF [67–69], the CHA_2DS_2-VASc score is the only one shown to be useful for stroke prediction in HF. Due to the lack of a convenient and accurate model to predict stroke and the accompanied increased mortality in HF, Freudenberger *et al.* proposed a new scoring system for stroke prediction in patients with an ejection fraction of less 35%, with a full model of their score, including 14 risk factors, and to provide better clinical practicability a simpler more practical score of only eight of these components: age, blood oxygen urea, ejection fraction, hemoglobin, gender, diastolic blood pressure, diabetes mellitus, and prior stroke. In their study population ($n = 2305$), the new developed score performed modestly but was superior (statistically) to CHA_2DS_2-VASc score in stroke prediction (area under the curve [AUC] 0.660, 95% CI 0.58–0.74 vs 0.52, 95% CI 0.398–0.63, $p = 0.001$) [15•].

Several studies investigated the impact of renal function on stroke risk in HF. Melgaard *et al.* showed an increased risk of ischemic stroke and intracranial bleeding in HF patients with stable chronic kidney disease, but this association could only be found in patients without renal replacement therapy [70]. These findings are in agreement with the results of another study showing an association between estimated glomerular filtration rate and stroke risk in HF patients [64].

Therapy

Given the increased risk of thromboembolic complications in patients with HF, anticoagulation should be considered in these patients also in the absence of AF. Nevertheless, current guidelines do not recommend anticoagulation for patients with HF in general [1].

Table 1: Warfarin vs antiplatelet therapy in patients with sinus rhythm.

	WASH	HELAS	WATCH	WARCEF
Year of publication	2004	2006	2009	2012
Number of patients	279	197	1587	2305
Treatment arms	Aspirin vs warfarin Placebo 99 Aspirin (300 mg) 91 Warfarin (INR 2–3) 89	Aspirin vs warfarin Ischemic heart disease: 61 Aspirin (325 mg) 54 Warfarin (INR 2–3) Dilatative cardiomyopathy: 38 Warfarin (INR 2–3) 44 Placebo	Aspirin/clopidogrel vs warfarin 523 Aspirin (162 mg) 524 Clopidogrel (75 mg) 540 Warfarin (INR 2.5–3)	Aspirin vs warfarin 1163 Aspirin (325 mg) 1142 Warfarin (INR 2.5–3)
AF	ca. 6% (baseline)	None (exclusion criteria, patients with AF in follow-up were withdrawn)	10% (follow-up)	ca. 4% (baseline)
Follow-up (mean)	27 months	ca. 20 months	21 months	3.5 years
Primary endpoints	Composite of (1) Death (2) Non-fatal myocardial infarction (3) Non-fatal stroke	Composite of (1) Non-fatal stroke (2) Peripheral or pulmonary embolism (3) Myocardial (re)infarction (4) Re-hospitalization (5) Exacerbation of heart failure (6) Death from any cause	Composite of (1) All-cause mortality (2) Non-fatal myocardial infarction (3) Non-fatal stroke	Composite of (1) Ischemic stroke (2) Intracerebral hemorrhage (3) Death from any cause
Secondary endpoints	(1) Death or cardiovascular hospitalization (incl. major hemorrhage) (2) Death or all-cause hospitalization (3) Total number of hospitalization (4) Composite of death, cardiovascular hospitalization and increase in diuretic therapy for worsening heart failure	(1) Cardiac and total mortality (2) Myocardial infarction or re-infarction (3) Heart failure exacerbation	(1) All-cause mortality (2) Nonfatal myocardial infarction (3) Nonfatal stroke (4) Hospitalization for heart failure	Composite of (1) Primary outcome (2) Myocardial infarction (3) Hospitalization for heart failure
Safety endpoints	Included in secondary endpoints	Intracranial hemorrhage, incidence of bleeding while on study drug, differences in bleeding index on study drug	Major bleeding	Major bleeding, minor bleeding
Results	Neither warfarin nor aspirin reduces risk of stroke in patients with HF	Neither warfarin nor aspirin reduced risk of stroke in patients with HF and without AF	Warfarin reduced stroke more than aspirin or clopidogrel but with a higher risk of bleeding	Warfarin was superior to aspirin concerning ischemic stroke but is accompanied with higher rates of intracerebral hemorrhages

Table 2: Efficacy and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and heart failure.

Sub-studies	RE-LY	ARISTOTLE	ROCKET-AF	ENGAGE AF
Year of publication	2013	2013	2013	2016
Number of patients	18.113 4.904 with HF 13.209 without HF	14.671 3.207 with HF (EF > 40%) 2736 with HF (EF < 40%) 8728 without HF	14.171 9.033 with HF 5.138 without HF	14.071 6.344 HF HYHA I–II 1801 NYHA III–IV 5.926 without HF
Treatment arms	Dabigatran vs warfarin	Apixaban vs warfarin	Rivaroxaban vs warfarin	Edoxaban vs warfarin
Follow-up (median)	2.0 years	18 months	707 days	2.8 years
Primary endpoints	(1) Stroke (ischemic or hemorrhagic) (2) Systemic embolism	(1) Stroke (ischemic or hemorrhagic) (2) Systemic embolism	(1) Stroke (ischemic or hemorrhagic) (2) Noncentral nervous system embolism	(1) Stroke (ischemic or hemorrhagic) (2) Systemic embolism
Secondary endpoints	(1) Vascular death (2) Hospitalization (3) Intracranial bleeding (4) Total bleeding	(1) Composite of - Stroke - Systemic embolism - Death (2) Net clinical benefit composite of - Stroke - Systemic embolism - Major bleeding - Death from any cause	(1) All-cause death (2) Myocardial infarction (3) Composite of - Stroke - Systemic embolism - Vascular death	(1) Ischemic stroke (2) Hemorrhagic stroke (3) Cardiovascular death (4) Cardiovascular hospitalization (5) All-cause death
Safety endpoints	Major bleeding	Major bleeding	(1) Primary: major or non-major clinical relevant bleeding (2) Secondary: intracranial hemorrhage and hemorrhagic stroke	Major bleeding
Results	Dabigatran was superior to warfarin concerning stroke (annual rate 1.44 vs 1.92%) and bleeding risk (annual rate 3.10 vs 3.90%). No differences in efficacy and safety between HF and No-HF	Apixaban reduced risk for stroke (HR 0.89, 95% CI 0.81–0.98)/bleeding/death (HR 0.85, 95% CI 0.78–0.92) more than warfarin independently of presence of HF	Rivaroxaban was non-inferior to warfarin concerning efficacy (HR 0.94, 95% CI 0.76–1.17) and safety (HR 1.05, 95% CI 0.95–1.15) there was no difference between HF and No-HF	Edoxaban was non-inferior to warfarin concerning efficacy (stroke in no HF: HR 0.87, 95% CI 0.69–1.11, NYHA III–IV: HR 0.83, 95% CI 0.55–1.25) and even more safe (major bleeding in no-HF: HR 0.82, 95% CI 0.68–0.99, NYHA III–IV: HR 0.79, 95% CI 0.54–1.17), there was no difference between HF and No-HF

Vitamin K Antagonists

There are four randomized clinical trials investigating the effect of warfarin on stroke risk in patients with HF in comparison to aspirin: WASH [21], HELAS [22], WATCH [23], and WARCEF [71]. Details of the trials are summarized in Table 1.

The WASH and HELAS trials were small studies, which were underpowered but showed no suggestion for the efficacy of anticoagulant therapy for HF patients in sinus rhythm [21, 22, 72]. The WATCH and WARCEF trials were larger studies (with WARCEF being a double-blind trial) and showed no significant benefit for the primary outcome that included mortality but a significant risk reduction for stroke (a secondary outcome) in patients treated with warfarin compared to aspirin; however, the positive effect was neutralized by an increased risk of major bleeding [23, 71]. In WATCH, clopidogrel was superior neither to warfarin nor to aspirin [23].

A meta-analysis of these four trials based on 3665 patients showed that warfarin reduced the risk of cardiovascular events including stroke by 20% compared to antiplatelet therapy (risk ratio (RR) 0.79, 95% CI 0.63–1.00; $I^2 = 0\%$), but the risk of major bleeding was twofold higher (RR 2.00, 95% CI 1.44–2.78; $I^2 = 4\%$). Consequently, the stroke risk reduction of warfarin was outweighed by the increased bleeding risk [73••]. Interestingly, there was no significant increase of intracranial hemorrhage on warfarin compared to antiplatelet therapy [74].

Non-Vitamin K Antagonists

The efficacy and safety of these anticoagulation drugs were shown in AF patients in four randomized double-blind trials: RE-LY, ARISTOTLE, ROCKET AF, and ENGAGE AF [75–78].

In subgroup analyses, the effect of NOACs had been investigated in AF patients with and without HF (Table 2). In summary, NOACs (dabigatran [37], apixaban [34], or at least non-inferior rivaroxaban [35] and edoxaban [36]) showed relative efficacy and safety compared to warfarin; however, there were no differences between patients with and without HF. Based on these results, current HF management guidelines recommend to prefer NOACs over warfarin in patients with concomitant HF and AF [1].

A meta-analysis of RE-LY, ARISTOTLE, and ROCKET AF including 19,122 subjects showed a significant risk reduction for stroke in patients with both HF and AF combined with a decreased bleeding risk; in HF patients, NOACs were similar effective or even safer compared to those without HF [79].

However, it remains unclear whether NOACs have a positive impact of stroke risk reduction in patients with HF but in sinus rhythm. This question had been addressed in a randomized, double-blind, placebo-controlled trial (COMMANDER HF) investigating the efficacy and safety of rivaroxaban vs placebo in HF patients

without AF, where HF is related to ischemic heart disease and all patients are taking aspirin therapy [80].

Current Approach

Based on RE-LY, ARISTOTLE, ROCKET AF, and ENGAGE AF, European HF management guidelines recommend anticoagulation in patients with both HF and AF, with a preference for NOACs [1]. Because of an increased bleeding risk outweighing the stroke risk reduction using warfarin in patients with HF but without AF [20–23, 71], the therapy of these patients needs to be tailored to the individual risk profile (e.g., prior stroke, cardiac thrombi) [1].

Conclusions

Based on the current evidence, HF should be considered as an independent risk factor for stroke. The CHA_2DS_2-VASc score might be useful to predict stroke risk in HF patients with or without AF in clinical routine.

Thus far, there is only a recommendation for the oral anticoagulation use in patients with concomitant HF and AF, while in patients with HF and no AF, individualized risk stratification is preferred. Based on recent data, NOACs should be preferred over warfarin. Finally, the results of ongoing studies may clarify further aspects of anticoagulation in HF patients without AF.

Compliance with Ethical Standards

Conflict of Interest: Katja Schumacher, Jelena Kornej, and Eduard Shantsila each declare no potential conflicts of interest.
Gregory Y.H. Lip reports personal fees from Bayer, Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. No fees are directly received personally.

Human and Animal Rights and Informed Consent: This article does not contain any studies with human or animal subjects performed by any of the authors.

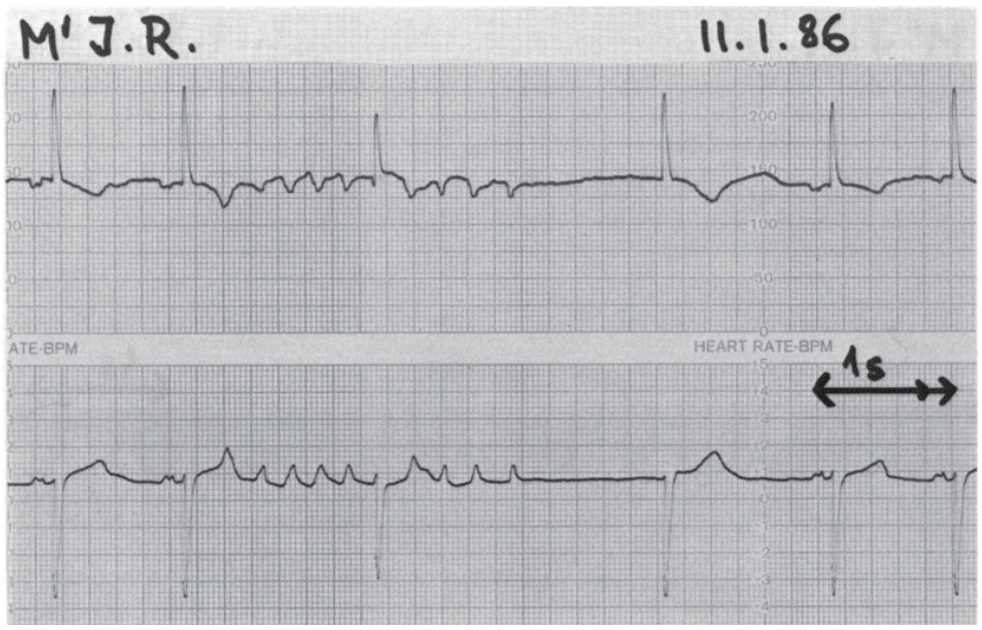
References available on request
Healthcare.India@springer.com

Source: Katja Schumacher, Jelena Kornej, Eduard Shantsila, Gregory Y. H. Lip Heart Failure and Stroke. Curr Heart Fail Rep. 2018; 15(5): 287–296. DOI 10.1007/s11897-018-0405-9. © The Author(s) 2018.

ECG Diagnostics

Atrial Tachycardia

A 74-year-old male with history of myocardial infarction, atrial fibrillation and flutter, on digoxin and amiodarone.



TECG Holter recording: The first two QRS are preceded by a P wave of unidentifiable origin (negative in the upper lead!). After the second QRS, fast irregular atrial activity is present – on average, 280 bpm – suggesting atrial tachycardia. This activity lasts for 2.2 s, with only one ventricular complex. This fast atrial activity stops, and the pause is terminated by a junctional escape. Diagnosis is atrial tachycardia lasting only 2.2 s.

Source: Jan Adamec, Richard Adamec, Hein J. J. Wellens (eds). ECG No. 104. Practical ECG Holter: 100 Cases. 1st ed. New York: Springer-Verlag; 2011, pp 7-8. DOI 10.1007/978-1-4419-9955-9_4. © Springer Science+Business Media, LLC 2012.

Guideline Recommendations

I. Blood pressure goals according to different guidelines.

Population	Guidelines	BP goal (SBP/DBP)
Elderly (aged ≥ 80 years old)	ESC/ESC	< 150/90 mmHg
	NICE	
	Canadian	
	NJC8[a]	
Diabetes mellitus	ESC/ESC	< 140/85 mmHg
	Canadian	< 130/80 mmHg
	NJC8	< 140/90 mmHg
	ADA	< 140/80 mmHg
Chronic kidney disease without proteinuria	ESC/ESC	< 140/90 mmHg
	Canadian	
	NJC8	
	KDIGO	
Chronic kidney disease with proteinuria	ESC/ESC	< 130 mmHg
	KDIGO	< 130/80 mmHg

[a] In NJC8 guidelines, it is defined as age ≥ 60 years old

II. The choice of treatment in hypertensive population with comorbidities.

Special condition	Guidelines	Anti-hypertensive drugs
General population	ESH/ESC	Diuretic, ACE-I, ARB, CCB
	NICE	< 55 years old: ACE-I
		≥ 55 years old: CCB
	Canadian	Thiazide-diuretic(Grade A) < 60 years old: BB
	NJC8	Non-black: thiazide-diuretic, ACE-I, ARB, CCB Black: thiazide-diuretic, CCB
Diabetes	ESH/ESC	ACE-I, ARB
	ADA	
	Canadian	Thiazide-diuretic, ACE-I, ARB, CCB
	NJC8	
Chronic kidney disease	ESH/ESC	ACE-I, ARB
	Canadian	
	NJC8	
	KDIGO	
Stroke	ESH/ESC	Thiazide-diuretic, ACE-I, ARB, CCB
	Canadian	ACE-I +/thiazide diuretic
Myocardial infarction	ESH/ESC	Beta-blocker
	Canadian	Beta-blocker +/ACE-I
Coronary heart disease	ESH/ESC	Beta-blocker, CCB
	Canadian	ACE-I, ARB
Left ventricular hypertrophy	ESH/ESC	Thiazide-diuretic, ACE-I, ARB, CCB
	Canadian	ACE-I, ARB
Heart failure	ESH/ESC	No evidence
	NICE	Beta-blocker

Source: Christina Antza, Ioannis Doundoulakis, Stella Stabouli, Vasilios Kotsis. Comparison Among Recommendations for the Management of Arterial Hypertension Issued by Last US, Canadian, British and European Guidelines. High Blood Press Cardiovasc Prev. 2018; 25(1): 9–16. DOI 10.1007/s40292-017-0236-x. © Springer International Publishing AG 2017.

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