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Hypertension as Cardiovascular Risk Factor in Chronic Kidney Disease

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ABSTRACT: Hypertension is the leading modifiable cause of premature death and hence one of the global targets of World Health Organization for prevention. Hypertension also affects the great majority of patients with chronic kidney disease (CKD). Both hypertension and CKD are intrinsically related, as hypertension is a strong determinant of worse renal and cardiovascular outcomes and renal function decline aggravates hypertension. This bidirectional relationship is well documented by the high prevalence of hypertension across CKD stages and the dual benefits of effective antihypertensive treatments on renal and cardiovascular risk reduction. Achieving an optimal blood pressure (BP) target is mandatory and requires several pharmacological and lifestyle measures. However, it also requires a correct diagnosis based on reliable BP measurements (eg, 24-hour ambulatory BP monitoring, home BP), especially for populations like patients with CKD where reduced or reverse dipping patterns or masked and resistant hypertension are frequent and associated with a poor cardiovascular and renal prognosis. Even after achieving BP targets, which remain debated in CKD, the residual cardiovascular risk remains high. Current antihypertensive options have been enriched with novel agents that enable to lower the existing renal and cardiovascular risks, such as SGLT2 (sodium-glucose cotransporter-2) inhibitors and novel nonsteroidal mineralocorticoid receptor antagonists. Although their beneficial effects may be driven mostly from actions beyond BP control, recent evidence underline potential improvements on abnormal 24-hour BP phenotypes such as nondipping. Other promising novelties are still to come for the management of hypertension in CKD. In the present review, we shall discuss the existing evidence of hypertension as a cardiovascular risk factor in CKD, the importance of identifying hypertension phenotypes among patients with CKD, and the traditional and novel aspects of the management of hypertensives with CKD.

Key Words: blood pressure ■ diabetes ■ epidemiology ■ heart failure ■ hypertension ■ kidney ■ risk factor

Blood pressure (BP) is one of the most important determinants of the cardiovascular and renal health of populations. This is why lowering the prevalence of hypertension, defined as a systolic BP >140 mm Hg or a diastolic BP >90 mm Hg, has been set as a major objective by the World Health Organization.[1] A pooled analysis of >1400 population-based studies, in which 19.2 million adults aged ≥18 years had their BP measured, has shown that both age-standardized systolic and diastolic BPs decreased substantially between 1975 and 2015,[2] suggesting an increased awareness and a global improvement in BP control. Yet, this amelioration occurred essentially in high-income and in some middle-income countries, whereas the prevalence of elevated BP rather increased in lower-income countries. Moreover, the worldwide number of individuals with hypertension continues to rise due mainly to the growth and the aging of populations. A rightward shift in the distribution of BP in low- and middle-income countries might also play a role in the increased prevalence of patients with hypertension.[3,4] The most recent epidemiologic survey has analyzed the trajectory of BP in 200 countries and territories between 1990 and 2019.[5] This very large survey (>100 million participants included) has confirmed the ongoing improvement in the detection, treatment, and control of hypertension but with a large variability between countries; low-income countries are still lagging behind.

Chronic kidney disease (CKD) is defined as a persistent estimated glomerular filtration rate (eGFR) <60 mL/(min·1.73m^2), albuminuria (albumin/creatinine ratio [UACR] ≥30 mg/g), or other markers of kidney damage for at least 3 months. Based on the levels of eGFR and albuminuria, CKD is classified into 5 stages according to the level of GFR (G1–G5) and three categories according

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Nonstandard Abbreviations and Acronyms:

AASK	African American Study of Kidney Disease Cohort Study
ARTS-DN	ARTS-Diabetic Nephropathy
BP	blood pressure
CKD	Chronic kidney disease
CRIC	Chronic Renal Insufficiency Cohort
eGFR	estimated glomerular filtration rate
KNOW-CKD	Korean Cohort Study for Outcome in Patients With CKD
MUCH	masked uncontrolled hypertension
RAS	renin-angiotensin system
SGLT2	sodium-glucose cotransporter-2

to the absence or presence of albuminuria (A1, A2, and A3).[6] CKD affected about 9% of the World population in 2017, but with large variations between regions, the burden being greater in low-income regions where the CKD prevalence ranged between 8% and 16%.[7,8] The prevalence of CKD is higher in females than in males and differs according to race. Of note, the prevalence of CKD is usually calculated based on the CKD-EPI formula with correction for gender and race and figures vary if other equations are used.[9] Recently, a new creatinine-based and cystatin C–based formula to estimate GFR without race has been proposed.[10] This new equation has generated many comments suggesting that it should be used only in the United States as other formulas based on local cohorts are probably more accurate in Europe and Africa.[11]

Considering all stages, including dialysis, CKD is a leading cause of death worldwide. In contrast to many other medical conditions, the death rate attributed to CKD has increased markedly in last decades (+41% between 1990 and 2017).[7,12] Most of the time, the exact cause of CKD remains unspecified, but among recognized causes, the major ones are diabetes, a high BP, and an age-related reduction of kidney function.[7] In all CKD stages, patients have a higher risk of developing cardiovascular complications than subjects or patients with a normal renal function.[13] This is because patients with CKD often cumulate traditional cardiovascular risk factors (dyslipidemia, diabetes, smoking) and nontraditional risk factors, such as CKD-related risk factors that increase in prevalence as kidney function declines (anemia, acidosis, hyperparathyroidism).[14] Thus, patients with CKD have a greater risk of dying prematurely from a cardiovascular event than progressing to end-stage kidney disease (ESKD). Consequently, only about 0.1% to 0.25 % of patients with CKD actually reach stage 5 and will be in need of a kidney replacement therapy, for example, dialysis or transplantation.[8,15,16] Another important aspect is that the economic burden of CKD is proportionally much higher than that of other diseases with a similar prevalence.[17] The CKD costs increase exponentially with each CKD stage progression but the main financial burden is due to the high treatment cost of patients with end-stage kidney disease (ESKD).[17] In many middle- and low-income countries, the accessibility to renal replacement therapies and the global costs of renal care represent a major health issue.[18]

HYPERTENSION: A CARDIOVASCULAR AND RENAL RISK FACTOR IN THE GENERAL POPULATION

Hypertension is highly prevalent in the adult population (≈30%) and the percentage of subjects presenting with hypertension increases markedly with age.[5,19,20] Numerous epidemiological studies have demonstrated that an elevated BP is not only a risk factor but also a leading cause of several cardiac, cerebral, and vascular complications, such as stroke, coronary heart disease, heart failure, atrial fibrillation, peripheral artery disease, cognitive dysfunction, and dementia.[21–23] Data from observational studies have shown that death from both coronary heart disease and stroke increases exponentially from BP levels as low as 115 mm Hg systolic and 75 mm Hg diastolic upward and the risk is present in all age groups between 40 and >80 years of age.[23,24] Of note, the association of BP with cardiovascular events has been demonstrated whatever the method used to measure BP, for example, office as well as out-of-office BPs, using either 24-hour ambulatory BP recorders or home BP measuring devices.[25]

The association between BP and CKD is more complex because hypertension can be a cause and a consequence of a decrease in kidney function. Several large prospective observational studies in the general population and in treated patients with hypertension have demonstrated that BP is an independent risk factor for kidney outcomes; the higher the BP, the greater the risk of CKD, and ESKD.[26–33] The BP-associated risk of incident CKD appears already in patients with mild to moderate elevations of BP and affects males as well as females.[31,32] In the general population, the presence of albumin in the urine significantly multiplies the deleterious effects of an elevated BP on cardiovascular morbidity and mortality.[34]

Because renal disease itself can raise BP, it is often difficult, if not impossible, to conclude whether the occurrence and progression of CKD is due exclusively to hypertension or rather to the underlying primary renal disease or eventually to the combination of both factors. To clarify this issue, some specific analyses had to be conducted in subjects with no evidence of primary renal disease, for example, subjects with a

normal eGFR and no albuminuria or hematuria.[32] This has been done, for example, within a large cohort of 316 675 adults who received care within the Kaiser Permanente of Northern California.[30] In this setting, CKD subjects with or without hypertension were distributed into six categories according to their level of BP and compared to subjects with a BP <120/80 mm Hg. The adjusted relative risk for developing ESKD increased dose-dependently from 1.62 (95% CI, 1.27–2.07) for BP values of 120 to 129/80 to 84 mm Hg to 4.25 (95% CI, 2.63–6.86) for BP values of 210/120 mm Hg or higher. Using the same database, Sim et al[28] have reported a similar observation but in a cohort of treated patients with hypertension. In this population, a U-shape distribution of the adjusted hazard ratios for mortality and ESKD was observed; both higher and lower treated BPs were associated with a worsened outcome when compared with BP values in the range of 130 to 139 mm Hg systolic and 60 to 79 mm Hg diastolic.[28] A U-shape association between the level of BP and the risk of developing adverse clinical outcomes has also been reported in the KNOW-CKD (Korean Cohort Study for Outcome in Patients With CKD).[35] The clinical determinants of the risk of ESKD were also assessed by combining the use of registries of both a community mass screening and chronic dialysis programs in Japan.[36] Interestingly, in the mass screening setting, positive urine test for albumin or blood, a high diastolic BP, but not systolic BP, and male sex were significant predictors of ESKD.

HYPERTENSION IN CKD: MEASUREMENTS AND CLINICAL PHENOTYPES

Among complications that can occur in the trajectory of patients with CKDs, hypertension is one of the earliest one.[37] Indeed, when eGFR ranges between 60 and 89 mL/(min·1.73m^2), about 30% of subjects with CKD are already hypertensive based on clinic BP, and this percentage increases to >80% when eGFR falls below 30 mL/(min·1.73m^2) and almost 100% in CKD stage 5.[37]

However, with the development of technologies enabling to measure BP reliably out-of-clinic, it became rapidly apparent that office BP measurements frequently misestimate the true BP of patients with hypertension. Thus, the use of 24-hour ambulatory BP monitoring (ABPM) systems or home BP measuring devices has led to the characterization of several new hypertension phenotypes and 24-hour BP patterns. This is the case, for example, of white-coat and masked hypertension, when office and out-of-office BP measurements diverged, or the dipping and nondipping patterns according to the percentage of the BP reduction during nighttime or nighttime hypertension (Figure 1).[38] Moreover, the quality of the BP control under antihypertensive treatment could be integrated resulting in additional phenotypes, such as controlled or uncontrolled masked hypertension.

These phenotypes are particularly relevant in patients with CKD because of their high prevalence, and this is the case mainly for the nondipping status and masked hypertension. The absence of dipping during the night is significantly more prevalent in patients with underlying renal disease than in age-, sex-, and race-matched controls with essential hypertension, that is, 53% versus 30%.[39] In the CRIC Study (Chronic Renal Insufficiency Cohort), an ongoing cohort study that enrolled participants aged 21–74 years with an eGFR between 20 and 70 mL/(min·1.73 m^2), reverse dippers (patients whose BP increases during the night) and nondippers accounted for 54.8% of the 1492 participants with a valid 24-hour ambulatory BP profile.[40] In the AASK (African American Study of Kidney Disease Cohort Study), the nondipping pattern, defined as a decrease in BP during the night of ≤10%, and the reverse dipping were present in as much as 80% of nondialyzed patients.[41] In a large cohort of patients with hypertension in Spain, the nondipper prevalence was 61% in those patients with hypertension with CKD and 43% in those without CKD.[42] In another Spanish cohort, nondipping was associated with female sex, reduced renal function, and previous cardiovascular events, whereas nocturnal hypertension was associated with male sex, smoking, and increased urinary albumin excretion.[43] In patients with CKD on chronic hemodialysis, the nondipping pattern is present in >80% of individuals.[39] In kidney transplant recipients, the prevalence of the nondipping pattern is high but extremely variable ranging between 50% and 95% with an average of 54% (95% CI, 45%–63%) in a recent review and meta-analysis.[44,45] There are several pathophysiological reasons to explain why BP does not decrease during the night in CKD. Among them, one can cite a high activity of the sympathetic nervous system and the hyperactivity of several other neuro-hormonal systems.[46] However, one interesting hypothesis is that patients with a reduced renal function, whatever the cause, need to maintain a high BP throughout the night to remain in sodium balance as part of a pressure-natriuresis mechanism.[46] Thus, in a small group of patients with CKD, Fukuda et al[47] have demonstrated that these patients require a longer duration until BP falls during the night. In addition, the time to dipping was strongly associated with the level of renal dysfunction, the lower the GFR the longer the time until nighttime BP starts to decrease. In many patients with a nondipping pattern, there is an impaired capacity to excrete sodium during daytime that may be due to either a reduced GFR or to a primary increase in tubular sodium reabsorption.[46]

Masked hypertension, defined as a normal BP in the clinic and hypertension out-of-office, is highly prevalent in patients with a reduced kidney function. However, the

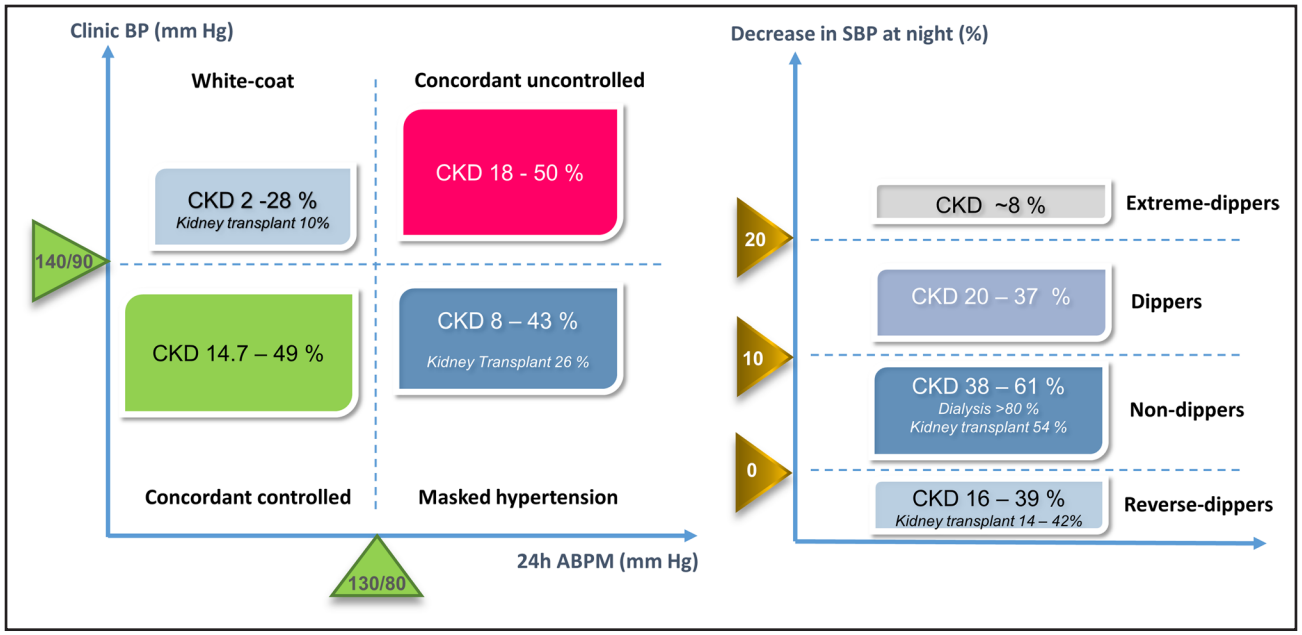

Figure 1. Hypertension phenotypes and 24-hour blood pressure (BP) patterns based on office and out-of-office measurements. ABPM indicates ambulatory BP monitoring; CKD, chronic kidney disease; and SBP, systolic BP. Figure and numbers are adapted from references.[39,40,41,42,44,45,49,50,51,52]

prevalence of masked hypertension can vary substantially depending on whether it is assessed using ambulatory daytime BP only or using both daytime and nighttime BP values.[48,49] In the context of CKD, this is an important methodological aspect because most cases of masked hypertension in CKD are due to an elevated nighttime BP.[41] In a first meta-analysis, Bangash and Agarwal et al[50] reported a low prevalence (8.3%) of masked hypertension in patients with CKD. Later on, in a meta-analysis including studies with patients with normotension as well as patients with hypertension, the prevalence of masked hypertension was estimated at 19%.[51] Analyses that are more recent report significantly higher rates of masked hypertension in CKD. In the CRIC cohort, masked hypertension is present in 28% of participants.[40] In the Chronic Kidney Disease Japan Cohort,[52] the prevalence is 31%, and in the AASK cohort, 43% of patients have masked hypertension when the prevalence is calculated by integrating both daytime and nighttime ambulatory BP.[41] In the Spanish ABPM Registry, 32% of patients with CKD with a controlled office BP had a masked hypertension.[53] In kidney transplant recipients, 2 pooled analyses of 11 and 10 studies have reported an average prevalence of masked hypertension of 26% (95% CI, 19%–33%).[44]

One of the major characteristics of masked hypertension in patients with CKD is that BP is frequently uncontrolled particularly during the night, thus fulfilling the definition of masked uncontrolled hypertension (MUCH).[41,54] In a retrospective analysis of a cohort of patients with non-dialysis CKD and hypertension, 0.8% had isolated daytime MUCH, 63.1% had isolated nighttime MUCH, and 36.1% had day-night MUCH.[54] MUCH has a high prevalence in treated patients with CKD.[40,41,55] In an ancillary ambulatory BP study of SPRINT (Systolic Blood Pressure Intervention Trial), the prevalence of MUCH was 34%, and this percentage was comparable in those patients randomized to intensive versus standard BP targets (office systolic BP <120 versus <140 mm Hg).[56] In SPRINT patients with CKD (n=361), MUCH was present in 30% of patients in the intensive group and in 33% of the standard group.[56]

Apparent resistant hypertension is still another frequent hypertension phenotype in CKD. When compared with people without CKD, the prevalence of resistant hypertension is two-fold higher in patients with CKD and increases as eGFR declines and albuminuria rises.[57] In the Chronic Renal Insufficiency Cohort Study from Germany, the prevalence of apparent treatment resistance, defined as a BP ≥140/90 mm Hg on ≥3 antihypertensive drugs, or the use of ≥4 antihypertensive drugs with BP at goal at baseline visit, was 40.4 %. In addition to a poor adherence to therapy, older age, male sex, Black race, diabetes, and higher body mass index were independently associated with higher odds of having an apparent resistant hypertension.[57,58] In the CRIC cohort, a similar rate was reported[59] and several other studies reported a relatively high prevalence of resistant hypertension in kidney disease patients.[60,61] For the management of patients with an apparent resistance to therapy hypertension, the determination of out-of-office BPs is also crucial as in many cases BP is elevated only in the office because of the white-coat effect thus leading to a pseudo-resistance.

The description of these various hypertension phenotypes emphasizes the importance of an adequate

assessment of BP in general but particularly among patient's populations in which nighttime BP is elevated.[62] This is clearly the case of patients with a reduced kidney function, whatever the cause of CKD, as well as those with type 2 diabetes.[46] Several studies have demonstrated that patients may be misclassified as normotensive or hypertensive when considering only clinic BP.[53,63,64] In the context of CKD, this may have important clinical implications not only to assess the prevalence of hypertension in the population but also to evaluate the impact of hypertension on morbidity and mortality and to guide antihypertensive treatments to provide an optimal cardiovascular and renal protection. For these reasons, the Kidney Disease Improving Global Outcomes Blood Pressure Working group recommends that "… out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP (level of evidence 2B)."[6] This recommendation is strongly supported by both European Society of Cardiology/European Society of Hypertension and American Heart Association/American College of Cardiology hypertension guidelines.[65,66] One could add to the recommendation that physicians managing patients with CKD should always verify that BP is within the normal range during both day and night at diagnosis as well as under treatment to avoid a wrong management.

HYPERTENSION: A CARDIOVASCULAR RISK IN CKD

As mentioned previously, hypertension is a major cardiovascular risk in the general population. When associated with CKD, the impact of hypertension on target organ damages and cardiovascular outcomes increases several folds for many reasons.[13] One of them is the fact that a low eGFR and albuminuria per se are associated with an increased risk of cardiovascular morbidity and mortality independently of traditional risk factors.[67] In addition, patients with CKD often cumulate several other risk factors, such as diabetes, obesity, and dyslipidemia, and finally, CKD-specific risk factors accumulate as kidney diseases worsen. However, the specific phenotypes and the patterns of BP associated with CKD play an important role in increasing the prevalence of cardiovascular complications because they are often under-diagnosed or misdiagnosed resulting in the situation of uncontrolled BP.

Thus, in treated patients with hypertension, nighttime BP is an independent risk factor for new cardiovascular events independently of classic risk factors and after adjustment for clinic BP.[68] In CKD, an elevated nighttime systolic BP (>125 mm Hg) is associated with a two- to four-fold increase in the risk of fatal and nonfatal cardiovascular events and renal death,[69] the risk being higher in men than in women.[70] In another study, target organ damages such as proteinuria or left ventricular hypertrophy were more frequent in patients with CKD with an elevated nighttime BP than in those with a controlled BP in the clinic.[41] At last, in 217 patients with CKD, the nondipping pattern was associated with an increased cardiovascular risk, but not when adjusted for other risk factors.[71]

Regarding masked hypertension, several large observational studies have demonstrated that it is associated with an increased risk of target organ damages in the general population as well as in patients with CKD and that its global cardiovascular risk is comparable to that of patients with untreated hypertension.[40,51,72–76] Thus, independent associations of masked hypertension with a greater left ventricular mass index, an increase in carotid intima-media thickness, and an increase in brachial-ankle pulse wave velocity were reported consistently. Masked hypertension is also associated with a lower eGFR, a higher proteinuria, and a higher risk of CKD.[75] In the analysis of a multicenter prospective cohort study of 489 patients with hypertension with CKD, Minutolo et al[77] investigated the impact of having clinic or 24-hour ambulatory BPs at goal on overall prognosis, including fatal and nonfatal cardiovascular events, dialysis therapy initiation, and all-cause mortality. Cardiovascular events included death and nonfatal cardiovascular events that required hospitalization such as myocardial infarction, congestive heart failure, stroke, revascularization, peripheral vascular disease, and nontraumatic amputations. In this cohort, 15% of patients had masked hypertension. Whenever 24-hour ambulatory BP was not at goal (ie, with a controlled or uncontrolled clinic BP), patients had a bad prognosis for both cardiovascular and renal outcomes, the worst situation being observed when both clinic and 24-hour ambulatory BP were not at goal. In that case, the adjusted risk of the composite cardiovascular outcome and renal outcomes were high with a hazard ratio of 2.83 (95% CI, 1.50–5.34) and 2.96 (95% CI, 1.83–4.78), respectively. The hazard ratios were even higher among patients with masked hypertension with a normal office BP, respectively, 3.17 (95% CI, 1.5–6.7) and 3.9 (95% CI, 1.5–7.9). This increased risk may be due to the fact that physicians treat patients primarily based on office BP. If this latter is normal no treatment is initiated despite patients being hypertensive; hence, patients' cardiovascular risk is very high. More recently, the same investigators have reported the results of a prospective observational cohort of patients with CKD showing once again that the absence of nighttime reductions in BP is associated with worsening of CKD and more frequent cardiovascular events independently of ambulatory BP levels.[78] Similar analyses have been conducted in various groups of patients with CKD suggesting that the assessment of the cardiovascular and renal risk of patients with CKD is better when based on 24-hour ambulatory BP monitoring, which includes nighttime BPs, or home BP rather than office BP.[79,80] In a prospective cohort study

of 588 patients with nondialyzed patients with CKD conducted in China, similar results were observed.[81] As compared to patients with normotension, patients with masked hypertension had an increased risk for total mortality (hazard ratio, 8.88 [95% CI, 1.04–75.59]), renal events (hazard ratio, 3.70 [95% CI, 1.23–11.12]), and major adverse cardiac and cerebrovascular events (hazard ratio, 8.66 [95% CI, 1.09–68.79]).

Taken together, these figures confirm that hypertension is a strong cardiovascular risk in patients with a reduced kidney function. Hypertension contributes greatly to the development of cardiac, cerebral, and vascular complications and hence to the high cardiovascular mortality of the CKD population. They also emphasize the need to consider not only office BP but also the 24-hour profile of BP (using validated devices) to avoid an insufficient management.

HYPERTENSION MANAGEMENT IN CKD

An optimal control of BP is essential to prevent the occurrence of cardiovascular events and to delay the progressive decline of kidney function towards ESKD. Unfortunately, observational studies have repeatedly demonstrated that the quality of BP control remains largely insufficient worldwide with a control rate ranging between 30% and 65%, depending on the chosen BP target (BP <140/90 or <130/80 or <120/80 mm Hg).[82–88] Of note, as CKD progresses to more advanced stages, more patients become poorly controlled.[82] Today, one of the main controversial issue is the definition of the target BP to be achieved. Some national and international societies, such as the American College of Cardiology and the American Heart Association or the European Society of Hypertension, do not take into consideration the presence or the absence of proteinuria and recommend a BP target <130/80 mm Hg in the United States[65] and in the range of 130 to 139 mm Hg in Europe, although in some situations of secondary prevention, a lower target may be recommended.[66] In the United Kingdom, the 2021 NICE (National Institute for Clinical Excellence) guidelines recommend a BP target <140/90 in patients with CKD with a urinary albumin/creatinine ratio <70 mg/mmol and <130/80 mm Hg only in the presence of an albumin/creatinine ratio ≥70 (https://www.nice.org.uk/guidance). The most recent debate came with the publication of Kidney Disease Improving Global Outcomes Blood Pressure Working group 2021 recommendations proposing to target a systolic BP <120 mm Hg for all patients with CKD, provided BP is measured as in the SPRINT trial, that is, unattended automatic office BP. Unfortunately, this method is far to be common and is most of the time not applied in clinical practice.[6] In addition, this recommendation is criticized because the SPRINT trial enrolled very few stage 4 and 5 patients with CKD, and lowering BP <120 mm Hg may involve a risk of aggravation of renal function. Thus, adopting this threshold for all patients with CKD seems to be quite uncertain in term of benefits outweighing the harms and less feasible considering that <30% of patients with hypertension achieve the <130/80 mm Hg in the real life. More recently, in the STEP trial (Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients Trial),[89] a randomized control trial, which enrolled 8511 patients aged 60 to 80 years with a high BP and a high cardiovascular risk, lowering BP to a mean of 127 mm Hg or 135 mm Hg did not modify the rate of eGFR decline or the number of patients reaching an eGFR <30 mL/(min·1.73m^2). Therefore, as suggested in a recent review, targeting 130/80 mm Hg appears to be a reasonable option supported by the results of randomized controlled trials and meta-analyses.[90,91]

Regarding the management of BP in patients with CKD, no major changes have occurred until recent years. The treatment strategy is always based on the implementation of lifestyle changes, mainly a reduction in sodium intake and an increase in potassium intake in early CKD stages. As far as drug therapy is concerned, the prescription of blockers of the renin-angiotensin system (RAS) remains as a first-line choice because of their ability to reduce both BP and albuminuria and to delay CKD progression, as demonstrated in randomized controlled trials.[65,66,92] In addition to RAS blockers, guidelines also recommend the use of calcium antagonists and diuretics preferentially as dual or triple single-pill combinations with RAS blockers.[66] However, in the last couple of years, several interesting new observations and approaches to treat hypertension in patients with CKD and to reduce the risk of cardiovascular events and kidney disease progression in this population were published. The first observation published by Agarwal et al[93] addressed the use of thiazide diuretics in patients with advanced CKD and a poorly controlled BP. In contrast to general recommendations, authors demonstrated in a randomized placebo-controlled study that chlorthalidone effectively lowers BP in patients with stage 4 CKD reducing 24-hour ambulatory systolic BP from baseline to 12 weeks by −11.0 mm Hg (95% CI, −13.9 to −8.1) versus −0.5 mm Hg (95% CI, −3.5 to 2.5) in the placebo group. Whether these effects are specific to chlorthalidone and could be obtained with other thiazide diuretics remains to be demonstrated. However, earlier studies have shown a comparable effect of furosemide and hydrochlorothiazide on BP and urinary sodium excretion in patients with hypertension with CKD stage 4 and 5[94] and comparable effects of torasemide and butizide on renal electrolyte excretion in patients with advanced CKD.[95]

Regarding the use of beta-blockers, their indications in CKD are majorly limited to heart failure, arrhythmia, coronary heart disease, comorbidities that are often present in patients with CKD.[96] Nevertheless, when considering the upregulation of sympathetic nervous system in CKD, associated with an increased risk of cardiovascular events and renal disease progression,[97] there is still a

rationale for their use. Whether beta-blockers are more effective in reducing cardiovascular events in patients with CKD needs further head-to-head studies. Of note, when considering the evidence of increased adverse cardiovascular outcomes in hypertensives with abnormal circadian BP variation and morning BP surge, frequently met in CKD population, evening dosing of antihypertensive medication seems logical. The concept was developed by Hermida et al[98,99] showing that administration of some antihypertensive medications in the evening induces a significant reduction in cardiovascular events in hypertension, including patients with CKD. However, the publication of most recent results[99] with >19 000 patients enrolled, was heavily criticized for several important methodological reasons.[100] Therefore, the World Hypertension League and the European Society of Hypertension do not support this general approach, although in some specific situations, it might be useful to ascertain a good control of BP during the night.[101,102] Besides, the recently published results of the TIME study (Treatment In Morning versus Evening Study), which however included a minor proportion of patients with CKD (3.1% [n=327] in the evening dose group versus 3.3% [n=355] in the morning dose group), do not support benefits on major cardiovascular outcomes for the evening dosing.[103] Other prospective, randomized controlled outcome trials will further elucidate the efficacy of chronotherapy in hypertensives including patients with impaired renal function.[104]

The second important development concerns another subgroup of diuretics, that is, mineralocorticoid receptor antagonists with the recent publication of the results of 2 major randomized placebo-controlled trials (FIDELIO-DKD and FIGARO-DKD [Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease]) assessing the impact of finerenone, a new highly selective nonsteroidal aldosterone antagonist, on cardiovascular and renal events in patients with diabetic nephropathy.[105–107] The pre-specified patient-level analysis named FIDELITY (The FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis) pooled data from these 2 trials.[108,109] Studies enrolled patients with a urine albumin-to-creatinine ratio of 30 to 5000 mg/g and an eGFR of ≥25 mL/(min·1.73m^2) and under optimal RAS blockade. The primary endpoints were the occurrence of cardiovascular events, a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure, and the progression of the diabetic nephropathy defined as a composite of a sustained ≥57% decrease in eGFR from baseline over ≥4 weeks or renal death. The results of FIGARO and FIDELIO and the pooled analysis have demonstrated that finerenone effectively reduces cardiovascular events by 14% (P=0.0018) and renal endpoints by 23% (P=0.0002).[108] Finerenone also improved heart failure outcomes irrespective of baseline eGFR or UACR categories, thus confirming the role of aldosterone antagonists in the management of heart failure.[110] The incidence of hyperkalemia was more frequent in the finerenone group, although it remained relatively low. Treatment discontinuation due to hyperkalemia occurred more frequently with finerenone than with placebo (2.4% versus 0.8%) and was, as expected, more common in patients with an eGFR <60 mL/(min·1.73m^2).[109]

In these trials, the precise role of a finerenone-induced reduction of BP is not clear. Indeed, results from the FIDELITY analysis in relation to kidney outcomes showed that BP was relatively well controlled at baseline with a mean BP below 140/80 mm Hg and that the mean change in systolic BP at 44 months was modest, respectively, −2.8 mm Hg in the finerenone group and −0.08 mm Hg in the placebo group. Although the contribution of finerenone-induced BP changes was considered to be small,[111] there was a BP-lowering effect if patients were hypertensive. Moreover, throughout the trial, the prevalence of treatment-resistant hypertension defined as an office BP ≥140/90 mm Hg and taking ≈3 antihypertensives (including a diuretic) was lower in the finerenone group and more patients achieved the target office BP when receiving finerenone.[111] However, in the ARTS-DN study (The MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy), a phase-2b study designed to compare the efficacy and safety of different doses of finerenone and placebo in patients with type 2 diabetes and CKD, the placebo-corrected mean difference in systolic BP from baseline to day 90 was −4.7 (95% CI, −8.2 to −1.3) mm Hg in the finerenone 20 mg/d group.[112] In a subset of this study, 24-hour ABPM was performed to assess daytime as well as nighttime BP changes induced by finerenone.[113] In a post-hoc analysis of this subset of patients, 52.2% had masked uncontrolled hypertension (n=60/115) and 76.5% (n=88/115) had nocturnal hypertension. In patients with nocturnal hypertension, finerenone lowered nighttime by 9 mm Hg at the dose of 10 mg and by 12 mm Hg at the dose of 20 mg. Of note, despite its short duration of action, finerenone reduced BP over 24 hours when given in the morning. These results obtained on a small number of patients would suggest that finerenone might potentially have induced a greater reduction of BP than that measured in the office in FIDELIO and FIGARO. Unfortunately, no 24-hour ambulatory BP data are available so far for these 2 large trials.

The third major development in the management of patients with CKD is undoubtedly that of inhibitors of the SGLT2 (sodium-glucose cotransporter-2). Since 2015, several very large randomized placebo-controlled trials have demonstrated the favorable impact of SGLT2 inhibitors on cardiovascular and renal outcomes. The first trials were performed in patients with type 2 diabetes[114–119] but thereafter several trials were done in patients with heart failure[120–122] and nondiabetic nephropathies.[123–127] Several

meta-analysis of these trials have been published.[128,129] However, in terms of kidney endpoints the most relevant is probably the most recent one published by the Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium.[130] Indeed, authors have centered their meta-analysis on kidney disease progression (defined as a sustained ≥ 50% decrease in eGFR, a sustained low eGFR, ESKD, or death from kidney failure), acute kidney injury, and a composite of cardiovascular death or hospitalization for heart failure. The analysis included 13 trials with >90 000 patients with or without diabetes as well as patients with heart failure and CKD patients with diabetic and nondiabetic kidney diseases. Not surprisingly, authors globally confirmed that, compared to placebo, being on an SGLT2 inhibitor reduces the risk of CKD progression by 37% and this irrespective of the presence or absence of diabetes. In patients on an SGLT2 inhibitor, the risk of cardiovascular death was lowered by 14% (RR, 0.86 [0.81–0.92]), but the risk of a noncardiovascular death remained unchanged (RR, 0.94 [0.88–1.02]). In the 4 CKD trials, the risk of dying from cardiovascular events or being hospitalized for heart failure[123] was reduced by 23% (0.77 [0.74–0.81]) by SGLT2 irrespective of the cause of CKD. SGLT2 inhibitors were safe and were not associated with an increase in acute kidney injury. Indeed, the risk of acute kidney injury was reduced by 23% (0.77 [0.70–0.84]), and the effect was comparable in patients with and without diabetes. This latter finding was recently confirmed in a pre-specified analysis of DAPA-CKD (Dapagliflozin And Prevention of Adverse Outcomes in CKD).[131] Investigations in patients with nondiabetic nephropathies have now suggested that SGLT2 inhibition may have a favorable impact in patients with IgA nephropathy and patients with focal segmental glomerulosclerosis.[123,127] What is the role of BP changes induced by SGLT2 inhibitors on these impressive improvements in renal endpoints and cardiovascular morbidity and mortality?

SGLT2 inhibitors inhibit the reabsorption of glucose in the renal proximal tubule thereby producing a sustained glycosuria associated with significant increases in urinary sodium, water, and uric excretion due to the osmotic diuresis provoked by these compounds. The drug-induced natriuresis is likely the main mechanism whereby SGLT2 inhibitors actually lower BP. However, other mechanisms than the osmotic diuresis might contribute to the cardiac protection induced by SGLT2 inhibitors, such as an increase in ketone production.[132] In patients with a lower eGFR, who has a very modest glucosuric response to SGLT2 inhibitor, a reduction of sympathetic activity is likely one of the main mechanism whereby these drugs lower BP.[133] Thus, in a meta-analysis of 6 randomized, double-blind, placebo-controlled trials, which assessed the effects of SGLT2 inhibitors on out-of-office BP, 24-hour ambulatory systolic and diastolic BP were lowered significantly by −3.76 mm Hg (95% CI, −4.23 to −2.34) and −1.83 mm Hg (95% CI, −2.35 to −1.31; I^2=0.76) respectively.[134] Nighttime systolic BP was lowered significantly by −2.61 mm Hg when compared with placebo (95% CI, −3.08 to −2.14). These results were confirmed in an even larger systematic review and meta-analysis in which the effects of SGLT2 inhibitors on office and ambulatory BP were assessed in both patients with and without diabetes.[135] Based on 24-hour ambulatory systolic BP, the mean BP reduction induced by SGLT2 inhibitors was −4.39 mm Hg (95% CI, −5.4 to −3.3) during daytime and −2.41 mm Hg (95% CI, −3.3 to −1.5 mm Hg) during the night. In their analysis, Mancia et al[136] studied the changes in ambulatory BP induced by empagliflozin from baseline to week 12 in patients receiving 0, 1, or ≥2 antihypertensive medications as well as in patients receiving diuretics or RAS blockers. The reductions of 24-hour ambulatory BP induced by empagliflozin were of similar magnitude than reported in the above-mentioned meta-analyses. Interestingly, however, the effect of empagliflozin was not different between subgroups by number of concomitant antihypertensive agents. Moreover, empagliflozin lowered BP irrespective of the use of diuretics or ACE inhibitors or angiotensin receptor blockers. In fact, in a small randomized, placebo-controlled double-blind study, Lytvyn et al[137] have reported an additive effect of empagliflozin when associated with the ACE inhibitor ramipril in terms of changes in glomerular hyperfiltration and also in terms of BP reductions. Thus, the association of empagliflozin and ramipril resulted in an additional 4 mm Hg reduction in clinic systolic BP (P=0.0112) and 3 mm Hg reduction in diastolic BP (P=0.0032). However, no difference in BP were found using 24-hour ambulatory BP monitoring.

Few studies have assessed whether the SGLT2-induced reductions of BP contributed to their renal and cardiac benefits, and surprisingly, the improvement in cardiac and renal outcomes appeared to occur independently of the on-trial BP and of the early drop in systolic BP, suggesting a BP-independent effect of SGLT2 inhibitors on cardiovascular and heart failure events.[115,119] Nevertheless, in the absence of more reliable measurements of BP, such as out-of-office measurements, the genuine contribution of changes in BP to the renal and cardiovascular risk reduction remains to be studied in more details. However, as far as renal endpoints are concerned, the ability of SGLT2 inhibitors to decrease intraglomerular hyperfiltration is certainly playing a very important role and in this context, any decrease in systemic BP contributes to protect kidney function. Figure 2 summarizes the multiple potential mechanisms involved in the cardiac and renal protection afforded by SGLT2 inhibitors.

In patients with type 2 diabetes, additional new antidiabetic agents are in development, which may have a favorable effect on cardiovascular morbidity and on renal disease progression. This is the case of tirzepatide, a dual GIP (gastric inhibitory peptide) and GLP-1 (glucagon-like

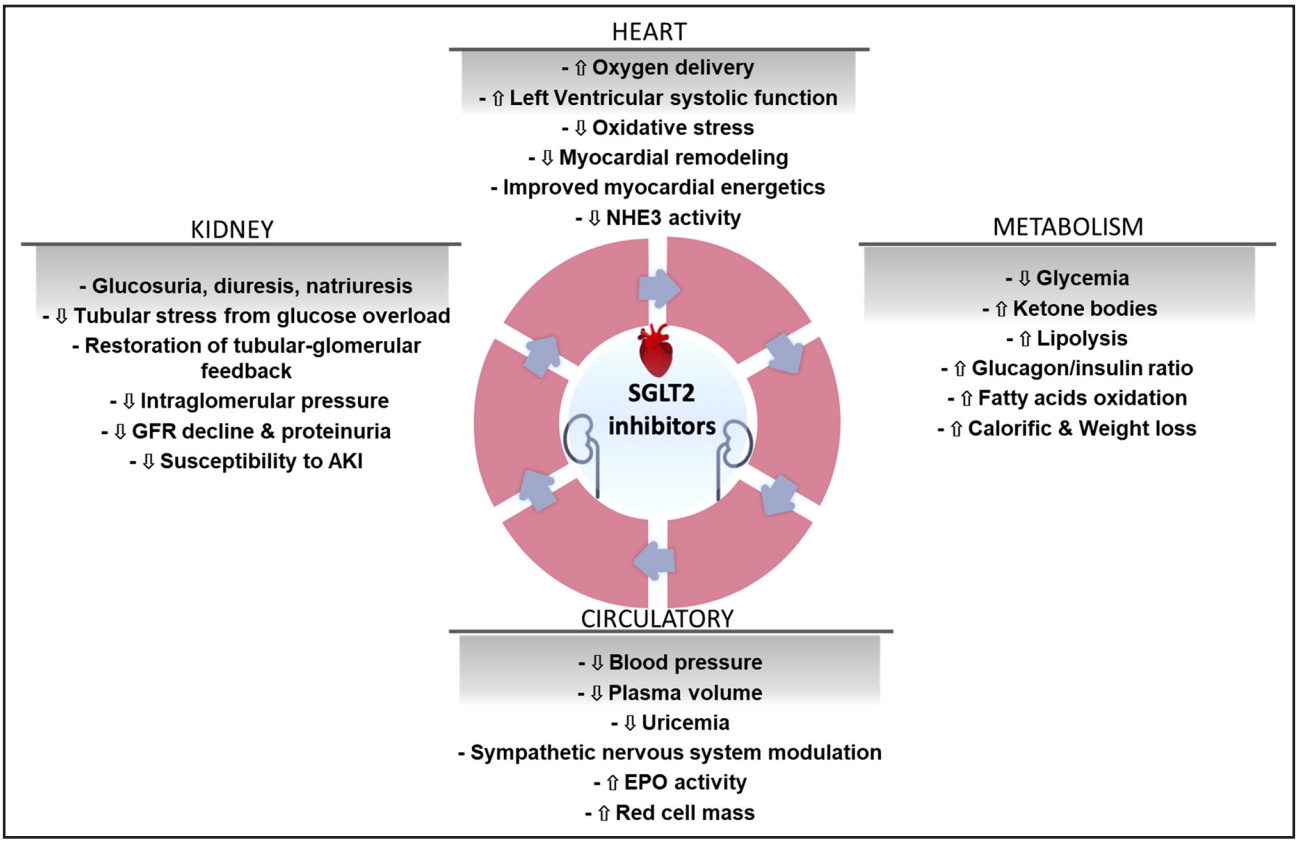

Figure 2. Multiple potential mechanisms and protective effects of SGLT2 (sodium-glucose cotransporter-2) inhibitors on cardiac and renal function.

AKI indicates acute kidney injury; EPO, erythropoietin; GFR, glomerular filtration rate; and NHE3, sodium-hydrogen exchanger 3.

peptide-1) receptor agonist. Indeed, when compared with insulin glargine, tirzepatide lowered significantly the renal risk of diabetic patients and slightly reduced the incidence of cardiovascular events.[138,139] At 52 weeks, mean systolic (−2·8 to −4·8 mm Hg) and diastolic (−0·8 to −1·0 mm Hg) BP decreased with tirzepatide and increased with insulin glargine (systolic 1·3 mm Hg increase and diastolic 0·7 mm Hg increase). In patients with obesity, recent data suggested that tirzepatide significantly lowers 24-hour ambulatory BP at lower doses.[140]

Finally, despite the effective BP-lowering agents that halt the harmful effects of Ang II (angiotensin) and aldosterone release (RAS blockers, new nonsteroidal mineralocorticoid receptor antagonists), in some cases, the inhibition of these neuro-humoral pathways is still insufficient. This gap has been the driving force of hypertension research agenda to explore alternative therapeutic approaches and to improve the effectiveness of current drugs. Therefore, several preclinical and clinical studies in different stages are ongoing and aim to test novel agents like ACE2/Ang (1–7)/MasR axis activators,[141] endothelin antagonists,[142,143] aldosterone-synthase inhibitors,[144] dual inhibitors of neprilysin, soluble guanyl cyclase A stimulators, dual activating bispecific peptides (ie, peptides, which mimic the action of an endogenous peptide, acting on 2 separate signaling pathways), antioxidants, and aminopeptidase inhibitors.[141] In the future, these prominent therapies might prove to be safe and efficient not only for lowering BP but also for preventing target end-organ damage, especially for patients with high cardiovascular burden like patients with CKD.

CONCLUSIONS

Hypertension is a major cardiovascular risk factor in the general population but even more so in patients with CKD, who cumulate several other risk factors including the reduced kidney function. patients with CKD are characterized by several specific BP profiles and hypertension phenotypes that deserve to be diagnosed accurately to avoid misdiagnoses. To this purpose, out-of-office BP measurements that include also the nighttime period are now strongly recommended and should be used more widely to verify that BP is under control during the day as well as during the night. Today, a high percentage of patients with CKD have a poorly controlled BP, mainly because nighttime BP is elevated. Therefore, they remain at very high risk of developing cardiovascular complications and worsening their kidney function. However, the future may seem more optimistic with the development of new therapeutic strategies. During the last 5 to 10 years, an impressive number of

large randomized controlled trials have been conducted in patients with nephropathies and a high cardiovascular risk, including numbers of patients, which had never been reached before. These trials have demonstrated the remarkable efficacy and safety of new therapeutic approaches, such as SGLT2 inhibition or aldosterone receptor blockade, to prevent major cardiovascular endpoints and to delay kidney disease progression in patients with diabetic and nondiabetic nephropathies. There is, therefore, a great hope that one might be able to improve significantly the cardiovascular and renal prognosis of patients with CKD.

ARTICLE INFORMATION

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