Hypertension in Kidney Transplantation: a consensus statement of the "Hypertension and the Kidney" working group of the European Society of Hypertension (ESH).

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Abstract

Hypertension is common in kidney transplantation recipients and may be difficult to treat. Factors present before kidney transplantation, related to the transplantation procedure itself and factors developing after transplantation may contribute to blood pressure elevation in kidney transplant recipients. The present consensus is based on the result 3 recent systematic reviews, the latest guidelines and the current literature. The current transplant guidelines, which recommend only office blood pressure assessments for risk stratification in kidney transplant patients should be reconsidered, given the presence of white-coat hypertension and masked hypertension in this population and the better prediction of adverse outcomes by 24-hr ambulatory blood pressure monitoring as indicated in recent systematic reviews. Hypertension is associated with adverse kidney and cardiovascular outcomes and decreased survival in kidney transplant recipients. Current evidence suggests calcium channel blockers could be the preferred first-step antihypertensive agents in kidney transplant patients, as they improve graft function and reduce graft loss, while no clear benefit is documented for RAS inhibitor use over conventional treatment in the current literature. Randomized control trials demonstrating the clinical benefits of blood pressure lowering on kidney and major cardiovascular events and recording patient-related outcomes are still needed. These trials should define optimal blood pressure targets for kidney transplant recipients. In the absence of kidney transplant-specific evidence, blood pressure targets in kidney transplant recipients should be similar to those in the wider CKD population.

Key words: hypertension, blood pressure, kidney transplantation, treatment, targets, consensus.

Hypertension is probably one of the most common problems in kidney transplantation. It is widely acknowledged that hypertension is a risk for cardiovascular and cerebrovascular complication, and is associated with reduced graft and patient survival. However, hypertension is often overlooked and neglected by clinicians, presumably caused by the multi-complexity of the kidney transplant recipient's condition, and many blood pressure-related issues remained unresolved (1).

Blood pressure measurement

Hypertension is highly prevalent after kidney transplantation and it is a potentially modifiable risk factor. However, very few efforts have been made thus far to improve the diagnosis of hypertension by assessing blood pressure (BP) by means other than the traditional office BP readings. In contrast, considerable efforts have been made in the general population and other categories of high-risk patients (2, 3), including patients with pre-dialysis CKD or patients on hemodialysis, to enhance the use of 24h ambulatory BP monitoring (ABPM) or home BP readings by automatic BP devices for hypertension diagnosis and risk stratification. Improving the diagnosis of hypertension in kidney transplant patients would consequentially imply a better therapeutic approach, which could have beneficial effects on hard outcomes.

The guidelines from the National Institute for Health and Clinical Excellence (NICE) recommend that all individuals with BP>140/90 mm Hg or higher during a visit in the office, should undergo ABPM, following a cost-effective evaluation of ABPM use for the diagnosis of uncomplicated hypertension (4, 5). The European Society of Hypertension guidelines emphasized the need for more extensive use of home BP and 24-hour BP measurements in hypertensive patients (2). More recently, the US Preventive Services Task Force has issued a recommendation supporting ABPM (6).

All the above considerations are not extended to kidney transplant patients. In fact, the only guidelines which take into consideration the issue of BP measurements in kidney transplantation are the 2017 American College of Cardiologists/American Heart Association (ACC/AHA) recommendations (7). In these guidelines, kidney transplantation is mentioned as a special comorbidity, which may affect clinical decision-making in hypertension. In this recommendation, there was no specific indications about the use of home BP or ABPM. The recent KDIGO indicated that BP should be measured in a standardized fashion; however it was not stated whether BP measurement should be attended or unattended. Out-of-office BP measurements were only recommended as a complement of standardized BP readings (8). However, several lines of evidence support the use of out-of-office BP measurements in kidney transplant patients. For instance, office and out-of-the-office BP measurements were compared in 260 kidney transplant recipients followed up for 3.9 years (9). Overall, 25% of outpatient visits were associated with inadequate BP control using office BP measurement but not 24h-ABPM ("white-coat hypertension") whereas the opposite was found in 12% of outpatient visits ("masked hypertension"): finally, office BP measurement could lead to inappropriate therapeutic decisions in 37% of outpatient visits (9). Out-of-the-office BP measurement could thus avoid inadequate therapeutic decisions in kidney transplant recipients. Moreover, home BP and 24-hr BP measurement are better associated with atherosclerotic complications and hypertension-related target-organ damage than office BP. In a comprehensive survey conducted among 170 kidney transplant patients with a functioning graft, the average systolic 24h ABPM was directly associated to intima-media thickness (IMT), while office BP was not (10). A further analysis assessed night-time BP phenotype using the same cohort and indicated that 36% of these patients were non-dippers, using the night-day systolic BP ratio, which depends less on BP level than the nocturnal BP fall. Furthermore, a direct association between night-day systolic BP ratio and IMT was

documented. The association between BP and IMT was less robust using 24-hour average SBP (10). In another recent study in 221 kidney transplant recipients (of whom 142 had echocardiographic results), 33% had masked hypertension and 32% had LVH, and masked or sustained hypertension were independent predictors for LVH (11). Another study in 113 kidney transplant recipients found masked hypertension at 39% of the population (12). These associations suggest that night-time BP and non-dipping may be hidden (i.e. undetected by conventional BP measurements) markers of the BP burden in this population and support the hypothesis that targeting nocturnal hypertension may reduce the high risk for CV events in kidney transplant patients. An additional important point, which should prompt the use of ABPM in kidney transplant patients, is the fact that night-time systolic BP was the best predictor of kidney function deterioration over time (13). This loss of nocturnal dipping is associated with future lower glomerular filtration rate (GFR) and increased risk of allograft loss (14).

The most recent systematic review confirmed that altered circadian BP profile and nocturnal hypertension are frequent in the transplant population (15). Moreover, the use of ABPM in kidney transplant recipients indicated a great proportion of both masked hypertension and white-coat hypertension (15).

BP and target-organ damage

Albuminuria and proteinuria are risk factors for subsequent kidney function deterioration and ultimately graft loss, and are associated with BP control. Ducloux et al showed that hypertension at 1 year after transplantation was associated with urinary protein excretion (RR, 1.84, 95% CI, 1.06 to 3.18) (16). Kidney transplant recipients with microalbuminuria had higher systolic BP than patients normoalbuminuria (17). The associations between elevated BP and albuminuria/proteinuria were found in other studies (18, 19). Furthermore,

observational studies in kidney transplant recipients suggest associations of high BP levels with endothelial dysfunction and increased pulse wave velocity, a direct measure of arterial stiffness (20).

Du Cailar et al showed that hypertension was associated with left ventricular hypertrophy (LVH) in 165 kidney transplant recipients, and that BP reduction resulted in a reduction of LVH in this population (21). Interestingly, high sodium intake blunted the reduction of LVH despite the improved BP control (21). Riggato et al. indicated that left ventricular mass regressed from 161 g/m^2 at 1 year to 146 g/m^2 during the first 2 years after kidney transplantation in 143 patients with LVH (22). However, failure of LVH to regress was observed in many patients and was associated with persistent hypertension (22). Of note, high pulse pressure was particularly associated with the lack of LVH regression (22). In children, LVH can also regress after kidney transplantation, and BP value is correlated with LV mass (23).

A recent systematic review and meta-analysis in 22 studies (2078 patients) confirmed that ABPM correlated better than office BP with left ventricular mass index intima-media thickness and endothelial dysfunction, and was also a stronger predictor of renal function decline (24). In addition, altered circadian BP profile predicted renal and cardiovascular damages (24).

Impact of hypertension on renal and cardiovascular risk

Before the calcineurin-inhibitors' (CNI) era, the prevalence of hypertension in kidney transplantation ranged between 50 and 60% after the first year of transplantation (25). After the use of this drug class, the incidence of hypertension increased markedly to reach 60% to 90% of kidney transplant recipients 3 to 5 years after transplantation (26, 27). Epidemiological studies have identified several determinants of hypertension including pre-

transplant hypertension, age of the donor, male sex, obesity, and African-American ethnicity, but also delayed graft function, use of CNI and glucocorticoids, recurrent disease, acute rejection, and post-transplant proteinuria (28).

Post-transplant hypertension is associated with lower graft and patient survival. Indeed, an analysis of BP data of 24,404 patients included in the Collaborative Transplant Study has shown that the higher the BP the higher the risk of graft failure (29, 30). Even after censoring the data for death, hypertension remained a major independent risk factor for graft failure. In this large patient population, the best graft survival was observed in patients with a systolic BP below 140 mmHg. However, in this analysis, no information was available on the possible more favorable impact on graft survival of lower target values. In an earlier analysis of the same study patients with a systolic BP <120 mmHg had the best graft survival (29). Of note, hypertension at 3 months and 1 year was not found to be related to graft survival in one study (26). However, tthe association of hypertension with shorter graft survival was observed in most studies (24, 31-35), including studies in pediatric kidney transplantation (36).

Hypertension is also associated with the risk for cardiovascular events and death (24). Kidney transplant recipients admitted for myocardial infarction were more frequently hypertensives than non-transplanted patients in a recent study (37). In another study, each 10-mmHg increment of systolic BP >140 mmHg was associated with a hazard ratio of death of 1.18 (95% CI, 1.12 to 1.23), and this risk persisted after adjusting for allograft function (31). Kidney transplant patients thus constitute a high cardiovascular risk population, and accumulates several cardiovascular risk factors that might affect patient survival (38). In observational studies and analyses of large databases, post-transplantation hypertension was also associated with a reduced survival of kidney transplant patients even in children (29, 31, 35, 39).

Using ambulatory BP monitoring, the prevalence of uncontrolled hypertension was 64% of patients (40) but the prevalence of resistant hypertension (using office BP and the 140/90 mmHg cut-off value definition) 6.8% (41). The rate of BP control in kidney transplantation ranged around 50% (42). In a more recent study using ABPM in hypertensive cadaveric kidney-transplant recipients aged below 70 years, with functioning kidney for at least 1 year, the prevalence of true resistant hypertension was 18.9 %; patients with resistant hypertension were older, more often men, had a worse cardiovascular risk profile, worse graft function and higher percentage of treatment with steroids (43). It must be emphasized that adherence to medication has been explored for anti-rejection treatments but not for antihypertensive medications (44, 45): it does not seem to be a preoccupation for physicians although kidney transplant recipients tend to prioritise anti-rejection treatments over antihypertensive medications (46).

Pathophysiology of hypertension in kidney transplantation

Parameters that affect cardiac output, total peripheral vascular resistance or both in kidney transplant recipients may contribute to hypertension development at the various stages after kidney transplantation (Table 1) (47, 48). They can be divided in three groups: 1) factors present before kidney transplantation; 2) factors related to the transplantation procedure itself; and 3) factors developing after the transplantation (Table 1).

Extracellular fluid expansion

Hypertension occurring in the peri-operative period often relates to volume overload. As a result of kidney failure, extracellular fluid volume is often expanded on the moment of transplantation. In addition, peri-operative intravenous fluids and delayed graft function after transplantation contribute to volume overload, while acute rejection at any stage after

transplantation is characterized by reduced sodium excretion (49, 50). Low nephron numbers of the graft as well as impaired graft function developing during long-term follow-up, due to chronic allograft nephropathy, or ongoing rejection, may also contribute to increased sodium reabsorption and thus to (salt-sensitive) hypertension (51). Thrombotic microangiopathy (as part of humoral rejection) induce activation of the RAAS, and may lead to increased BP (47). Immunosuppressant therapy may also affect the extracellular fluid volume with consequences for BP. Glucocorticoids cause hypertension by increasing kidney sodium reabsorption, through various mechanisms, including weight gain (52). CNI also promote hypertension due to increased sodium retention (52-54). Indeed, it has been demonstrated that CNI induce the activation the furosemide sensitive Na-K-2Cl cotransporter type 2 (NKCC2) at the thick ascending limb and the thiazide-sensitive Na-Cl cotransporter (NCC) at the distal convoluted tubule (53, 55). Finally, weight gain in the post-transplantation period is associated with high BP due to RAAS activation, increased SNA and subsequent sodium retention and extra-cellular fluid expansion (56).

Increased sympathetic nerve activity

Kidney failure, as caused by the original kidney disease, is associated with a rise in sympathetic nerve activity (SNA), manifested already in early stages of CKD and directly associated with disease severity (57). As kidney allografts are surgically denervated at the time of transplantation, only increased SNA originating from the native kidneys might affect BP (51). Bilateral nephrectomy does indeed decrease SNA and has been previously described as last resort to control BP in ESKD patients, including kidney transplant recipients (57). Reinnervation takes place over time after transplantation and is a continuous process, which may potentially contribute to progression of hypertension in later stages after transplantation (58). In a recent study, nerve sprouting was found at 5 months following transplantation and

was associated with hypertensive arteriolar damage; regeneration of periadventitial nerves was complete 2 years after transplantation (59). Future studies will have to assess whether renal denervation could be valuable to tackle hypertension in this population. Immunosuppressive medications may affect SNA, but this seems to be limited to CNI. Specifically, sympathetic overactivity related to ciclosporin overexposure has been shown to cause an acute hypertensive response (60).

Peripheral vascular resistance

Increased SNA, originating from the native kidneys or induced after reinnervation of the kidney transplant in a later stage, or also induced by CNI, may be responsible for higher PVR after transplantation. This response is predominantly mediated by alpha-1 receptors. Increased RAAS activation, particularly via its effector peptide angiotensin II, elicits an increase in vascular tone of resistance vessels and contributes to hypertension. Furthermore, SNA and RAAS activation, graft failure and rejection induce sodium retention and increase PVR, beyond their effects on extracellular fluid volume (61). Finally, added to their effects on SNA and RAAS, CNI cause vasoconstriction via endothelin-1, thromboxane A2, and reduced production of vasodilator compounds, such as nitric oxide and prostacyclin (47, 62, 63). This vasoconstriction observed with CNI, together with increased sodium reabsorption may also affect the nychthemeral rhythm, with less dipping of BP and increased night-time BP (64).

Isolated systolic hypertension due to arterial stiffness

Increased arterial stiffness leads to early return of reflected waves from periphery with deleterious leading to elevated systolic BP and pulse pressure, and decrease diastolic BP (65-67). Several observational studies have clearly shown that PWV greatly improves over the first months following kidney transplantation. (66, 68, 69) Despite this short-term

improvement, arterial stiffness in kidney transplant patients remains much higher than that in healthy individuals and further deteriorates over long-term follow-up following renal function decrease, contributing to increased systolic BP, abnormal dipping pattern and other unfavorable features (70, 71).

Renal artery stenosis

Renal artery stenosis is found in 1-7% kidney transplant recipients, usually within the first 12 months after transplantation (72, 73). Causes of renal artery stenosis are usually different from those observed in patients with native kidney renal artery stenosis (74). Vascular damage at the vicinity of the anastomosis between the donor renal artery and recipient artery is the usual cause. Stenosis of the iliac or hypogastric arteries upstream of the transplant renal artery is less frequent. The implication of CMV infection and renal ischemia-reperfusion injury have been debated (72, 73). Most importantly, several lines of evidence suggest that immunological factors may increase the risk transplant renal artery stenosis, including the association with acute rejection, diffuse renal artery stenosis (which suggests immune-mediated vascular endothelial injury) (75) and association with de novo class II donor specific antibodies (76).

Blood pressure target in kidney transplantation

Being a kidney transplant recipient is a diagnostic criterion for CKD according to KDIGO (77). Thus, unless otherwise specified, it would be expected that BP targets for CKD patients should apply to kidney transplant recipients. However, guideline developers have occasionally chosen to focus of different CKD definitions based on estimated GFR (eGFR) and/or albuminuria levels, without discussing whether the specific situation of kidney transplant recipients (Tables 2 and 3). As recently pointed out, current guidelines regarding

BP targets in patients with CKD are heterogenous (78) and derive from a reduced number of studies (79, 80). Several guidelines presently exist but they propose different BP thresholds in patients with CKD, and they do not provide information on specific goals in kidney transplantation (81-85). According to the ESH guidelines, «BP should be lowered to <140/90 mmHg and towards 130/80 mmHg in patients with CKD» but no BP goal was discussed for kidney transplant recipients. In contrast, according to the KDIGO 2012, KDIGO 2021 and AHA/ACC 2017 guidelines, office BP target should be <130/80 mmHg in kidney transplantation (8, 81-85). A lower BP goal (<120 mmHg for SBP) based on the secondary analysis from the SPRINT trial showing reduced mortality in patients with CKD may meet heavy criticism (86); it is important to note that BP measurement was unattended in this study.

Therapeutic options

First-line antihypertensive classes for the treatment of patients with CKD and hypertension include angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), accompanied by diuretics (thiazide or loops) and calcium channel blockers (CCBs) (79). Many physicians are reluctant to use ACEIs and ARBs during the early stage of transplantation characterized by many cardiovascular and non-cardiovascular issues (including infections, acute rejection, anemia, change in diuretic use, cardiac tolerance to transplantation). Later on, usually after 3 months following transplantation, management of hypertension should be more standardized but this is not the case, and recent reviews do not mention any specific class of antihypertensive medications in kidney transplantation (28).

A previous Cochrane systematic review indicated that ACEIs may expose transplant recipients to a higher risk of hyperkalemia, and that CCBs could be associated with better renal protection (87). Recently, Pisano et al. conducted a systematic review and meta-analysis

to compare benefits and harms of antihypertensive drug classes in kidney transplant recipients (88). The Ovid-MEDLINE, PubMed and CENTRAL databases were searched for randomized controlled trials comparing antihypertensive agents vs comparators. Seventy-one randomized clinical trials were found. Both CCB and ACEIs reduced the risk of graft loss; however, ACEIs was associated with a slight reduction in kidney function and increased the risk for hyperkalemia compared to other drug groups. No effect of ARBs was found on the risk of death, graft loss and non-fatal CV events. RAS blockade (vs control treatment) was associated with a reduced risk for graft failure. Unfortunately, only few data on mortality, graft loss and rejection were available (88). These results are important to propose evidence-based antihypertensive treatments in kidney transplant recipients. However, hypertensive management must take into account efficacy on cardiovascular and renal outcomes of the antihypertensive medications but also tolerability and potential drug interactions with immunosuppressive drugs.

Patient- and health care providers - perceptions and patient-related outcomes

The issue of hypertension is frequently underestimated by kidney transplant recipients and their caregivers. They usually admit that hypertension « is a silent killer » and can « lead to eventual organ failure » but the common idea is that hypertension is « easily controlled » (89). These results highlight the importance to communicate on the importance to manage hypertension in this specific population as it is the major non-immunological risk factor for graft loss. The risk for hypertension is not only under-recognized by patients and caregivers but also by health professionals who think this “surrogate for graft failure, cardiovascular disease and death” is a “manageable issue”, “very easy to treat”. For patients and caregivers, there are “lots of drugs to sort this out” on top of “diets and exercise”. However, the global perception of hypertension as a minor issue in kidney transplantation in patients and health

professionals raises the link between hypertension and is impact on quality of life in many ways. There is therefore a misconception regarding the importance of resistant hypertension in kidney transplant recipients and the need to treat hypertension in this population.

Unresolved issues and perspectives

As discussed above, most guidelines either do not offer specific recommendations for systolic and diastolic BP thresholds for hypertension diagnosis, and they do not propose specific BP targets in recipient kidney transplants (78), with the noticeable exception of the recent 2021 KDIGO guidelines (however, this document did not provide a definitive recommendation for this population) (8) . Thus, future trials should define what are the optimal BP targets for kidney transplant recipients. Until such transplant-specific evidence are available, BP targets in kidney transplant recipients should be similar to those in the wider CKD population. Studies involving home BP and ABPM (90) will add substantial insight to the aforementioned issues.

An adequate hypertension management should take into account pathophysiology and individualized BP targets. The recent systematic reviews focused on ABPM provide convincing data suggesting that the current recommendation by transplant guidelines to diagnose and monitor hypertension exclusively by office BP measurements must be reconsidered (15, 24).

Although the report of Pisano et al. provided interesting data on the benefit of antihypertensive medications, more research efforts by the nephrology community seem necessary also in the field of antihypertensive agents (1, 88). Randomized control trials demonstrating the clinical benefits of BP lowering with specific antihypertensive classes on hard renal and CV outcomes are urgently needed.

Recently, SGLT2 inhibitors emerged as a major breakthrough in nephroprotection in diabetic and non-diabetic patients as these medications decrease BP, reduce albuminuria and decrease the risk of ESKD vs placebo (91-93). The FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease (FIDELIO-DKD) was a randomized, double-blind, placebo-controlled, parallel-group, event-driven trial assessing the efficacy and safety of finerenone vs placebo. This study showed a beneficial renal effect of finerenone (eGFR decrease of at least 40%, ESRD or death from renal causes) (94, 95). Importantly, the tolerance of finerenone was good, and the rate of severe hyperkalemia leading to hospitalisation was rare in patients on finerenone (but higher than placebo: 1.4% vs 0.6%), and therefore could be used in many patients with CKD including kidney transplant recipients. Of note, the impact on BP of SGLT2 inhibitors and finerenone in these trials was rather mild, at the range of 3-4 mmHg for systolic BP (91-95) indicating nephroprotective properties that are largely BP-independent. Whether SGLT2 inhibitors and finerenone could provide beneficial similar cardiovascular and renal effects in kidney transplant recipients is presently unknown (96, 97). These questions should certainly be studied in randomized controlled trials.

Conclusions

Overall, recent guidelines have witnessed changes in the evaluation and monitoring of BP as well as BP targets in the general and CKD populations. Available evidence in kidney transplant recipients suggests that white-coat hypertension and masked hypertension are also prevalent in this population. Additionally, 24-h ABPM is associated with better prediction of adverse outcomes than office readings. Based on this, the group suggests that 24-h ambulatory BP monitoring should be used for routine evaluation and monitoring of BP in kidney transplant recipients. At present there is controversy regarding the BP targets for patients with

CKD. In the absence of specific evidence for kidney transplant recipients, we suggest that the same BP targets as for other CKD patients should be used. Nevertheless, the group would encourage future studies examining what are the optimal BP targets and most effective and protective antihypertensive agents in kidney transplant recipients.

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Box-1. Consensus on blood pressure control in kidney transplantation

Suggestions for clinical practice

- Factors present before kidney transplantation; factors related to the transplantation procedure itself, and factors developing after transplantation that may contribute to hypertension in kidney transplant recipients should be identified, and corrected when possible.
- Home readings and, especially 24 h ambulatory blood pressure monitoring should be incorporated into the assessment and monitoring of blood pressure in kidney transplant recipients.
- In the absence of kidney transplant-specific evidence, office blood pressure targets in kidney transplant recipients should be similar to those in the wider CKD population (i.e.<130/80 mmHg).

Research needs

- Whether the use of home or 24 h ambulatory blood pressure monitoring improves outcomes specifically in the kidney transplant population, as opposed to the use of office blood pressure, should be studied.
- Randomized clinical trials should explore whether blood pressure targets recommendations in kidney transplant recipients should be different from those in the overall CKD population.
- Randomized clinical trials with hard outcomes should explore whether existing nephroprotective and cardioprotective antihypertensive classes offer the same benefits in patients with kidney transplantation.
- The role of recently identified nephroprotective and cardioprotective drugs such as SGLT2 inhibitors (diabetic and non-diabetic CKD) or finerenone (diabetic CKD) in

the management of blood pressure and overall kidney and cardiovascular risk in kidney transplant recipients should be specifically studied.

References

1. Halimi JM, Persu A, Sarafidis PA, Burnier M, Abramowicz D, Sautenet B, et al. Optimizing hypertension management in renal transplantation: a call to action. Nephrol Dial Transplant. 2017;32(12):1959-62.
2. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens. 2014;32(7):1359-66.
3. Kario K, Shimbo D, Hoshide S, Wang JG, Asayama K, Ohkubo T, et al. Emergence of Home Blood Pressure-Guided Management of Hypertension Based on Global Evidence. Hypertension. 2019:HYPERTENSIONAHA11912630.
4. McManus RJ, Caulfield M, Williams B, National Institute for H, Clinical E. NICE hypertension guideline 2011: evidence based evolution. BMJ. 2012;344:e181.
5. Lovibond K, Jowett S, Barton P, Caulfield M, Heneghan C, Hobbs FD, et al. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study. Lancet. 2011;378(9798):1219-30.
6. Piper MA, Evans CV, Burda BU, Margolis KL, O'Connor E, Whitlock EP. Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2015;162(3):192-204.
7. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):e13-e115.
8. Cheung AK, Chang TI, Cushman WC, Furth SL, Hou FF, Ix JH, et al. Executive summary of the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int. 2021;99(3):559-69.
9. Mallamaci F, Tripepi R, D'Arrigo G, Porto G, Versace MC, Marino C, et al. Long-term blood pressure monitoring by office and 24-h ambulatory blood pressure in renal transplant patients: a longitudinal study. Nephrol Dial Transplant. 2019;34(9):1558-64.
10. Mallamaci F, Tripepi R, Leonardis D, Mafrica A, Versace MC, Provenzano F, et al. Nocturnal Hypertension and Altered Night-Day BP Profile and Atherosclerosis in Renal Transplant Patients. Transplantation. 2016;100(10):2211-8.
11. Hamdani G, Nehus EJ, Hanevold CD, Sebestyen Van Sickle J, Woroniecki R, Wenderfer SE, et al. Ambulatory Blood Pressure, Left Ventricular Hypertrophy, and Allograft Function in Children and Young Adults After Kidney Transplantation. Transplantation. 2017;101(1):150-6.
12. Kayrak M, Gul EE, Kaya C, Solak Y, Turkmen K, Yazici R, et al. Masked hypertension in renal transplant recipients. Blood Press. 2014;23(1):47-53.
13. Mallamaci F, D'Arrigo G, Tripepi R, Leonardis D, Porto G, Testa A, et al. Office, standardized and 24-h ambulatory blood pressure and renal function loss in renal transplant patients. J Hypertens. 2018;36(1):119-25.
14. Wadei HM, Amer H, Griffin MD, Taler SJ, Stegall MD, Textor SC. Abnormal circadian blood pressure pattern 1-year after kidney transplantation is associated with subsequent lower glomerular filtration rate in recipients without rejection. Journal of the American Society of Hypertension : JASH. 2011;5(1):39-47.
15. Pisano A, Mallamasci F, D'Arrigo G, Bolignano D, Wuerzner G, Ortiz A, Kanaan N, Sarafidis P, Loutradis C, Persu A, Burnier M, Boletis IN, London G, Halimi JM, Sautenet B, Rossignol P, Vogt L, Zoccali C. Assessment of hypertension in kidney transplantation by ambulatory pressure monitoring: a systematic review and meta-analysis. J Hypertens. 2021.
16. Ducloux D, Motte G, Kribs M, Abdelfatah AB, Bresson-Vautrin C, Rebibou JM, et al. Hypertension in renal transplantation: donor and recipient risk factors. Clin Nephrol. 2002;57(6):409-13.
17. Halimi JM. Albuminuria, proteinuria, and graft survival in kidney transplantation. Am J Kidney Dis. 2011;58(6):1037; author reply -8.
18. Halimi JM, Laouad I, Buchler M, Al-Najjar A, Chatelet V, Houssaini TS, et al. Early low-grade proteinuria: causes, short-term evolution and long-term consequences in renal transplantation. Am J Transplant. 2005;5(9):2281-8.
19. Fernandez-Fresnedo G, Plaza JJ, Sanchez-Plumed J, Sanz-Guajardo A, Palomar-Fontanet R, Arias M. Proteinuria: a new marker of long-term graft and patient survival in kidney transplantation. Nephrol Dial Transplant. 2004;19 Suppl 3:iii47-51.

20. Ozkayar N, Altun B, Yildirim T, Yilmaz R, Dede F, Arik G, et al. Blood pressure measurements, blood pressure variability and endothelial function in renal transplant recipients. Clin Exp Hypertens. 2014;36(6):392-7.
21. du Cailar G, Oudot C, Fesler P, Mimran A, Bonnet B, Pernin V, et al. Left ventricular mass changes after renal transplantation: influence of dietary sodium and change in serum uric acid. Transplantation. 2014;98(2):202-7.
22. Rigatto C, Foley RN, Kent GM, Guttmann R, Parfrey PS. Long-term changes in left ventricular hypertrophy after renal transplantation. Transplantation. 2000;70(4):570-5.
23. Becker-Cohen R, Nir A, Ben-Shalom E, Rinat C, Feinstein S, Farber B, et al. Improved left ventricular mass index in children after renal transplantation. Pediatr Nephrol. 2008;23(9):1545-50.
24. pisano A MF, D'Arrigo G, Bolignano D, Wuerzner G, Ortiz A, Burnier M, Kanaan N, Sarafidis P, Persu A, Ferro CJ, Loutradis C, Boletis IN, London G, Halimi JM, Sautenet B, Rossignol P, Vogt L, Zoccali C. Blood pressure monitoring in kidney transplantation: a systemic review on hypertension and target organ damage. J Hypertens. 2021.
25. Bachy C, Alexandre GP, van Ypersele de Strihou C. Hypertension after renal transplantation. Br Med J. 1976;2(6047):1287-9.
26. Campistol JM, Romero R, Paul J, Gutierrez-Dalmau A. Epidemiology of arterial hypertension in renal transplant patients: changes over the last decade. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2004;19 Suppl 3:iii62-6.
27. Zhang R, Leslie B, Boudreaux JP, Frey D, Reisin E. Hypertension after kidney transplantation: impact, pathogenesis and therapy. Am J Med Sci. 2003;325(4):202-8.
28. Weir MR, Burgess ED, Cooper JE, Fenves AZ, Goldsmith D, McKay D, et al. Assessment and management of hypertension in transplant patients. J Am Soc Nephrol. 2015;26(6):1248-60.
29. Opelz G, Wujciak T, Ritz E. Association of chronic kidney graft failure with recipient blood pressure. Collaborative Transplant Study. Kidney Int. 1998;53(1):217-22.
30. Opelz G, Dohler B, Collaborative Transplant S. Improved long-term outcomes after renal transplantation associated with blood pressure control. Am J Transplant. 2005;5(11):2725-31.
31. Kasiske BL, Anjum S, Shah R, Skogen J, Kandaswamy C, Danielson B, et al. Hypertension after kidney transplantation. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2004;43(6):1071-81.
32. Cosio FG, Dillon JJ, Falkenhain ME, Tesi RJ, Henry ML, Elkhammas EA, et al. Racial differences in renal allograft survival: the role of systemic hypertension. Kidney Int. 1995;47(4):1136-41.
33. Mange KC, Cizman B, Joffe M, Feldman HI. Arterial hypertension and renal allograft survival. JAMA. 2000;283(5):633-8.
34. Ponticelli C, Montagnino G, Aroldi A, Angelini C, Braga M, Tarantino A. Hypertension after renal transplantation. American journal of kidney diseases : the official journal of the National Kidney Foundation. 1993;21(5 Suppl 2):73-8.
35. Tutone VK, Mark PB, Stewart GA, Tan CC, Rodger RS, Geddes CC, et al. Hypertension, antihypertensive agents and outcomes following renal transplantation. Clinical transplantation. 2005;19(2):181-92.
36. Seeman T. Hypertension after renal transplantation. Pediatr Nephrol. 2009;24(5):959-72.
37. Didier R, Yao H, Legendre M, Halimi JM, Rebibou JM, Herbert J, et al. Myocardial Infarction after Kidney Transplantation: A Risk and Specific Profile Analysis from a Nationwide French Medical Information Database. J Clin Med. 2020;9(10).
38. Diaz JM, Gich I, Bonfill X, Sola R, Guirado L, Facundo C, et al. Prevalence evolution and impact of cardiovascular risk factors on allograft and renal transplant patient survival. Transplantation proceedings. 2009;41(6):2151-5.
39. Groothoff JW, Gruppen MP, Offringa M, Hutten J, Lilien MR, Van De Kar NJ, et al. Mortality and causes of death of end-stage renal disease in children: a Dutch cohort study. Kidney Int. 2002;61(2):621-9.
40. Fernandez Fresnedo G, Franco Esteve A, Gomez Huertas E, Cabello Chaves V, Diz Gomez JM, Osorio Moratalla JM, et al. Ambulatory blood pressure monitoring in kidney transplant patients: RETENAL study. Transplant Proc. 2012;44(9):2601-2.
41. Gago Fraile M, Fernandez Fresnedo G, Gomez-Alamillo C, de Castro SS, Arias M. Clinical and epidemiological characteristics of refractory hypertension in renal transplant patients. Transplant Proc. 2009;41(6):2132-3.

42. Forconi C, Gatault P, Miquelestorena-Standley E, Noble J, Al-Hajj S, Guillemain R, et al. Polymorphism in programmed cell death 1 gene is strongly associated with lung and kidney allograft survival in recipients from CMV-positive donors. J Heart Lung Transplant. 2017;36(3):315-24.
43. Arias-Rodriguez M, Fernandez-Fresnedo G, Campistol JM, Marin R, Franco A, Gomez E, et al. Prevalence and clinical characteristics of renal transplant patients with true resistant hypertension. J Hypertens. 2015;33(5):1074-81.
44. Joost R, Dorje F, Schwitulla J, Eckardt KU, Hugo C. Intensified pharmaceutical care is improving immunosuppressive medication adherence in kidney transplant recipients during the first post-transplant year: a quasi-experimental study. Nephrol Dial Transplant. 2014;29(8):1597-607.
45. Low JK, Williams A, Manias E, Crawford K. Interventions to improve medication adherence in adult kidney transplant recipients: a systematic review. Nephrol Dial Transplant. 2015;30(5):752-61.
46. Nevins TE, Nickerson PW, Dew MA. Understanding Medication Nonadherence after Kidney Transplant. J Am Soc Nephrol. 2017;28(8):2290-301.
47. Ponticelli C, Cucchiari D, Graziani G. Hypertension in kidney transplant recipients. Transpl Int. 2011;24(6):523-33.
48. Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. Ann Intern Med. 2003;139(9):761-76.
49. Cosio FG, Pelletier RP, Pesavento TE, Henry ML, Ferguson RM, Mitchell L, et al. Elevated blood pressure predicts the risk of acute rejection in renal allograft recipients. Kidney Int. 2001;59(3):1158-64.
50. Wadei HM, Textor SC. Hypertension in the kidney transplant recipient. Transplant Rev (Orlando). 2010;24(3):105-20.
51. Kasiske BL. Possible causes and consequences of hypertension in stable renal transplant patients. Transplantation. 1987;44(5):639-43.
52. Ratcliffe PJ, Dudley CR, Higgins RM, Firth JD, Smith B, Morris PJ. Randomised controlled trial of steroid withdrawal in renal transplant recipients receiving triple immunosuppression. Lancet. 1996;348(9028):643-8.
53. Hoorn EJ, Walsh SB, McCormick JA, Furstenberg A, Yang CL, Roeschel T, et al. The calcineurin inhibitor tacrolimus activates the renal sodium chloride cotransporter to cause hypertension. Nat Med. 2011;17(10):1304-9.
54. Ciresi DL, Lloyd MA, Sandberg SM, Heublein DM, Edwards BS. The sodium retaining effects of cyclosporine. Kidney Int. 1992;41(6):1599-605.
55. Borschewski A, Himmerkus N, Boldt C, Blankenstein KI, McCormick JA, Lazelle R, et al. Calcineurin and Sorting-Related Receptor with A-Type Repeats Interact to Regulate the Renal Na(+)-K(+)-2Cl(-) Cotransporter. J Am Soc Nephrol. 2016;27(1):107-19.
56. Tuck ML, Sowers J, Dornfeld L, Kledzik G, Maxwell M. The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. N Engl J Med. 1981;304(16):930-3.
57. Neumann J, Ligtenberg G, Klein, II, Koomans HA, Blankestijn PJ. Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. Kidney Int. 2004;65(5):1568-76.
58. Gazdar AF, Dammin GJ. Neural degeneration and regeneration in human renal transplants. N Engl J Med. 1970;283(5):222-4.
59. Mauriello A, Rovella V, Borri F, Anemona L, Giannini E, Giacobbi E, et al. Hypertension in kidney transplantation is associated with an early renal nerve sprouting. Nephrol Dial Transplant. 2017;32(6):1053-60.
60. Klein IH, Abrahams AC, van Ede T, Oey PL, Ligtenberg G, Blankestijn PJ. Differential effects of acute and sustained cyclosporine and tacrolimus on sympathetic nerve activity. J Hypertens. 2010;28(9):1928-34.
61. Laffer CL, Scott RC, 3rd, Titze JM, Luft FC, Elijovich F. Hemodynamics and Salt-and-Water Balance Link Sodium Storage and Vascular Dysfunction in Salt-Sensitive Subjects. Hypertension. 2016;68(1):195-203.
62. Watschinger B, Sayegh MH. Endothelin in organ transplantation. Am J Kidney Dis. 1996;27(1):151-61.
63. Perico N, Ruggenenti P, Gaspari F, Mosconi L, Benigni A, Amuchastegui CS, et al. Daily renal hypoperfusion induced by cyclosporine in patients with renal transplantation. Transplantation. 1992;54(1):56-60.
64. van den Dorpel MA, van den Meiracker AH, Lameris TW, Boomsma F, Levi M, Man in 't Veld AJ, et al. Cyclosporin A impairs the nocturnal blood pressure fall in renal transplant recipients. Hypertension. 1996;28(2):304-7.

65. Sigrist M, Bungay P, Taal MW, McIntyre CW. Vascular calcification and cardiovascular function in chronic kidney disease. Nephrol Dial Transplant. 2006;21(3):707-14.
66. Ferro CJ, Savage T, Pinder SJ, Tomson CR. Central aortic pressure augmentation in stable renal transplant recipients. Kidney Int. 2002;62(1):166-71.
67. Georgianos PI, Sarafidis PA, Lasaridis AN. Arterial stiffness: a novel cardiovascular risk factor in kidney disease patients. Curr Vasc Pharmacol. 2015;13(2):229-38.
68. Karpetas A, Sarafidis PA, Georgianos PI, Protogerou A, Vakianis P, Koutroumpas G, et al. Ambulatory recording of wave reflections and arterial stiffness during intra- and interdialytic periods in patients treated with dialysis. Clin J Am Soc Nephrol. 2015;10(4):630-8.
69. Koutroumbas G, Georgianos PI, Sarafidis PA, Protogerou A, Karpetas A, Vakianis P, et al. Ambulatory aortic blood pressure, wave reflections and pulse wave velocity are elevated during the third in comparison to the second interdialytic day of the long interval in chronic haemodialysis patients. Nephrol Dial Transplant. 2015;30(12):2046-53.
70. Saran M, Czyzewski L, Wyzgal J, Pacek A, Szarpak L. Comparative Analysis of Arterial Stiffness and Body Composition in Early and Late Periods After Kidney Transplantation. Transplant Proc. 2018;50(6):1829-33.
71. Korogiannou M, Xagas E, Marinaki S, Sarafidis P, Boletis JN. Arterial Stiffness in Patients With Renal Transplantation; Associations With Co-morbid Conditions, Evolution, and Prognostic Importance for Cardiovascular and Renal Outcomes. Front Cardiovasc Med. 2019;6:67.
72. Bruno S, Remuzzi G, Ruggenenti P. Transplant renal artery stenosis. J Am Soc Nephrol. 2004;15(1):134-41.
73. Halimi JM, Al-Najjar A, Buchler M, Birmele B, Tranquart F, Alison D, et al. Transplant renal artery stenosis: potential role of ischemia/reperfusion injury and long-term outcome following angioplasty. J Urol. 1999;161(1):28-32.
74. Wong W, Fynn SP, Higgins RM, Walters H, Evans S, Deane C, et al. Transplant renal artery stenosis in 77 patients--does it have an immunological cause? Transplantation. 1996;61(2):215-9.
75. Chen W, Kayler LK, Zand MS, Muttana R, Chernyak V, DeBoccardo GO. Transplant renal artery stenosis: clinical manifestations, diagnosis and therapy. Clin Kidney J. 2015;8(1):71-8.
76. Willicombe M, Sandhu B, Brookes P, Gedroyc W, Hakim N, Hamady M, et al. Postanastomotic transplant renal artery stenosis: association with de novo class II donor-specific antibodies. Am J Transplant. 2014;14(1):133-43.
77. Summary of Recommendation Statements. Kidney Int Suppl (2011). 2012;2(1):8-12.
78. Castillo-Rodriguez E, Fernandez-Fernandez B, Alegre-Bellassai R, Kanbay M, Ortiz A. The chaos of hypertension guidelines for chronic kidney disease patients. Clin Kidney J. 2019;12(6):771-7.
79. Sarafidis PA, Ruilope LM. Aggressive blood pressure reduction and renin-angiotensin system blockade in chronic kidney disease: time for re-evaluation? Kidney Int. 2014;85(3):536-46.
80. Sarafidis P, Loutradis C, Ortiz A, Ruilope LM. Blood pressure targets in patients with chronic kidney disease: MDRD and AASK now confirming SPRINT. Clin Kidney J. 2020;13(3):287-90.
81. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36(10):1953-2041.
82. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269-324.
83. Cheung AK, Chang TI, Cushman WC, Furth SL, Ix JH, Pecoits-Filho R, et al. Blood pressure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019;95(5):1027-36.
84. Verbeke F, Lindley E, Van Bortel L, Vanholder R, London G, Cochat P, et al. A European Renal Best Practice (ERBP) position statement on the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the management of blood pressure in non-dialysis-dependent chronic kidney disease: an endorsement with some caveats for real-life application. Nephrol Dial Transplant. 2014;29(3):490-6.
85. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guidelines for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int (Suppl). 2012;2:337-414.

86. Cheung AK, Chertow GM, Greene T, Kimmel PL, Rahman M, Reboussin D, et al. Benefits and risks of intensive blood-pressure lowering in advanced chronic kidney disease. J Intern Med. 2018;284(1):106-7.
87. Cross NB, Webster AC, Masson P, O'Connell PJ, Craig JC. Antihypertensive treatment for kidney transplant recipients. Cochrane Database Syst Rev. 2009(3):CD003598.
88. Pisano A, Bolignano D, Mallamaci F, D'Arrigo G, Halimi JM, Persu A, et al. Comparative effectiveness of different antihypertensive agents in kidney transplantation: a systematic review and meta-analysis. Nephrol Dial Transplant. 2020;35(5):878-87.
89. sautenet Bea. Perspectives on blood pressure by kidney transplant recipients, caregivers and their health providers. Nephrology (Carlton). 2021.
90. Sarafidis PA, Persu A, Agarwal R, Burnier M, de Leeuw P, Ferro C, et al. Hypertension in dialysis patients: a consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH). J Hypertens. 2017;35(4):657-76.
91. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380(24):2295-306.
92. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436-46.
93. Wanner C, Inzucchi SE, Zinman B. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016;375(18):1801-2.
94. Ingelfinger JR, Rosen CJ. Finerenone - Halting Relative Hyperaldosteronism in Chronic Kidney Disease. N Engl J Med. 2020.
95. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. New England Journal of Medicine. 2020;0(0):null.
96. Mahling M, Schork A, Nadalin S, Fritsche A, Heyne N, Guthoff M. Sodium-Glucose Cotransporter 2 (SGLT2) Inhibition in Kidney Transplant Recipients with Diabetes Mellitus. Kidney Blood Press Res. 2019;44(5):984-92.
97. AlKindi F, Al-Omary HL, Hussain Q, Al Hakim M, Chaaban A, Boobes Y. Outcomes of SGLT2 Inhibitors Use in Diabetic Renal Transplant Patients. Transplant Proc. 2020;52(1):175-8.

Table 1: Potential factors contributing to hypertension development

	Factors	Phase after Tx	Putative mechanisms
Before transplantation	Increased sympathetic afferent renal nerve signaling from native kidneys	From start	Increased contractility and HR, PVR increase, RAAS activation, expansion ECFV
Transplantation-related	Fluid overload during dialysis	First days	Expansion ECFV
	Increased body weight	Months - years	RAAS activation, sodium retention, expansion ECFV, increase PVR
	Deceased donor from hypertensive family	Months - years	Miscellaneous, expansion ECFV
	High donor age	Months - years	Low nephron number, expansion extra cellular fluid volume
	IV fluids	First days	Expansion ECFV
	Sodium retention due to perioperative high dose glucocorticoids	First days	Expansion ECFV
	Delayed graft function (e.g., acute tubular necrosis)	First days	Impaired sodium excretion and expansion ECFV
After transplantation	High SNA directly after start of CNI (e.g, ciclosporin, tacrolimus)	First days/weeks	Increased contractility and heart rate, PVR increase, RAAS activation, expansion ECFV
	(Hyper) acute rejection	First days/weeks	Sodium retention and expansion ECFV
	Sodium retention due to chronic use of CNI and/or glucocorticoids	From start	Expansion ECFV
	Thrombotic microangiopathy (various causes)	Weeks - years	RAAS activation, sodium retention, expansion ECFV, increase PVR
	High central sympathetic outflow caused by CNI-induced neurotoxicity	Months	Increased contractility and HR, PVR increase, RAAS activation, expansion ECFV
	CNI-associated nephrotoxicity	Months - years	Sodium retention and expansion ECFV
	Ongoing rejection	Months - years	Sodium retention and expansion ECFV
	Artery stenosis of the graft	Years	RAAS activation, sodium retention, expansion ECFV, increase PVR
	Chronic allograft nephropathy	Years	Sodium retention and expansion ECFV
	Increased sympathetic afferent renal nerve signaling from graft	Years	Increased contractility and HR, PVR increase, RAAS activation, expansion ECFV

Tx, transplantation. HR, heart rate. PVR, peripheral vascular resistance. RAAS, renin-angiotensin-aldosterone system
SNA, sympathetic nerve activation. CNI, calcineurin inhibitor. IV, intravenous.
ECFV: extra cellular fluid volume

Table 2: Current BP thresholds for hypertensive drug therapy for CKD patients, according to recent guidelines.

Guideline	Office SBP/DBP (mmHg)	24h ABPM/HBPM (mmHg)	Specific mention of kidney transplant patients?
KDIGO 2012 (ref 84)	• >140 or >90 if UACR <30 mg/g • >130 or >80 if UACR ≥30 mg/g	No formal thresholds	>130 or >80 mmHg
ERBP 2014 comment on KDIGO 2012 (ref 83)	No specific comment	No specific comment	No specific comment
AHA 2017 (ref 81)	≥130 or ≥80 if estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk ≥10%*, **	No formal thresholds, but a correspondence to 130/80 HBPM or daytime ABPM is provided (110/65 nighttime ABPM or 125/75 24 h ABPM))	≥130 or ≥80 mmHg
ESC-ESH 2018 (ref 80)	• ≥140 or ≥90 if age <65 y • ≥160 or ≥90 if age ≥80 y	No formal thresholds, but a correspondence of 140/90 to 135/85 HBPM or daytime ABPM is provided (120/70 nighttime 160 would correspond to 145 HBPM or daytime/24h ABPM	No
KDIGO 2019 (ref 82)	Careful review needed	Evidence should be explored	No change from 2012
KDIGO 2021 (ref 8)	• "High BP"	No formal thresholds	No transplant patients in large randomized trials

* There is a discrepancy between the text (indicating that diabetes or CKD patients are ASCVD risk ≥10%) and the online calculator ((link provided: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/ where diabetes is included in the calculator but CKD is not)

** CKD is here defined as "stage 3 or higher or stage 1 or 2 with albuminuria ≥300 mg/d, or ≥300 mg/g"
UACR: urinary albumin creatinine ratio; ASCVD: atherosclerotic cardiovascular disease

Table 3: Current BP target for CKD patients, according to recent guidelines.

Guideline	Office SBP/DBP (mmHg)	24h ABPM/HBPM (mmHg)	Specific mention of kidney transplant patients?
KDIGO 2012 (ref 84)	≤140 and ≤90 if UACR <30 mg/g ≤130 and ≤80 if UACR ≥30 mg/g	No formal targets	<130/80 mmHg
ERBP 2014 comment on KDIGO 2012 (ref 83)	Caution required in patients with isolated systolic hypertension and coronary artery disease Target should refer to resting conditions most of the time	No specific comment	Questions whether KDIGO 2012 target is realistic and whether "one size fits all"
AHA 2017 (ref 81)	<130/80 mmHg**	No formal targets. See table 2 for correspondence	<130/80 mmHg
ESC-ESH 2018 (ref 80)	130-139/70-79*	No formal targets. See table 2 for correspondence	No
KDIGO 2019 (ref 82)	Careful review needed	Evidence should be explored	Concern about SBP <120 mmHg
KDIGO 2021 (ref 8)	SBP<120 mmHg (standardized office BP)***	No formal targets	SBP < 130/80 mmHg for most patients

* The CKD concept may not be coincident: CKD is defined as an eGFR <60 mL/min/1.72 m2 with or without proteinuria
** CKD is defined here as "stage 3 or higher or stage 1 or 2 with albuminuria ≥300 mg/d, or ≥300 mg/g"
UACR: urinary albumin creatinine ratio
***: based on the SPRINT trail where BP measurement was unattended