REVIEW

# Pathogenesis and treatment of hypertension in haemodialysis patients with chronic kidney disease

# Patogeneza i leczenie nadciśnienia tętniczego u hemodializowanych chorych z przewlekłą chorobą nerek

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### Abstract

Hypertension is frequently diagnosed among patients with chronic kidney disease (CKD) and often remains poorly controlled in end stage kidney disease (ESKD) especially in haemodialysis patients. These patients are characterized by higher blood pressure variability than the general population. Volume overload is a primary factor contributing into the pathogenesis of hypertension in this cohort. In the diagnosis and monitoring of hypertension in haemodialysis patients with chronic kidney disease self-measured of blood pressure at home done during the days between haemodialysis sessions should be considered. Home blood pressure measurements are of greater prognostic value than haemodialysis unit recording. Target-values of blood pressure in haemodialysis patients are still matter of debate. However, self-measured systolic blood pressure values at home between 120 to 130 mmHg are associated with the best prognosis in haemodialysis patients with CKD. Among not pharmacological methods of antihypertensive treatment in haemodialysis patients with CKD reducing volaemia by increasing ultrafiltration during haemodialysis procedures, individualization of sodium concentration in the dialysis fluid and low sodium diet should be listed. While, in the pharmacotherapy  $\beta$ -adrenergic antagonists seem to be the drugs of first choice.

Key words: hypertension, haemodialysis, chronic kidney disease

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### Streszczenie

U chorych z przewlekłą chorobą nerek (PChN) często występuje nadciśnienie tętnicze. U wielu chorych z PChN leczenie nadciśnienia tętniczego nie jest w pełni skuteczne. Dotyczy to szczególnie chorych ze schyłkową niewydolnością nerek leczonych hemodializami. Chorzy ci charakteryzują się również większą zmiennością ciśnienia tętniczego niż populacja ogólna. Głównym czynnikiem w patogenezie nadciśnienia tętniczego u chorych ze schyłkową niewydolnością nerek leczonych hemodializami jest hiperwolemia. W rozpoznawaniu i monitorowaniu nadciśnienia tętniczego u tych chorych należy preferować wykonywanie samodzielnych domowych pomiarów ciśnienia tętniczego w dniach bez zabiegów hemodializy. Domowe pomiary ciśnienia tętniczego mają większą wartość prognostyczną niż pomiary ciśnienia tętniczego wykonywane w stacji dializ. Docelowe wartości ciśnienia tętniczego u chorych ze schyłkową niewydolnością nerek leczonych hemodializami są nadal przedmiotem kontrowersji. Wykazano jednak, że najlepszym rokowaniem charakteryzują się chorzy ze skurczowym ciśnieniem tętniczym wynoszącym w samodzielnych domowych pomiarach 120–130 mm Hg. Niefarmakologicznymi metodami leczenia przeciwnadciśnieniowego

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u chorych ze schyłkową niewydolnością nerek leczonych hemodializami są: zmniejszenie wolemii przez zwiększenie ultrafiltracji w trakcie hemodializy, indywidualizacja stężenia sodu w płynie dializacyjnym oraz zmniejszenie zawartości sodu w diecie. W farmakoterapii lekami pierwszego wyboru są antagoniści receptorów  $\beta$ -adrenergicznych. **Słowa kluczowe:** nadciśnienie tętnicze, hemodializa, przewlekła choroba nerek

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### Introduction

Hypertension is highly prevalent in patients with chronic kidney disease (CKD), particularly in patients with end-stage kidney disease (ESKD) treated with haemodialysis [1, 2] and it is the important risk factor contributing to the high cardiovascular morbidity and mortality in this population [3, 4]. In the early years of renal replacement therapy with haemodialysis, hypertension requiring pharmacologic therapy was seen only in 10% to 15% of the patients, most probably due to strict patients' selection, dialysate and dietary sodium restriction, attention to dry-weight and longer time of haemodialysis sessions [5]. However, more recent data suggest that the prevalence of hypertension in patients on chronic haemodialysis exceeds the number seen in the general population [6] or those with CKD not required haemodialysis [7]. Although, nowadays hypertension is present in 50% to 90% of patients on haemodialysis [8-10], it remains a controversial prognostic marker in patients with CKD stage 5. In patients receiving chronic haemodialysis, approximately 45% of overall mortality is attributable to the cardiac disease. Acute complications of coronary heart disease in patients with renal dysfunction account only 20% of cardiac deaths [11]. In these patients cardiovascular diseases are more likely to manifest as calcification of the coronary arteries media [12, 13], left ventricular hypertrophy [14, 15], and sudden cardiac death [16]. In contrast to the guidelines for the general population, in which systolic blood pressure of  $\leq 140$  mmHg is considered the treatment target, a debate remains regarding the target blood pressure in haemodialysis patients [17]. Hypertension in haemodialysis patients is an unique diagnostic, prognostic and therapeutic challenge [18]. The main aim of this review is to systematize the current state of knowledge concerning hypertension in haemodialysis patients, especially pathophysiology, variability, measurement methods, target-values of blood pressure, and mode of antihypertensive treatment.

### Pathophysiology of hypertension in haemodialysis patients

The pathogenesis of hypertension in ESKD patients include increased extracellular volume, increased sympathetic and renin-angiotensin-aldosterone (RAA) systems activity, secondary hyperparathyroidism, endothelial cell dysfunction, increased oxidative stress and exposure to erythropoiesis-stimulating agents (ESAs) [19] (Table I).

Volume overload is the main factor participating in the pathogenesis of arterial hypertension in dialysis patients [20, 21]. The inability to excrete sodium and water via failured kidney contributes to increased extracellular volume, increased cardiac output and, as a consequence, increased blood pressure in haemodialysis patients.

The inadequate activity of RAA system has long been implicated in the etiology of hypertension in haemodialysis patients [19]. In a study of 51 haemodialysis patients, there were significant differences in the plasma renin activity (PRA) between normotensive subjects (n = 9), hypertensive subjects whose blood pressure was controlled by ultrafiltration and dietary sodium restriction (n = 24), and subjects with persistent hypertension (n = 18) [22]. PRA was the lowest in the normotensive group, significantly higher in the group with controlled hypertension, and

 $\begin{tabular}{ll} \textbf{Table I.} Causes of hypertension in haemodialysis patients with chronic kidney disease \end{tabular}$ 

Causes of hypertension in haemodialysis patients with chronic kidney disease
Increased extracellular volume — volume overload
Increased sympathetic nervous system activity
Increased renin-angiotensin-aldosterone system activity
High salt diet
Secondary hyperparathyroidism
Endothelial cell dysfunction
Increased oxidative stress
Exposure to erythropoiesis — stimulating agents (ESAs)

the highest in the persistently hypertensive group. In 17 out of 18 persistently hypertensive subjects, bilateral nephrectomy resulted in significant reductions in blood pressure. Post-nephrectomy PRA was measured in 12 subjects, and was significantly lower, suggesting that elevated baseline PRA may have contributed to the poorly controlled hypertension. Angiotensin II and aldosterone which are primary mediators of RAA system, both contribute to left ventricular hypertrophy (LVH) and endothelial cell dysfunction independently of blood pressure [19].

Patients with ESKD are characterized by higher sympathetic nervous system (SNS) activity (measured by skeletal muscle sympathetic nerve activity [MSNA]), mean arterial blood pressure, and vascular resistance than healthy controls, or CKD stage 5 patients who have had bilateral nephrectomy [23]. Furthermore, in renal transplant recipients, MSNA remained elevated following renal transplantation, but subsequently decreased following native kidneys nephrectomy. It suggests that it is not uraemia per se, but rather signaling from diseased kidneys that results in elevated MSNA and hypertension. However, while the initial trigger for increased SNS activity is likely renal ischaemia with a consequential increase of renal afferent nerve activation, other mediators that are also affected by CKD stage 5 such as nitric oxide, angiotensin II, and superoxide and may further modify blood pressure. Nocturnal decrease of blood pressure is frequently absent in patients with CKD and it is associated with adverse outcomes [24]. There is evidence that more frequent haemodialysis sessions, whether through increased removal of uremic toxins or improvement of volume status, may lower SNS activity. In a study of stable non-diabetic haemodialysis patients whose blood pressure was controlled with or without antihypertensive drugs, conversion from standard three times a week (12h/week total HD time) to haemodialysis six times a week (12h/ /week total HD time) resulted in significant reduction in ambulatory blood pressure (systolic and diastolic) and MSNA. The subjects who had studies repeated following conversion back to standard haemodialysis regimen demonstrated an increase in MSNA back to baseline values [25].

The secondary hyperparathyroidism that accompanies CKD may contribute to the high prevalence of hypertension in these patients. The evidence based on a retrospective study in CKD patients demonstrating that systolic and diastolic blood pressure were significantly increased in subjects with increased plasma concentration of parathyroid hormone (PTH) [26]. Furthermore, a possible mechanism was suggested by the findings of increased platelet cytosolic calcium in the group with increased PTH plasma concentration. Mean blood pressure correlated highly significant with cytosolic calcium and plasma PTH concentration. Treatment with active vitamin D (alfacalcidol) significantly lowered plasma PTH level, and mean blood pressure. Kuczera et al. observed a decrease of blood pressure in haemodialysis patients with chronic kidney disease and secondary hyperparathyroidism treated with calcimimetic cinacalcet [27]. These observations were confirmed recently in the analysis of the results from EVOLVE study [28].

Erythropoiesis-stimulating agents used to correct the anaemia associated with CKD may also lead to blood pressure increase [29]. The proposed mechanisms specific to haemodialysis patients include increase of ET-1 release and increased sensitivity to angiotensin II and adrenergic stimuli. The effect of blood pressure is dependent on the dose, but not necessary the pre-treatment blood pressure as both previously normotensive and hypertensive patients can have ESAs related blood pressure increase [19].

### Blood pressure variability among haemodialysis patients

In the majority of HD patients (85%) decrease of blood pressure during haemodialysis procedures is observed [30]. Agarwal et al. observed that home BP increases over time after haemodialysis treatment and this relationship was non-linear and reach plateau after approximately 2 days. It is important to stress that probing dry-weight does not perturb the time-dependent relationship of home BP but steepens the slope for ambulatory BP. Increase in interdialytic weight gain reduces the intercept BP but steepens the slope of BP changes. Furthermore, the timing of home BP monitoring influences the accuracy and precision of the measurements and the time elapsed after dialysis must to be considered in interpreting the home BP recordings in haemodialysis patients [31]. Taking into account facts mentioned above, it should be stated that blood pressure in haemodialysis patients is characterized by high variability. In fact, variability in blood pressure within patients is similar to that between patients [32].

The percentage of interdialytic weight gain (overall weight gain/estimated dry weight x 100) predicts increased pre-HD systolic blood pressure and greater reduction in systolic blood pressure from pre- to post-HD, particularly in non-diabetics, younger patients, and those with greater estimated dry weight [33]. In one large, observational study, increased interdialytic weight gain (IDWG) was associated with increased mortality [34].

In the minority of HD patients (15%) blood pressure increases during haemodialysis [30]. The main cause of blood pressure increase in these patients is the increase of vascular resistance. Using cardiac output estimated from echocardiograms and blood pressure measurements before and after haemodialysis, it was found there was a significant increase in vascular resistance from pre- to post-haemodialysis in the intradialytic hypertension patients compared to patients whose blood pressure did not increase during haemodialysis. There were no significant differences in the change in cardiac output (or in the individual pre- or post-dialysis measurements) between the 2 groups. These authors and others have sought to identify specific mediators of the increase in blood pressure that may be related to over secretion of endogenous vasoconstrictive substances. In the study by Chou et al. [35], there was no evidence that surges in sympathetic nervous system activity (assessed using plasma catecholamines) or in RAA system activity (assessed using plasma renin activity) could explain such an increase in vascular resistance. They did find, however, imbalances in endothelial cell-derived mediators after dialysis in the intradialytic hypertension patients. Specifically, there were higher plasma concentration of the vasoconstrictor - endothelin-1 (ET-1) and lower concentration ratios of the vasodilator nitric oxide to ET-1. Other studies have investigated changes in ET-1 during dialysis in intradialytic hypertension and found suggestive, but not confirmatory evidence, to support this hypothesis. Raj et al. [36] found decreases in ET-1 in hypotension-prone patients with a trend toward increases in ET-1 in the intradialytic hypertension group. El-Shafey et al. [37] found increased plasma ET-1 concentration in intradialytic hypertension patients. Based on the evidence that vasoconstriction may be a predominant mechanism for intradialytic hypertension and that ET-1 has been implicated as a causative mediator for this, further investigation has to be directed toward the overall role of endothelial cell dysfunction in intradialytic hypertension. It was found that patients with intradialytic hypertension had lower flow-mediated vasodilation [38]. This assessment of endothelial cell function occurred on a non-haemodialysis day so it was not influenced by the haemodialysis procedure. The intradialytic hypertension patients also had lower number of circulating endothelial progenitor cells than the controls. It is suggested that circulating endothelial progenitor cells number is a marker of cardiovascular risk (lower number indicates higher risk) [39]. These were measured prior to dialysis, so that they also were not influenced by the haemodialysis procedure. It is of note that in the Inrig et al. study [38], the change of plasma ET-1 concentration from pre- to post-haemodialysis was not different between the intradialytic hypertension patients and haemodialysis controls. So, while endothelial cell dysfunction appears to be more pronounced in intradialytic hypertension patients, the most recent research has focused on specific mechanisms, by which the endothelial cells influence intradialytic blood pressure [40].

# How to measure blood pressure in chronic kidney disease patients on haemodialysis?

Among the features of the ideal method of measuring blood pressure simplicity and low cost, reliable diagnosis of hypertension, prognostic value in assessing the risk of organ damage and prognostic significance should be listed. There are several methods of blood pressure measurement in haemodialysis patients with chronic kidney disease: automatic 44-hour recording of blood pressure (Ambulatory BP Monitoring - ABPM), not standardized measurements done before and after haemodialysis, standardized measurements done before and after haemodialysis (Dialysis Unit Blood Pressures) and individual measurements (at home) performed between haemodialysis procedures (Home BP Monitoring) (Table II). The identification and treatment of hypertension in CKD has to face peculiar problems because of the marked alterations in 24-hour blood pressure (BP) profile, in particular of a reduced BP dipping at night, and the high prevalence of specific hypertension phenotypes, such as white coat hypertension (WCH), masked hypertension (MH) [41], hypertension caused by fear of haemodialysis or of puncture a needle.

Taking into account already discussed high blood pressure variability in haemodialysis patients, the automatic 44-hour recording of blood pressure (ABPM) is a "gold standard" among methods of measuring blood pressure in haemodialysis patients with chronic kidney disease. ABPM extended to 44-hour in comparison to 24-hour covers the whole mid-week dialysis interval [18]. This method is also

 
 Table II. Methods of blood pressure measurement in haemodialysis patients

Methods of measuring blood pressure in haemodialysis patients	s:
Home blood pressure monitoring — HBPM	
Automatic 44-hour recording blood pressure — Ambulatory BP Monitoring	
Measurements done before and after haemodialysis — Dialysis Un Blood Pressure	it

helpful in identifying patients without physiological nocturnal decrease of blood pressure (dipping pattern) and has a prognostic value in assessing the risk of left ventricular hypertrophy [42]. Unfortunately, it is expensive and its acceptance by the patients is low.

Another method of blood pressure monitoring is non-standardized measurements done before and after haemodialysis. It is a routine clinical practice characterized by low cost and great simplicity. However, a low consistence between not standardized monitoring of blood pressure and automatic 44-hour recording of blood pressure is observed [43]. Agarwal et al. reported a 13.5 mmHg increase of systolic blood pressure in the measurement performed directly before haemodialysis [43]. Blood pressure measured before and after dialysis does not correlate well with those recorded outside the dialysis unit [44]. BP assessed before and after dialysis, even if obtained using standardized methods, correlates poorly with interdialytic ambulatory BP [43, 45]. Khangura et al. reported that blood pressure measured before haemodialysis had no significant prognostic value for risk of left ventricular hypertrophy [47]. In contrast, BP assessed outside the dialysis unit, whether obtained by interdialytic automatic BP measurement, or self-measured BP at home is useful in diagnosing left ventricular hypertrophy [42]. Thus, dialysis unit measurement is only distantly related to ambulatory BP, or target organ damage. This poor relationship calls into question the use of BP obtained before and after dialysis for the diagnosis and treatment of hypertension among patients on haemodialysis [46].

Among the methods used in dialysis unit it is also possible to do standardized measurements before and after haemodialysis. In this method the blood pressure is measured in a quiet and warm room, after 5 minutes of rest. Then, the arithmetic average of three consecutive measurements (taken every few minutes) should be calculated. Although this method is also characterized by great simplicity, to use it in everyday clinical practice in dialysis units would require multiplying the number of employees and thus would significantly increase the cost. However, standardized measurements taken after haemodialysis are more consistent with automatic 44-hour recording of blood pressure than not standardized measurements taken before and after haemodialysis [42].

The last method used for the assessment for blood pressure among haemodialysis patients is home blood pressure monitoring — HBPM. This method is also characterized by low cost and great simplicity but patients have to be instructed in the appropriate usage of this method of measurement. Self-inflating automatic and semi-automatic oscillometric devices with shoulder cuff are recommended. Only the devices with proven accuracy should be used and patients should be advised to write down the measurements [48]. The measurements should be taken twice a day on days without haemodialysis. Every time the blood pressure measurements should be performed in a quiet room, with the patient in seated position, back and arm supported, after 5 minutes of rest and with two measurements per occasion taken 1-2 minutes apart [18]. Then, the arithmetic average of measurements from several days should be calculated [48, 49]. Among the advantages of this method low cost and great simplicity, as well as the ability to reliably identify hypertension and prognostic value of the risk of organ complications should be mentioned. Individual measurements (home BP monitoring) taken between haemodialysis have a prognostic value in assessing the risk of target organ damage and prognostic significance [42]. They are also characterized by high sensitivity (~80%) and high specificity (~84%) in the diagnosis of hypertension [45]. Thus, the diagnosis and treatment of hypertension should be primarily guided by the results of the home blood pressure monitoring performed between haemodialysis sessions.

### Diagnosis of hypertension and target-values of blood pressure in haemodialysis patients

There are number of published guidelines (e.g. the guidelines of European Society of Hypertension [48] or Polish Society of Hypertension [49]) that can be used in the clinical practice for blood pressure control in the non-dialysis-dependent CKD population. However, there are no clearly defined guidelines for hypertensive patients in the haemodialysis population [50–52].

Hypertension in haemodialysis patients should be defined on the basis of home BP or ABPM measurements. Thresholds and methods are defined by the ASH/ASN (American Society of Hypertension/ /American Society of Nephrology) [53], the EURE-CA-m (European Renal and Cardiovascular Medicine) working group of ERA-EDTA (The European Renal Association — European Dialysis and Transplant Association) [54] and the relevant ESH (European Society of Hypertension) Guidelines [55–57]. According to these recommendations hypertension in haemodialysis patients should be diagnosed on the basis of HBPM if an average BP  $\geq$  135/85 mmHg for measurements done in the morning and in the evening over 6 non-dialysis days (covering a period of 2 weeks) is observed [48, 49, 18]. Hypertension in HD patients should be also defined on the basis of ABPM if an average BP  $\geq$  130/80 mmHg over 44-hour monitoring, covering the whole mid-week dialysis interval, is observed [42, 18]. For haemodialysis patients no recommendations can be made on the basis of pre- or post-dialysis BP [18].

The thresholds for blood pressure targets in CKD patients treated with haemodialysis are still matter of debates. Agarwal et al. (2010) reported that the lowest risk of death is found in patients with HBPM SBP 120–130 mmHg [58]. Therefore it might be concluded that the target systolic blood pressure measured between haemodialysis sessions (HBPM) seems to be similar to general population, this means < 135 mmHg [48, 41].

#### Antihypertensive treatment in patients with chronic kidney disease on haemodialysis

Treatment methods of hypertension can be divided into three groups: non-pharmacological, pharmacological and invasive/surgical. Among the non-pharmacological methods of antihypertensive treatment in patients with chronic kidney disease on haemodialysis reducing volaemia, reducing sodium intake from dialysate or in the diet, should be listed. Reducing volaemia can be achieved in two ways. First, by reducing dry weight, what can be done by haemodialysis with increased ultrafiltration. Secondly, by reducing sodium intake, attained both by reducing the concentration of sodium in the dialysate and the use of a low sodium diet. Non-pharmacological interventions targeting sodium and volume excess are fundamental for BP reduction in this population and should be carefully implemented before pharmacological interventions [18].

# Non-pharmacological methods — reducing volaemia

Conceptually, slow reduction in estimated dry weight over time with little change in interdialytic weight gain could lower blood pressure without imposing excessive dietary restrictions on patients. Gradual dry weight reduction leads to the improved ambulatory blood pressure in hypertensive haemodialysis patients [59]. Techniques that monitor blood volume during haemodialysis may offer opportunity to better estimate dry weight in haemodialysis patients. The relation between dry-weight reduction and hypertension is well described in a randomized trial DRIP (Dry-Weight Reduction in Hypertensive Haemodialysis Patients) [59]. In this study standard ultrafiltration and additional ultrafiltration 0.1 kg/10 kg of weight were compared in 150 haemodialysis patients with hypertension during the eight-week follow-up. As a consequence, respectively weight loss of 1 kg and no decrease in body weight were observed. The weight loss of 1 kg was related to lowering blood pressure of 7/3 mmHg [59]. On the other hand, in another study looking at the potential long-term effects of volume status, as assessed by relative plasma slope (flatter indicating volume overload) during haemodialysis treatment, it was showed that volume overload was associated with increased mortality independently on ultrafiltration rate [59–63].

Another non-pharmacological method of antihypertensive treatment in haemodialysis patients is the reducing sodium intake achieved by reduction of sodium concentration in dialysate. Movilli et al. found a positive sodium balance during haemodialysis procedure in 72% haemodialysis patients with chronic kidney disease [64]. Relatively high dialysate sodium concentration (with sodium concentration equal 140 mmol/l) causes decreased sodium removal, which leads to volume overload and then to hypertension. Moreover, use of high sodium concentration in the dialysate results in the increase of serum sodium concentration, which leads to increased thirst and, as a consequence, to the volume overload and finally to hypertension [65]. De Paula et al. observed decreases of blood pressure due to individualization of sodium concentration in dialysate, equal to that found before 3 previous haemodialysis procedures [66].

Another method of reducing sodium intake is based on low sodium diet. Magden et al. found SBP decrease from 147 mmHg to 119 mmHg in 15 haemodialysis patients with chronic kidney disease using low sodium diet [67]. Moreover, Maduell et al. reported the decrease of blood pressure from 139/ /79 mmHg to 132/75 mmHg in 15 haemodialysis patients with chronic kidney disease in response to salt reduction from 10.2 g to 7.1 g per day [68]. Current daily intake of salt in Poland is around 14.2 g, which is three times more than the WHO recommendation amounting to 5-6 g per day. Many sources of sodium in the diet could be mentioned. Sodium is a natural component of animal food products, component of salt used for seasoning meals and addition to processed food (which is about 85% of sodium intake). Among food with extremely high sodium content, is instant soup (1.9 g — i.e. 2.4 g of salt in one portion), instant noodle soup (2.8 g — i.e. 4.1 g of salt/ /portion), pizza (7 g — i.e. 12.8 g of salt), Chinese food (5.5 g — i.e. 11 g of salt), Indian food (3.6 g i.e. 6.1 g of salt), kebab (4 g — i.e. 8.4 g of salt) and

*fast food*. Meal in fast food restaurants are composed by sandwich, fries and sauce consists of 4.5 g of salt which represents 90% of the daily recommended salt intake [69–71]. Daily sodium intake in haemodialysis patients should be limited to 65 mmol (i.e. 1.5 g of sodium or 4 g of sodium chloride) [18]. To achieve this, it is advisable to discontinue the use of salt as a seasoning of meals, preparing dishes with natural and fresh products and avoiding processed food [69–71].

#### **Renal denervation**

Renal denervation is the interventional method currently recommended in selected patients with resistant hypertension. Schlaich et al. in preliminary study described 9 haemodialysis patients with CKD treated by this method using Simplicity catheter. In this study, decrease of systolic blood pressure from 171 mmHg to 138 mmHg was identified 12 months after the renal denervation procedures [72]. Additionally, Hoye et al. described 9 dialysis patients (6 treated by haemodialysis, 3 by peritoneal dialysis) with chronic kidney disease and resistant hypertension treated with EnligHTNTM catheter. In this study, decrease of systolic blood pressure from 179 mmHg to 154 mmHg and decrease of SBP in ABPM from 173 mmHg to 152 mmHg were observed 12 months after renal denervation procedures [73]. To define the role of renal denervation in the hypertension treatment among haemodialysis patients further studies with sham procedures, higher number of participants and longer follow-ups are needed.

#### Pharmacotherapy

Two meta-analysis suggest that antihypertensive therapy (including  $\beta$ -adrenergic antagonists, angiotensin converting enzyme inhibitors [ACEIs], angiotensin II receptor blockers [ARBs], calcium channel blockers [CCBs] and mineralocorticoid receptor antagonists [MRAs]) positively influenced on the prognosis in the haemodialysis patients. The major finding of meta-analysis performed by Agarwal et al. [74] is that the overall benefit of antihypertensive therapy compared with the control (or placebo) group reduced the combined hazard ratio for cardiovascular events by 31% using a fixed-effects model and by 38% using a random-effects model. There was substantial heterogeneity between studies with respect to outcomes. However, when studies were divided based on inclusion of normotensive subjects in the randomized group, it explained most of between-study variance. Heterogeneity between normotensive and hypertensive groups was highly significant (p = 0.006). Although the hypertensive group had a pooled hazard ratio of 0.49 (95% CI: 0.35 to 0.67), the normotensive group had a pooled hazard ratio of 0.86 (95% CI: 0.67 to 1.12). In fact, even all-cause mortality, an outcome most commonly measured in the observational studies, was not increased with treatment. While, in a meta-analysis by Heerspink et al. [75] it was shown that treatment with agents that lower blood pressure reduces cardiovascular morbidity and mortality in patients on maintenance dialysis. The effects are consistent with or without the presence of hypertension and other comorbidities and across a range of drug classes. Furthermore, this analysis is not able to separate out the effects of blood pressure lowering for specific drug classes. The results do not show any differences in cardiovascular events caused by different drug classes. The data suggest that drugs inhibing renin-angiotensin-system activity,  $\beta$ -adrenergic antagonists, and calcium-channel blockers are all suitable for use in patients on dialysis

The selection of appropriate antihypertensive pharmacotherapy in haemodialysis patients is still matter of debate. Some arguments in this debate come from the results of HDPAL study [76]. The purpose of HDPAL - randomized, controlled trial was to determine among maintenance haemodialysis patients with left ventricular hypertrophy assessed by echocardiography and hypertension, whether  $\beta$ -adrenergic antagonists-based antihypertensive therapy was more effective than angiotensin converting enzyme-inhibitor-based antihypertensive therapy in causing a greater regression of left ventricular hypertrophy. In this study subjects were randomly assigned to either open label lisinopril (n = 100) or atenolol (n = 100), each administered three times per week after dialysis. Monthly monitored home blood pressure (BP) was controlled to < 140/90 mmHg with dry weight adjustment and sodium restriction. If the blood pressure target was not achieved calcium channel blockers and subsequently doxazosin, minoxidil and guanfacine were added. The primary outcome was the change in left ventricular mass index (LVMI) from baseline, to 12 months. Among hypertensive patients with left ventricular hypertrophy on maintenance haemodialysis, in the HDPAL trial, treatment based on either atenolol or lisinopril produced statistically and clinically significant reductions in BP from baseline that was sustained over the 12-month course of the trial. Despite a greater reduction in dry weight, compared with atenolol, the administration of lisinopril was associated with an increased risk of hospitalizations for congestive heart failure. In addition, lisinopril therapy was associated with an increased

risk of all-cause hospitalizations and cardiovascular morbidity. Specifically, lisinopril administration was also associated with an increased incidence of the combined risk of hospitalizations due to congestive heart failure, myocardial infarction, strokes and cardiovascular death. Furthermore, this therapy was also associated with an increased risk of hyperkalemia and emergent treatment for hypertensive crises. It seems then HDPAL trial shows that atenolol-based antihypertensive therapy is superior compared with lisinopril-based therapy in haemodialysis patients. Despite both groups being targeted to home BP of < 140/ /90 mmHg at each monthly visit, the lisinopril-based group required a statistically greater number of antihypertensive drugs and a greater need for lowering dry weight to lower BP. Moreover, in the lisinopril group, BP lowering remained numerically less using ambulatory BP monitoring and statistically less when assessed by home BP monitoring. Atenolol-based therapy may therefore have conferred cardiovascular protection by improving BP control. The conclusion from this study is that an initial strategy using atenolol ( $\beta$ -adrenergic antagonist therapy) is superior to ACE-inhibitor-based therapy, among haemodialysis patients with hypertension and left ventricular hypertrophy. In another study, Cice et al. observed that carvedilol reduces mortality compared with placebo in HD patients with dilated cardiomyopathy [77].

What is interesting, in haemodialysis patients not only typical antihypertensive drugs could reduce blood pressure. Kuczera et al. [27] observed the decrease of blood pressure in 58 haemodialysis patients with chronic kidney disease and secondary hyperparathyroidism treated with calcimimetic cinacalcet. Decrease an average of 7 mmHg of systolic blood pressure and an average of 2 mmHg of diastolic blood pressure after 6 months of cinacalcet therapy was described. These observations was recently confirmed by the analysis of results from the EVOLVE study [28].

## Conclusions

- Patients with chronic kidney disease treated with haemodialysis are characterized by higher prevalence of hypertension and higher variability in blood pressure than the general population. The main reasons for this variability are changes in volaemia.
- In the diagnosis and treatment of hypertension in haemodialysis patients with chronic kidney disease self-measured blood pressure at home done between haemodialysis sessions should be considered.

- Self-measured systolic blood pressure between 120 to 130 mmHg is associated with the best prognosis in haemodialysis patients with chronic kidney disease.
- Reduction of the volaemia by increasing ultrafiltration during haemodialysis procedures, individualization of sodium concentration in the dialysis fluid and low sodium diet are the most important methods in the treatment of hypertension in haemodialysis patients with chronic kidney disease.
- The use of antihypertensive pharmacotherapy in haemodialysis patients with chronic kidney disease reduces mortality in this group of patients.
- The drugs of first-line in hypertension treatment in haemodialysis patients with chronic kidney disease seem to be β-adrenergic antagonists.

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