UNIVERSITE François RABELAIS
Faculté de médecine de Tours
Denis Diderot

Année 2020/2021

THESE

POUR OBTENIR LE GRADE DE

DOCTEUR EN MEDECINE

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Né le 22/11/1993 à Meulan en Yvelines (78)

PRESENTEE ET SOUTENUE PUBLIQUEMENT

Le 22 octobre 2021

DANS LE CADRE DU TROISEME CYCLE DE MEDECINE SPECIALISEE EN NEPHROLOGIE

MESURE ET PRISE EN CHARGE PHARMACOLOGIQUE DE L'HYPERTENSION ARTERIELLE CHEZ LES PATIENTS TRANSPLANTES RENAUX : PERSPECTIVES DES PATIENTS ET DES MEDECINS

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RESUME

Mesure et prise en charge pharmacologique de l'hypertension artérielle chez les patients transplantés rénaux : perspectives des patients et des médecins

Contexte : La mortalité cardiovasculaire est la première cause de décès chez les patients transplantés rénaux. L'hypertension artérielle (HTA), dont la prévalence est proche de 80% chez ces patients, est le premier facteur de risque cardiovasculaire modifiable. Les pratiques concernant la prise en charge de l'HTA chez les patients transplantés rénaux sont variées et les données scientifiques manquantes. L'objectif de cette étude est de décrire les pratiques concernant la mesure de l'HTA et sa prise en charge pharmacologique par les professionnels de santé, et de confronter les résultats aux données recueillies auprès des patients transplantés rénaux.

Matériel et méthode : Un questionnaire a été diffusé aux médecins assurant le suivi de patients transplantés rénaux en France et aux patients transplantés rénaux. Les questions concernaient la mesure de la pression artérielle (PA), sa prise en charge thérapeutique et l'observance.

Résultats : Nous avons obtenu les réponses de 78 néphrologues et 86 patients. Pour la prise en charge thérapeutique médicamenteuse de l'HTA, les professionnels de santé privilégient les inhibiteurs calciques puis les inhibiteurs du système rénine angiotensine en première intention (58 % et 37%). Dès lors qu'une trithérapie anti hypertensive est nécessaire, les néphrologues introduisent les diurétiques non épargneurs de potassium dans plus de la moitié des cas (51%), en l'absence de protéinurie. Concernant la mesure de la PA, les réponses des praticiens et des patients sont similaires pour 8 questions, mais 8 questions comportent des différences significatives, notamment au sujet des mesures ambulatoires de PA. Une majorité de patients ressentent une amélioration de leur qualité de vie liée au traitement de l'HTA (80,2%) et 71,4 % déclarent entre observant.

Conclusion : La prise en charge thérapeutique de l'HTA est majoritairement faite en adéquation avec les recommandations KDIGO. La mesure de la PA ambulatoire est insuffisante et pourtant indispensable dans cette population à haut risque d'HTA résistante, d'HTA masquée et d'HTA nocturne. La mise en place d'études interventionnelles sur l'usage de la mesure ambulatoire de PA chez les patients transplantés rénaux semble indispensable.

Mots clés : Néphrologie, Transplantation, Pression artérielle, Cardio-vasculaire, Hypertension, Facteur de risque, Monitoring, Pharmacologie, Observance

ABSTRACT

Measurement and pharmacological management of hypertension in renal transplant patients: patient and physician perspectives

Context: Cardiovascular mortality is the leading cause of death in kidney transplant recipients. Hypertension, whose prevalence is close to 80% in these patients, is the first modifiable cardiovascular risk factor. Practices for the management of hypertension in kidney transplant recipients are diverse and scientific data are missing. The objective of this study is to describe the practices concerning the measurement of hypertension and its pharmacological management by healthcare professionalś and to compare the results with data collected from kidney transplant recipients.

Material and method: A survey was distributed to French nephrologists and kidney transplant recipients. The questions concerned blood pressure (BP) measurement, its therapeutic management, and compliance.

Results: We received responses from 78 nephrologists and 86 patients. For the therapeutic drug management of hypertension, healthcare professionals introduced calcium channel blockers followed by renin angiotensin system inhibitors as first-line therapy (58% and 37%). Once triple antihypertensive therapy is required, nephrologists introduce non-potassium-sparing diuretics in more than half of the cases (51%), in the absence of proteinuria. Regarding BP measurement, practitioner and patient responses were similar for 8 questions, but 8 questions had significant differences, particularly regarding ambulatory BP measurements. A majoritý of patients felt an improvement in their qualitý of life related to the treatment of hypertension (80%), and 71% reported being compliant.

Conclusion: Therapeutic management of hypertension is mostly done in accordance with the KDIGO recommendations. Ambulatory and home BP measurement is insufficient and yet indispensable in this population at high risk of resistant hypertension, masked hypertension and nocturnal hypertension. Interventional studies on the use of ambulatory and home BP measurement in kidney transplant patients seem indispensable.

Key words: Nephrology, Transplantation, Blood Pressure, Cardiovascular, Hypertension, Risk factor, Monitoring, Pharmacology, Compliance

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,

De mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

REMERCIEMENTS

A mon Maître et Président de thèse, Monsieur le Professeur Jean Michel HALIMI - Professeur des Universités, Praticien Hospitalier de Néphrologie

Merci pour ta bienveillance, ta disponibilité, ton encadrement.
Merci de pousser chacun de nous à donner le meilleur et aller plus loin dans ses connaissances.

A mon Maître et Directeur de thèse, Madame le Docteur Bénédicte SAUTENET - Maître de Conférence des Universités – Praticien Hospitalier de Néphrologie

Merci de ta confiance pour mener ce projet à bien.
Merci de ta gentillesse, ta bienveillance, ta disponibilité au long de ce travail et dans les soins de tous les jours.

A mon Maître et Juge, Monsieur le Professeur Mathias BUCHLER - Professeur des Universités, Praticien Hospitalier de Néphrologie

Merci pour l'encadrement pédagogique, mais surtout de m'avoir appris à cultiver la curiosité, dans l'apprentissage de la médecine ainsi que dans d'autres domaines variés.

A mon Maître et Juge, Monsieur le Professeur Philippe GATAULT - Professeur des Universités – Praticien Hospitalier de Néphrologie

Merci de ta disponibilité et de ton aide pour la diffusion de ce travail.
J'admire ton pragmatisme et ton enthousiasme au quotidien.

A mon Maître et Juge Madame le Docteur Christelle BARBET - Praticien Hospitalier de Néphrologie

Merci pour ta bienveillance avec chacun de nous, pour tes nombreux conseils tout au long de l'internat. Pour tes tapes amicales dans le dos et les potins.

Ce travail marque la fin de dix années d'études passionnantes. De nouvelles pages restent à écrire, mais c'est pour moi l'occasion de remercier quelques personnes qui comptent particulièrement.

A ma Famille,

A ma mère, Nathalie, qui m'a appris à oser, à croire en moi, à être créatif, qui m'a montré que le bonheur est dans les choses les plus simples et qui a toujours fait passer ses fils avant le reste.

A mon père, Philippe, à jamais un modèle, pour ton sens de la famille, du sacrifice et des responsabilités. Tu m'as transmis tes passions et bien plus encore.

A tous les deux, pour l'amour, le gout de la musique, des voyages, le gout du travail, du partage, mais surtout pour le plus beau des cadeaux qu'est cette famille à sept.

Vous êtes les parents que tout enfant mérite et je n'aurai pu réussir sans vous.

A mes frères, qui sont si précieux.

A Clément, que j'admire depuis mon plus jeune âge. Pour ta détermination à ne jamais baisser les bras.

A Ludovic, qui a toujours été une source d'inspiration. Toi qui es doué pour tout, y compris réunir les gens qui s'aiment et donner un sens au mot famille.

A Hugo, la meilleure personne que je connaisse. Pour ta joie de vivre et ton grand cœur.

A Nicolas qui brille dans tous les domaines et dont je suis si fier.

A Maria, ma grand-mère, qui a teinté notre enfance d'un amour aux saveurs de l'Italie.

A Marius, si petit et déjà le plus grand des bonheurs.

A Anne Claire et Justine qui font maintenant partie de cette famille.

A ceux qui sont partis plus tôt que prévus,

A Roger, mon grand-père, pour ton rire et tant de moments de bonheur partagés ensemble.

A Lucienne, ma grand-mère, mais surtout la plus forte des femmes que j'ai connu.

A Louis, qui s'est battu pour son pays, j'aurai aimé que tu me racontes ton histoire.

A Victorine, qui aurait été ma grande sœur et que j'aurai tant aimé connaître.

A mes Amis,

A Thomas que je prendrai toujours comme exemple, même si tu es devenu parfait, seulement après que je t'ai perverti.

A Matthieu, qui change les gens et fait ressortir le meilleur d'eux. Qui me donne des fous rire quand je rêve de lui. A Élise, qui te rend si heureux et te correspond si bien.

A Daz, mon ami de plus longue date, le plus courageux, qui me supporte depuis bientôt 15 ans.

Vous êtes tous les trois mes amis depuis toujours. Une chance de vous savoir prêt de moi peu importe la distance, même si je rêve de vous avoir au quotidien.

Parce que même si vous pensez qu'on a déjà tout vécu ensemble, le meilleur reste à venir. Et oui, pas de problème, je veux bien être le parrain de vos enfants.

A mes amis du lycée, Babouch, Camille, Charlotte, Guillaume, Gabrièle, Victor, les années passent mais jamais l'affection que j'ai pour vous. Loin des yeux parfois, mais jamais loin du cœur.

A mes amis de fac, à Ludo goalé de ouf, à Alexis meilleur voisin aux ECN, à Quentin le plus ricains des bretons, à Arthur mon personnage de Marvel préféré, à Giulia pour son rire et l'amour du même drapeau, à Chloé pour les films d'horreur, à Awa, promis un jour on ira à la fête de la carotte, A Juliette, pour sa passion des débats, à Gaylord, le meilleur dans tous les domaines.

A ceux que j'ai rencontré plus récemment,

Un grand merci à l'ensemble des médecins du service de Néphrologie.
A Hélène Longuet, la maman de la greffe, pour tes talents d'imitatrices, A Maud François, pour la rigueur et ta passion du café, à Nolwenn Rabot, Jean-François Valentin, Annabelle Goumard, Gabriela Golea, Nicolas Goin, Juliette Guegen, Léa Moret, Alexandre Ganéa, Georgio Tsangalis, Noujoud El Khoury.
A Eloi Chevallier, un brave parmi les braves. Pour tes qualités en tant que médecin et surtout tes qualités humaines.
A Claire Geneste, pour ta gentillesse et tes conseils de parentalité.

A mes co-internes, Mathieu, numéro 10 sur le terrain et dans la vie, Margaux ou plutôt Marijo, à Roxane Gamot, meilleur public, merci de me faire croire que je suis drôle, à Jessica, mais surtout à Claire Ferran, jamais fâchée...et toujours n°1 au tennis, à Paul, Valentin, Lucie, Élise.

A toutes ces rencontres, depuis le début de l'internat, à Chloé, gravée dans la roche, mais surtout dans les cœurs, à Marie, le plus fidèle des paratonnerres mais surtout, la plus fidèle des amies, à Mélanie et Oriane à qui je confierai mes enfants les yeux fermés, à Guillaume, pour les conversations jusqu'à 3 heures du matin, à P-O, le plus interniste des urgentistes, à Margot pour savoir s'il est déficitaire, à Clémentine, à Philou Sharap', à la triplette de Gastro, à Maelenn.
A Camille (Granger) et Thibault pour les sessions fromage.

A l'équipe de Réanimation, et en particulier à Victor, Marion, Timothée, et Marie-Charlotte.
A Emmanuelle Mercier, Charlotte Salmon et Denis Garot.
A l'ensemble du personnel médical et para médical qui étaient volontaires à une époque difficile.

A Mathilde,

La femme avec les plus beaux yeux du monde, parce qu'il parait que quand tu sais, tu sais.
Toi qui me donnes envie d'être la meilleure version de moi et m'encourage dans chacun de mes projets.
Tu me supportes, pour ce travail, mais surtout au quotidien, qui n'aurait d'ailleurs pas de sens, sans toi.
Le bonheur est dans les choses les plus simples et c'est la vie qui devient simple à tes cotés.
Je ne pourrai être plus heureux qu'avec toi. Tu es l'unique qui me donne envie d'être deux.

A ta Famille, Caroline, Frédérique, Clément, Arthur et maintenant Léa, qui marient parfaitement les mots « belle » et « famille ».
A tes amies, que j'aime tant, qui te ressemblent et t'entourent si bien.

Table des matières

ABBREVIATIONS

ABPM	Ambulatory Blood Pressure measurement
ACEi	Angiotensin-Converting Enzyme inhibitors
ARB	Angiotensin 2 Receptor Blockers
BP	Blood Pressure
CCB	Calcium Channel Blockers
CNI	Calcineurin Inhibitor
DBP	Diastolic Blood Pressure
eGFR	estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
JNC7	Joint National Committee 7
KDIGO	Kidney Disease Improving Global Outcomes
SBP	Systolic Blood Pressure

Measurement and pharmacological management of hypertension in renal transplant patients: patient and physician perspectives

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Abstract

Context: Cardiovascular mortality is the leading cause of death in kidney transplant recipients. Hypertension, whose prevalence is close to 80% in these patients, is the first modifiable cardiovascular risk factor. Practices for the management of hypertension in kidney transplant recipients are diverse and scientific data are missing. The objective of this study is to describe the practices concerning the measurement of hypertension and its pharmacological management by healthcare professionalś and to compare the results with data collected from kidney transplant recipients.

Material and method: A survey was distributed to French nephrologists and kidney transplant recipients. The questions concerned blood pressure (BP) measurement, its therapeutic management, and compliance.

Results: We received responses from 78 nephrologists and 86 patients. For the therapeutic drug management of hypertension, healthcare professionals introduced calcium channel blockers followed by renin angiotensin system inhibitors as first-line therapy (58% and 37%). Once triple antihypertensive therapy is required, nephrologists introduce non-potassium-sparing diuretics in more than half of the cases (51%), in the absence of proteinuria. Regarding BP measurement, practitioner and patient responses were similar for 8 questions, but 8 questions had significant differences, particularly regarding ambulatory BP measurements. A majoritý of patients felt an improvement in their qualitý of life related to the treatment of hypertension (80%), and 71% reported being compliant.

Conclusion: Therapeutic management of hypertension is mostly done in accordance with the KDIGO recommendations. Ambulatory and home BP measurement is insufficient and yet indispensable in this population at high risk of resistant hypertension, masked hypertension and nocturnal hypertension. Interventional studies on the use of ambulatory and home BP measurement in kidney transplant patients seem indispensable.

INTRODUCTION

Kidney transplantation is currently the preferred treatment for end-stage renal disease (1). It offers advantages in terms of quality of life, morbidity and mortality, as well as economic benefits beyond the first year after transplantation, compared to renal replacement therapy such as hemodialysis or peritoneal dialysis. The management of cardiovascular risk is crucial for the follow-up of kidney transplant recipients because it determines both graft survival and patient survival. According to mortality registries, atherosclerosis is the most common cause of death after kidney transplantation (44%, including cardiovascular and cerebrovascular disease) (2,3,4). The management of hypertension in kidney transplant recipients is considered as the primary therapeutic target for the management of the cardiovascular and renal risk (5). The prevalence of hypertension in kidney transplant recipients is 85% (6). Among them, up to 30 % would have resistant hypertension (7), i.e., blood pressure (BP) measures higher than 130/80 mmHg, despite the combination of at least three antihypertensive drugs including a thiazide diuretic. Hypertension in kidney transplant recipients is multifactorial. Hypertension might be the consequence of chronic graft failure, but there are additional factors like vascular factors for transplants from cadaveric donors - corresponding to 84% of kidney transplants performed in France - with an increasing number of expanded criteria donors or immunosuppressive drugs (8,9,10). Calcineurin inhibitors and glucocorticoids represent two of the three classical immunosuppressive drugs used in the immediate post-transplant phase and are responsible for arterial hypertension via a complex physiopathology (11).

Hypertension represents the first non-immunological and modifiable cause of graft loss. International recommendations for the management of hypertension in kidney transplant recipients suggest BP levels under 130/80 mmHg in all renal transplant patients, with a calcium channel blocker or angiotensin II receptor antagonist preferred as first-line therapy (12). There are many molecules available for the management of hypertension in transplant patients. Currently, according to a meta-analysis investigating the use of different therapeutic classes versus placebo in renal transplant patients, the use of calcium channel blockers reduces the relative risk of graft loss (13). However, no significant difference in all-cause mortality and cardiovascular events was observed, despite significantly lower blood pressure. The use of angiotensin-converting enzyme inhibitors (ACEi) was associated with a reduction in the relative risk of graft loss, but with lower GFR values, higher risk of hyperkalemia and anemia. No significant difference was observed with the use of angiotensin II receptor blocker (ARB).

Overall, no drug class has shown a significant difference in reducing cardiovascular mortality in kidney transplant recipients. The current recommendations are based on the value of the office BP. However, it is recommended to use 24-hour ambulatory BP measurement which is associated with improved monitoring of the different outcomes of hypertension on the target organs (14). In several studies, 24-hour ambulatory BP monitoring was positively correlated with renal graft function, compared with the office BP value. In addition, 24-hour BP measurement was positively correlated with the cardiac impact, estimated by echographic parameters. Current clinical practices are varied, both in terms of modalities for measuring BP (office BP and home BP), time between transplantation and the initiation of antihypertensive treatment, and drug classes used, which are often based on the combination of several molecules.

The aim of this study is to describe current practices concerning the measurement, the monitoring and the pharmacological management of hypertension in kidney transplant recipients and to compare the point of views from nephrologists and from patients.

MATERIAL AND METHOD

Study design

Health professionals survey

We sent an online survey (supplementary file-Annex 1) to nephrologists providing follow-up visits for kidney transplant recipients in France. Data were collected over a one-year period, from June 2020 to June 2021. All nephrologists providing post-transplant follow-up consultations, whether in a university or regional hospital, in France, could participate in the study.

Patient survey

The patients survey (supplementary file-Annex 2) was delivered to kidney transplant recipients in The University Hospital of Tours from October 2020 to June 2021 with a printed version during a consultation and an online version was delivered from January 2021 to June 2021 on a national interactive and community digital platform called "Docmadi" to all the kidney transplant recipients participating to this program. All kidney transplant recipients aged over

18 years, with a functional graft, i.e. not requiring a pre-replacement renal consultation, without unbalanced cognitive or psychiatric disorders, speaking French could participate to the survey.

Data collected

The health professional survey included a first part concerning the demographic data such as gender and age, place of practice, number of years of experience in kidney transplantation and number of studies performed as investigator in this area. The second part of the survey was composed of 20 questions about BP measurement. Sixteen of the 20 questions were common to patients and health professionals. The last part concerned the equipment available for BP measurement, the rhythm of BP monitoring, the pharmacological management of hypertension in kidney transplant patients, and the recommendations used.

The questionnaire submitted to the patients included a first part about demographic data (age, sex, time since transplantation, arterial hypertension, use of antihypertensive drugs), a second part about BP measurement and a third part concerning adherence to antihypertensive treatment and quality of life.

Authorization

The patient survey, the modalities of data collection and the whole project have been submitted to the Committee for the Protection of Persons (CPP) and have received the favorable opinion of the National Commission for Data Processing and Liberties (project number: 2020 083).

Statistical analysis

Data were collected using Microsoft Excel software and processed anonymously. We performed descriptive statistics, concerning qualitative and quantitative variables, using Excel® software. Data are presented as mean and standard deviations for quantitative parameters and percentages for categorical parameters. Statistical analyses were performed using R software, version 3.2.3 (R Foundation for Statistical Computing). Differences were considered significant at a p value < 0.05.

RESULTS

Health professionals and patients' characteristics

All practitioners who answered the survey were Nephrologists (n = 78). Demographic and professional data are summarized in the Table 1. The different locations of the study participants are detailed in the supplementary file (Figure S1).

The demographics data for the 86 patients who participated in the survey are summarized in the Table 2. Fifty-eight % of the patients (50/86) who answered the questionnaire had received a kidney transplant for more than 24 months. Seventy-four % (64/86) of the kidney transplant patients thought they had hypertension, and among the 26% patients (22/86) who did not think they had hypertension, 36% patients (8/22) were taking at least one antihypertensive drug. A total of 83% (71/86) patients reported taking at least one antihypertensive treatment.

Measurement of BP (office and ambulatory BP)

Sixteen questions relating to the methods of BP measurement during a post-transplant follow-up visit or in the ambulatory setting were common to both health professionals and patients. Eight questions showed similar results between patients and nephrologists and 8 answers showed significant differences (Figure 1). The answers similar between the 2 groups concerned the position of the cuff (at heart level, over the clothes), the condition of the patient (silent patient at the time of measurement, at rest for more than 5 minutes) and the patient position (always in the same position with the arm and back supported). The differences observed concerned the frequency of home and 24-hour BP measurement. The majority of the patients (90% (78/86)) reported having already measured their BP at home and 68% of them (53/78) according to a standardized protocol, including three morning and evening measurements on three consecutive days. Only 65% of the nephrologists (51/78) used home BP measurement systematically, and according to a standardized protocol in 90% (46/51) of cases, including fasting BP measurement in only 39% (18/46) of cases. Overall, only 23% of the nephrologists (18/78) used home BP measurement, in agreement with current good practice recommendations, including several measurements, at rest, fasting, morning and evening, over three consecutive days. About ambulatory BP measurement, 62% (53/86) of patients reported having already had a 24-hour measurement, while only 20% (16/78) nephrologists used 24-hour BP measurement routinely. Note that 62% (10/16) of the nephrologists using 24-hour BP measurement reported unexpected results when reviewing the data.

BP thresholds used for therapeutic adaptation

When nephrologists were asked which BP measurement methods they used to adapt the antihypertensive treatment of their patients, 35% (27/78) reported using self-measurement of BP on an ambulatory basis, whether it was over 24 hours or not, regardless of the value of office BP measurement. After confirmation of the blood pressure values, regardless of the measurement method used, 53% (41/78) of the practitioners used a systolic BP cut-off > 140 mmHg and/or a diastolic BP cut-off > 90 mmHg as a basis for adaptation of antihypertensive drugs, i.e., increasing the posology of an antihypertensive drug or adding a new drug (Figure 2). When asked to the patients: *"Do you know your BP objective? If yes, what is it?",* 40% (34/86) admitted not knowing their BP targets. Of those who answered yes to the question, only 19% (10/52) knew their target, i.e., 12% (10/86) of the patients.

Equipment available

Concerning office BP measurement, the nephrologist was the operator for 86% (67/78) of the situations and nurses for 14% (11/78). They used an oscillometric device in 90% (70/78) of cases. For 31% (24/78) of the nephrologists, they did not known if the device used had already been validated. Concerning the size of the cuffs available for BP measurement in consultation, 96% of the nephrologists (75/78) had a size M, 91% had a size L (71/78), more rarely a size S and XL, 35% (27/78) and 32% (25/78) respectively. Only 5% (4/78) had a size XS available.

Pharmacological treatment for hypertension management

When an ACEi or ARB is needed, 50 % (39/78) of nephrologists wait the first to third month post transplantation for introduction of the drug, 20 % (16/78) of nephrologists introduced them during the first month post-transplantation, 19 % (15/78) of nephrologists introduced them between the third- to sixth-month post transplantation, 6% (5/78) introduced them after 6 months and 4% (3/78) after 12 months (Figure 3). A serum creatinine increases of up to 20% was tolerated by 51 % (40/78) of nephrologist and 29% (23/78) tolerated an increase of up to 30% (Figure 4). The first-line therapeutic class used for confirmed hypertension was calcium channel blockers for 57% (45/78) of nephrologists, followed by ACEi /ARB for 37% (29/78) of nephrologists, for kidney transplant recipients without significant proteinuria or fluid overload. As a second line of treatment, nephrologists preferentially used ACEi/ARB or

calcium channel blockers (CCB), if not introduced as a first-line treatment. Thiazide diuretics were used in the third line for 51 % (40/78) of nephrologists, followed by beta-blockers used in fourth intention for 38 % (30/78) of nephrologists. We asked the nephrologists to rank each drug class for antihypertensive management. The maximum score of 7 was given for the first-line drug class and the minimum score of 1 for the last-line drug class. The results are shown in Figure 5. ACEi or ARB were introduced when proteinuria >0.5 g/d or >0.5g/g was present for 77% (60/78) of nephrologists, and 23 % of practitioners (18/78) were disposed to use a double blockade of the renin-angiotensin system by combining both an ACEi and an ARB when proteinuria >3g/g was present. In case of resistant hypertension (defined as blood pressure values over 130/80 mmHg despite antihypertensive tri-therapy, containing at least one thiazide diuretic), the preferred therapeutic class was a Beta Blocker for 54 % (42/78) of nephrologists, an anti-aldosterone for 21% of nephrologists (16/78) (Figure 6).

The data concerning the introduction of an anti-aldosterone treatment in case of resistant hypertension are summarized in Figure 7 and Figure 8, respectively. Note that a potassium chelator treatment was introduced with the anti-aldosterone treatment in case of serum potassium > 5 mmol/L. Almost half of the nephrologists (49% (38/78) were disposed to introduce anti-aldosterone therapy up to an eGFR (estimated Glomerular Filtration Rate) value of 30 mL/min in case of resistant hypertension. A majority of nephrologists (68% (53/78)) accepted a serum potassium level between 4 and 5 mol/L to introduce anti-aldosterone. Finally, 10% (8/78) of the nephrologists never introduced anti-aldosterone in case of resistant hypertension, independent of the GFR value and the serum potassium level.

Recommendations

The recommendations used by Nephrologists for the management of hypertension in renal transplant patients were KDIGO recommendations for 59 % (45/78) of practitioners, ESC recommendations for 27% (21/78) of practitioners, more rarely the American JNC7 recommendations for 4% (3/78) of practitioners.

Adherence and perception about BP management from patients

About BP monitoring, 81 % (70/86) of patients considered it adequate, with up to 80% of patients (69/86) feeling that monitoring and treatment of their hypertension had a beneficial impact on their quality of life. Seventy-one % (60/86) of patients reported being compliant with their antihypertensive treatment and only 7% of patients (6/86) considered their antihypertensive treatment too restrictive.

DISCUSSION

The overall results of this study show adherence to the recommendations of good practice for most items, with a good correlation when comparing the points of view from patients and practitioners. These items mainly concern the measurement of BP and its different modalities. The use of home blood pressure monitoring, and ambulatory blood pressure monitoring is insufficient. Patients considers the blood pressure management as an improvement in quality of life. Antihypertensives drugs used in priority are ACEi/ARB and CCB in top 2 then thiazide diuretics.

The post kidney transplant follow-up visit is in many aspects source of anxiety-for the kidney transplant recipients. The kidney function is assessed, sometimes blood tests are realized, and the visit often focuses on immunosuppression therapeutics due to the complexity of the kidney transplant recipient's condition. Overall, it appears that the post-transplant follow-up consultation is probably not the most appropriate time to adapt the antihypertensive treatment based on the office BP measurement alone. The value of the BP during the visit is probably more indicative, than decisive and may help to detect aberrant blood pressure values. However, the measurement of BP during the post-transplant follow-up consultation should be encouraged, if only to communicate the results to the patients and to discuss with them their blood pressure target, which is too often ignored by them (only 12% of the patients in our study knew their blood pressure target). It might be helpful for kidney transplant recipients to benefit from specific therapeutic education for BP management including reminders of blood pressure targets, hygiene and diet rules, discussion groups, training with advanced practice nurses, dietary consultations.

In our study, nephrologists used ambulatory BP measurements routinely in only 20% of cases. The results suggest that 24-hour ambulatory BP measurement is insufficiently used in routine practice by nephrologists. Patients reported that they had already measured their BP at home, almost systematically (91% of cases), much more frequently than prescribed by the nephrologists, suggesting a misunderstanding of this type of measurement from patients. About home BP measurement, only two thirds of patients did so according to a standard protocol (including several measurements, three days consecutive, fasting). Home BP measurement is mainly informative if performed according to a standard protocol, explained to the patient prior to the measurement, and consequently requires therapeutic education. Home BP measurement according to a standardized protocol allows to avoid the traps of measuring blood pressure in consultation, such as the so-called "white coat" hypertension - that can lead to a useless or even dangerous therapeutic escalation, associated with iatrogenic complications - or even masked hypertension, frequent in this population, that can reach 40 % of the patients according to the series (15,16).

Measurement of BP in the ambulatory setting over 24 hours makes it possible to identify different blood pressure profiles. In non-hypertensive patients, the BP value follows a circadian rhythm during the 24 hours, with an expected decrease of more than 10% of the nocturnal BP, called "dipper" profile. In hypertensive patients, including renal transplant patients, some have a stable BP during the day with no or insufficient decrease (<10% of BP compared to daytime values) during the night, called "non dipper" profile, while other patients have an increase in BP during the night, called "reverse dipper" (17). These patients, with a nocturnal hypertension profile, are particularly at high cardiovascular risk and at risk of graft loss (18-20). Indeed, these hypertension profiles cannot be diagnosed on the basis of office BP measurement and consequently managed. Ambulatory BP measurement (ABPM) should be proposed systematically to all kidney transplant patients, to reveal a possible masked hypertension, and to establish dipper, non-dipper, or reverse dipper blood pressure profiles. Once hypertension is known and managed, BP monitoring could be done via ABPM, according to a standardized protocol previously explained to the patients. ABPM should certainly be practiced on a regular basis and proposed each time the question of adapting antihypertensive treatment is considered. Indeed, the measurement of ABPM correlates better with target organ damage, i.e., the heart and the graft than office BP value (21,22). Routine ABPM would therefore provide the best understanding of the impact of hypertension on both cardiovascular mortality and graft survival.

It seems appropriate to involve, as much as possible, the kidney transplant recipient in the management of BP, insisting on hygienic and dietary rules, physical exercise, blood pressure objectives, self-measurement, and of course, the expected benefits of optimal BP control on graft survival and cardiovascular morbidity and mortality. The post-transplant follow-up visit is a good opportunity to discuss the problem of hypertension. The reported frequency of use of home self-measurement by kidney transplant patients shows that they are ready to take an active part in the monitoring of hypertension and more than 80% of patients thought that monitoring and managing their hypertension improved their quality of life.

The current KDIGO 2021 recommendations, the most recent and detailed to date in the field, recommend BP figures < 130/80 mmHg, based on consultation BP measurement, using a calcium channel blocker or ARB-II as first-line therapy. These recommendations are based on the results of meta-analyses comparing each therapeutic class versus placebo. With the use of dihydropyridine CCB, a 38% reduction of the graft loss was observed, over a period of 25 months (RR: 0.62; 95% CI: 0.43-0.90) and of 65% with the use of ARB (RR: 0.35; 95% CI: 0.15-0.84). In contrast, neither CCB nor ARB showed a reduction in all-cause mortality or cardiovascular events. For the other drug classes, including ACEi, beta-blockers, alpha-blockers, and anti-aldosterone agents, no significant difference was observed in graft function, all-cause mortality, or cardiovascular events compared with placebo. In our study, the drug class used as first-line therapy was CCB, in 57% of cases or ACEi/ARB in 37% of cases in the absence of proteinuria or fluid retention, i.e., good adherence to the recommendations in over 90% of cases. In summary, the four molecules preferred by nephrologists for the management of hypertension in transplant patients were calcium channel blockers in the first place, followed by ACEi/ARB, then thiazide diuretics and beta blockers. More rarely, nephrologists used alphas blockers, central antihypertensives and anti-aldosterone. The averages are globally equivalent for the three classes mentioned above, with homogeneous standard deviations, globally wider than for the therapeutic class used in first intention, testifying to the absence of recommendations concerning the use of these molecules and therefore a varied management, often based on the experience of the nephrologist or the habits of the center.

This is the first study assessing BP management in kidney transplant recipients with comparison of nephrologist and patients' point of view. Our study shows a good adequacy with the KDIGO 2021 recommendations, the most recent and most detailed on the management of hypertension in kidney transplant patients. To date, although no antihypertensive molecule alone against placebo has shown a reduction in the risk of cardiovascular mortality, the management of hypertension remains a priority, and probably relies on the combination of several molecules. Ambulatory and home BP measurement, better correlated with target organ damage, should be encouraged, and the implementation of interventional studies on ambulatory BP measurement in these patients seems to be essential.

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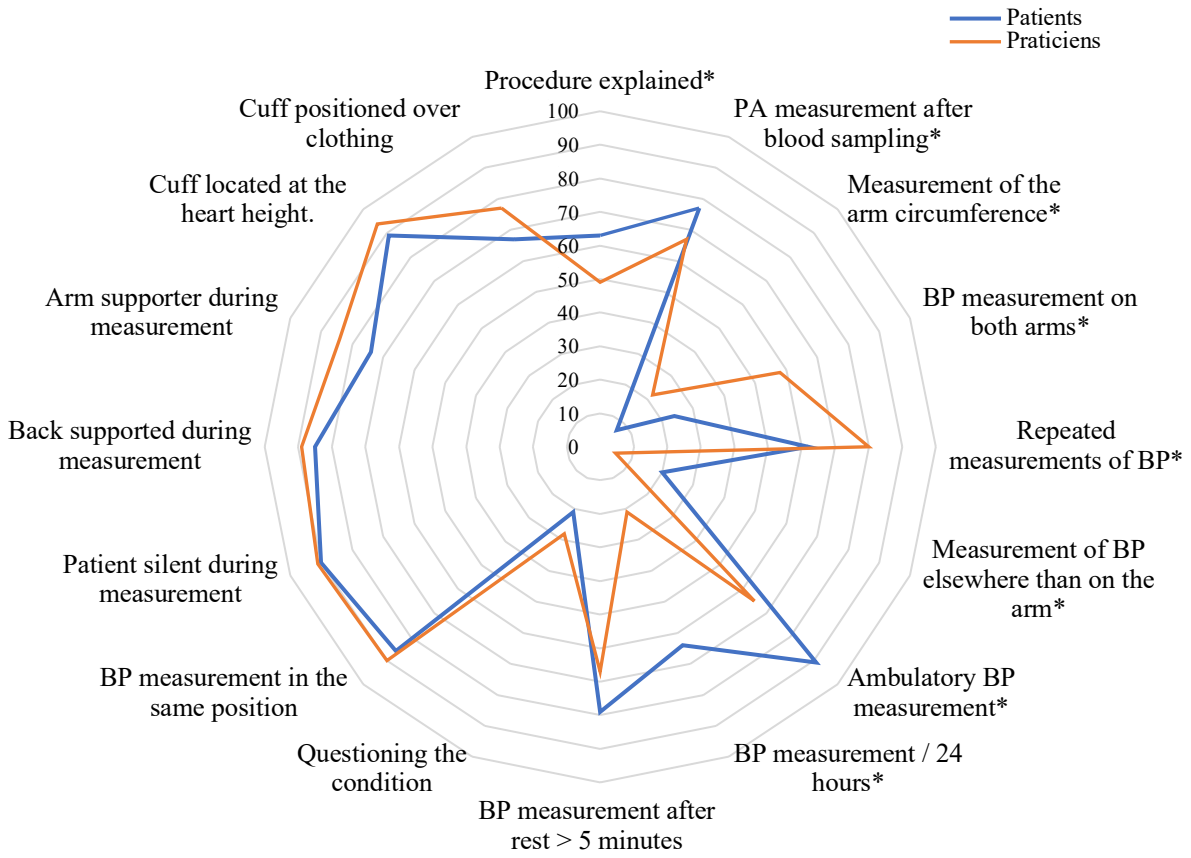
Table 1: Health professionals characteristics

Health professionals, n=78	**N (%)**
Gender	
Male	43 (55,1%)
Female	35 (45,9%)
Age (Years)	
18 - 30	4 (5,1 %)
31 - 40	33 (42,3%)
41 – 50	21 (26,9%)
51 - 60	14 (17,9%)
61 – 70	6 (7,7%)
Type of center	
University hospital	56 (71,8%)
Regional hospital	22 (28,2%)
Kidney transplant experience (years)	
< 10	28(35,9%)
10– 20	30 (38,5%)
21 – 30	12 (15,3%)
>30	8 (10,3%)
Number of trials as inverstigator	
None	34 (43,6%)
1 – 5	23 (29,5%)
5 – 10	9 (11,5%)
10 – 15	3 (3,9%)
>15	9 (11,5%)

Table 2: Patients' characteristics

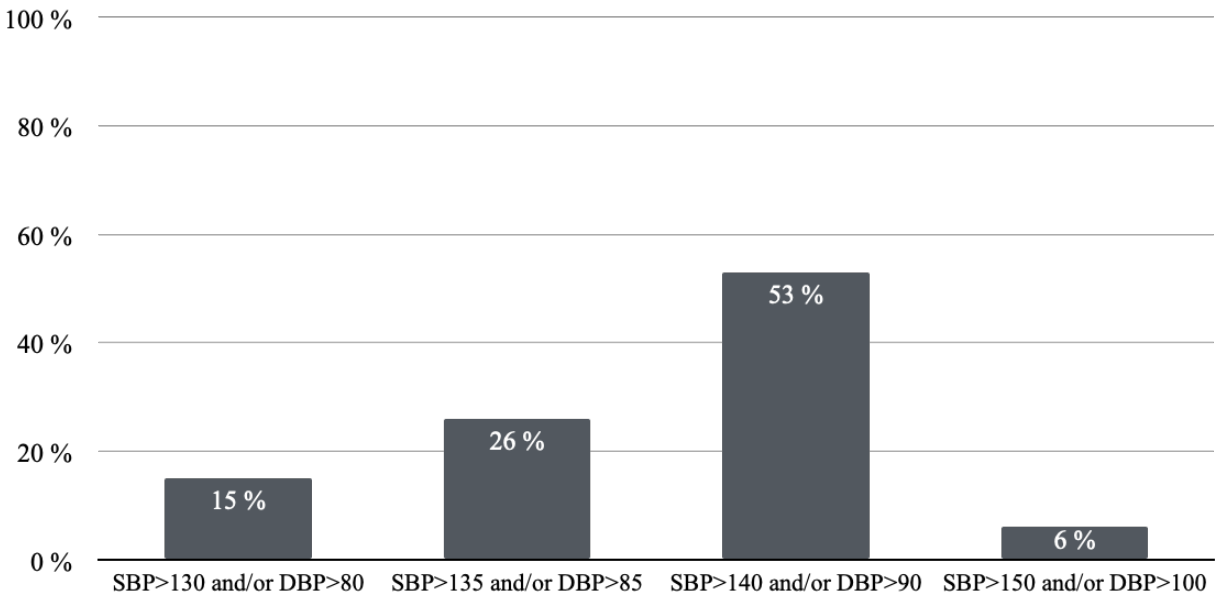
Patients, n=86	**N (%)**
Gender	
Male	53 (61,6%)
Female	33 (38,4%)
Age (Years)	
18-30	8 (9,3%)
31-40	8 (9,3%)
41-50	16 (18,6%)
51-60	19 (22,1%)
61-70	18 (20,9%)
71-80	14 (16,3%)
>80	3 (3,5%)
Time since transplantation (months)	
< 6	19 (22,1%)
6 – 12	10 (11,6%)
12 – 24	7 (8,1%)
> 24	50 (58,1%)
Hypertension	
Yes	64 (74,4%)
No	22 (25,6%)
Antihypertensive drugs	
Yes	71 (82,6%)
No	15 (17,4%)

Figure 1: Blood pressure measurement in kidney transplant recipients: comparison of nephrologists and patients' perspectives



* item with significant difference ($p < 0,05$)

Figure 2: Blood pressure targets (mmHg) used by nephrologists for drug modification in kidney transplant recipients



SBP: Systolic Blood Pressure
DBP: Diastolic Blood Pressure

Figure 3: Post-renal transplantation time to introduce ACEi or ARB for hypertension

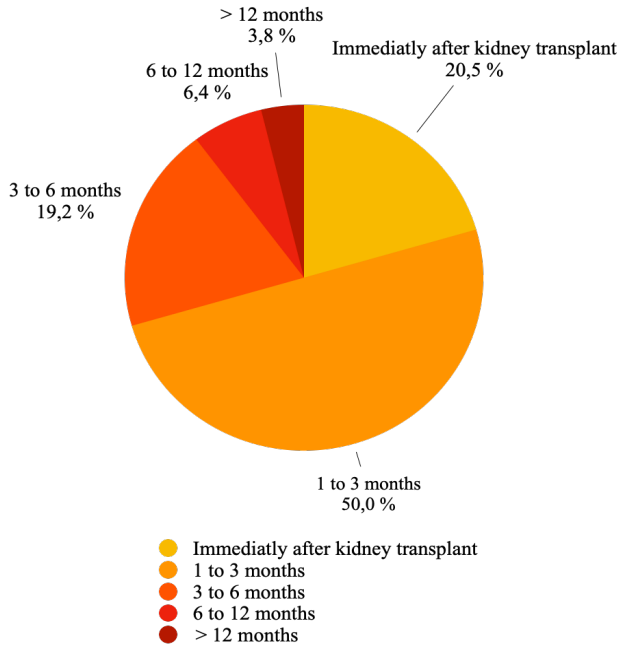


Figure 4: Proportion of increase in serum creatinine tolerated after introduction of an ACEi or ARB in kidney transplant patients

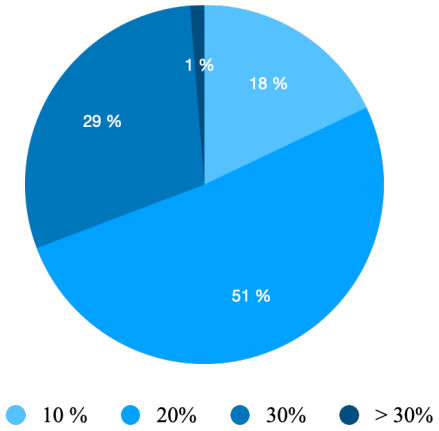


Figure 5: Therapeutic strategy for the management of hypertension in kidney transplant patients: Ranking of the different therapeutic classes in order of choice, express in means and standard deviations.

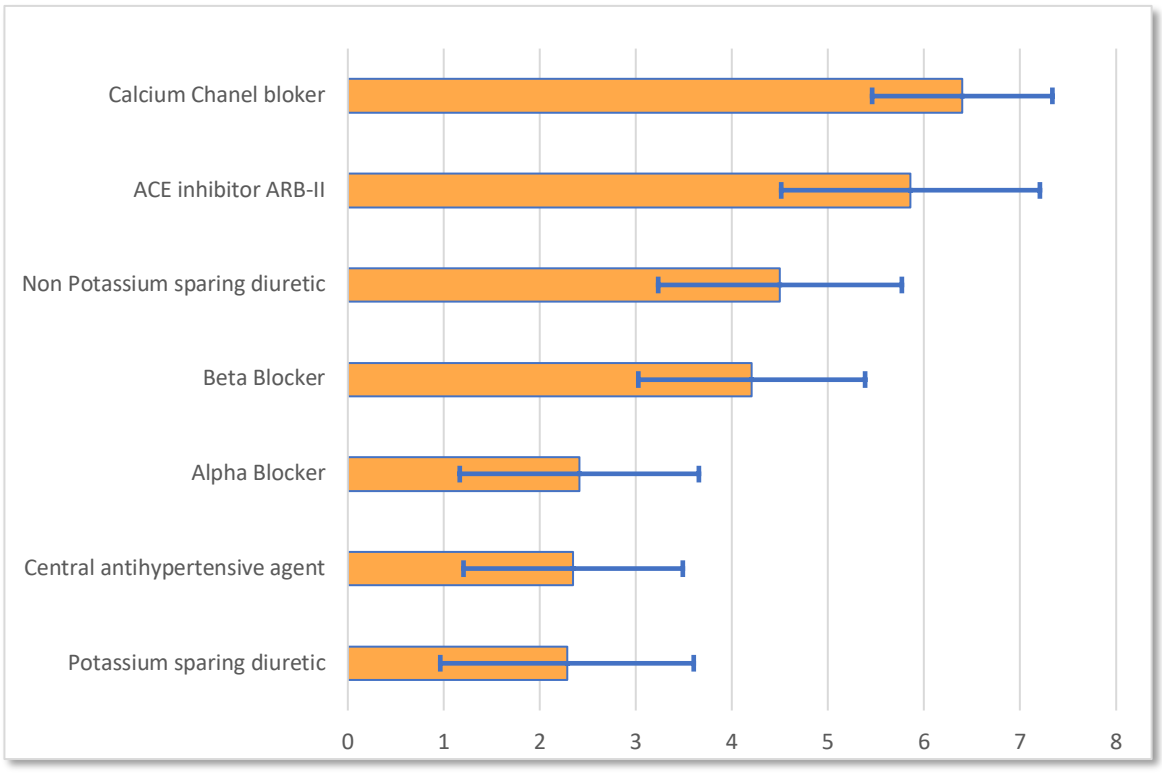


Figure 6: Therapeutic class used for resistant hypertension in kidney transplant patients

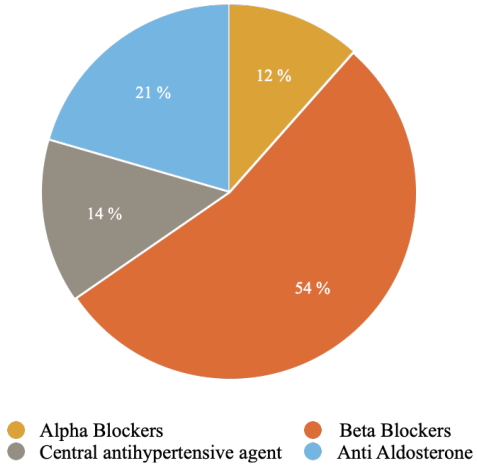


Figure 7: Maximum tolerated kalemia when introducing anti-aldosterone therapy in kidney transplant patients

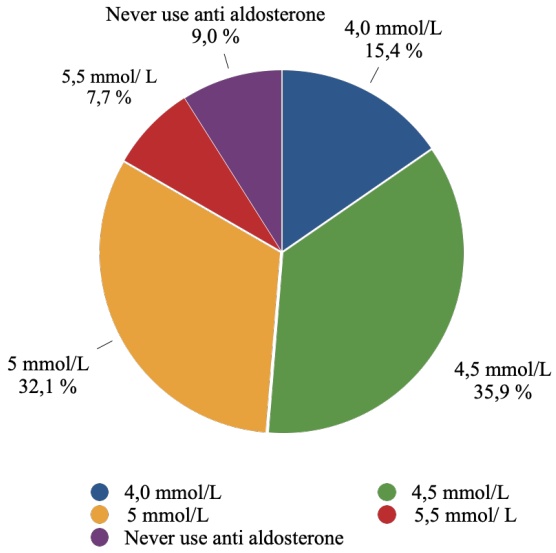
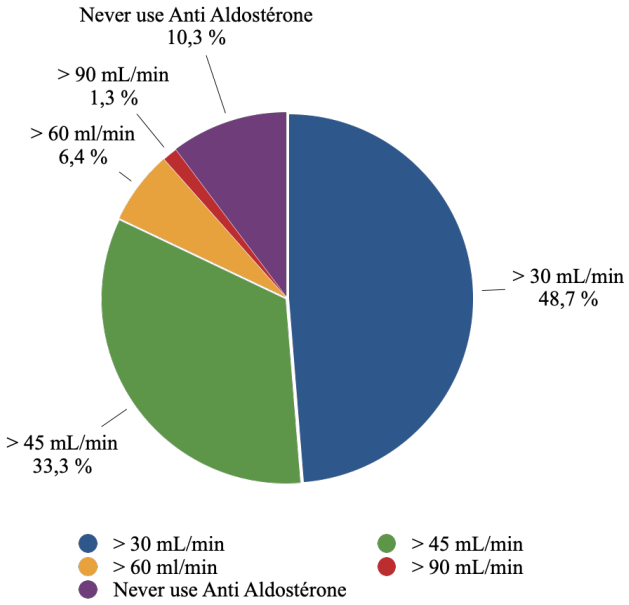


Figure 8: GFR limit for the introduction of anti-aldosterone therapy for resistant hypertension, in the absence of hyperkalemia, in renal transplant patients



Supplementary files

Annex 1: Health professional survey

Demographic Data

Gender:
Man
Woman

Age group:
18-30
31-40
41-50
51-60
61-70
>71

City
Country

Role:
Nephrologist
Cardiologist
General practitioner
Other

Years of experience in kidney transplantation
< 10
11– 20
21– 30
>30

No of transplantation trials as investigator
0
1-5
6 – 10
11 – 15
>15

Type of center
Regional / District hospital
University / Teaching hospital

Your email (if you wish to communicate it)

Practice of blood pressure (BP) measurement

1. Is the BP measurement explained at the first measurement?
   Yes
   No

2. Before BP measurement, does the patient rest for at least 5 minutes?
   Yes
   No

3. Before BP measurement, does the operator ask whether: in the last hour, the patient : smoked, ate or drank caffeine; or made some physical activity or effort, or: if the patient was nervous ?
   Yes
   No

4. Is the BP measurement taken before blood sampling or puncturing?
   Yes
   No

5. Does the operator ever measure the arm circumference?
   Yes
   No

6. Does the operator ever measure the BP in both arms at least once?
   Yes
   No

7. Are BP measurement made always in the same body position?
   (If the answer is Yes, precise in which position)
   Yes
   No
   Flat chair
   Upright chair
   Lying

8. Does the operator measure the BP only once or does he/she repeat the measurement after one minute?
   Yes
   No

9. During BP measurement, is the room calm (low noise and no distraction)?
   Yes
   No

10. During BP measurement, is the patient silent?
    Yes
    No

11. During BP measurement, is the patient's back supported by the chair or bed saddle?

Yes
No

12. During BP measurement, is the arm supported (on a table if seated, or on the bad if outstretched)?
    Yes
    No

13. During BP measurement, is the cuff positioned at the same height as the heart of the patient?
    Yes
    No

14. During BP measurement, is the point where the cuff is located uncovered?
    Yes
    No

15. During BP measurement, does the operator place two fingers on the patient's wrist to perceive his pulse (as shown into the figure)?
    Yes
    No

16. Is the BP measurement ever been taken at another location than the arm? (If Yes, precise which one)
    Yes
    No
    Wrist
    Ankle

17. Is BP always measured at home in your patients?
    Yes
    No

    17.1 If so, according to a standard protocol?
        Yes
        No

    17.2 If Yes to a standard protocol, is the BP measured at rest?
        Yes
        No

    17.3 If Yes to a standard protocol, is the BP measured on morning and evening?
        Yes
        No

    17.4 If Yes to a standard protocol, is the BP measured fasting?
        Yes
        No

    17.5 If BP always measured at home, on what periodicity? At least
        Once/1 month
        Once/ 3 months

Once/ 6 months
Once /12 months
If necessary

18. Is BP always measured over 24h in your patients?
Yes
No

18.1 If so, on what periodicity ? At least
Once /1 month
Once/3 months
Once/6 months
Once/12 months
If necessary

18.2 If so, on what duration ?
24 hours
48 hours

19. Are BP measurement done unattended or unobserved?
Yes
No

20. Who is the operator for the BP measure?
The physician
The nurse
Other

Your material

21. What kind of devices is used for BP measurement?
Auscultatory method
Oscillometric device
Other

22. Has your device been validated?
Yes
No
I don't know

23. What size of cuts do you have?
Extra small Pediatric
Small
Medium
Large
Extra large

Your management for anti-hypertensive therapeutics?

24. Wich measurement do you use to modify the antihypertensive drug of your patient?
BP measured in consultation
BP self-measured at home

BP measured over 24h

25. After confirmation of the BP measurement, when do you increase the posolgy of the antihypertensive drugs or add a new drug?
    PAS ≥150 mmHg and/or PAD ≥ 100 mmHg
    PAS ≥ 140 mmHg and/or PAD ≥ 90 mmHg
    PAS ≥ 135 mmHg and/or PAD ≥ 85 mmHg
    PAS ≥ 130 mmHg and/or PAD ≥ 80 mmHg

26. How long after the kidney transplantation do you allow the introduction of an ACE inhibitor r an ARB?
    Immediately after the transplantation
    After 1 to 3 months
    After 3 to 6 months
    After 6 to 12 months
    After 12 months

27. After the introduction of an ACE inhibitor or an ARB, what increase of serum creatinine do you allow?
    10 %
    20 %
    30 %
    > 30%

28. In a patient with resistant hypertension (patient with already non potassium sparing diuretic, ACE inhibitor or ARB and CCB, maximal posology tolerated), which type of medication do you introduce first?
    Potassium sparing diuretic / Anti aldosterone drug if possible
    Alpha blockers
    Beta blocker
    Central antihypertensive agent

29. Please indicate your strategy of treatment for hypertension by ranking the 7 different anti-hypertensive agent from 1 to 7, 1 is the first medication you use and 7 the last one (for a patient without fluid overload or heavy proteinuria)
    ACE inhibitor or ARB
    Alpha blockers
    Beta blockers
    CCB
    Central antihypertensive agent
    Non potassium sparing diuretic
    potassium sparing diuretic/ anti aldosterone drug

30. From which threshold of proteinuria do you introduce an ACE inhibitor or an ARB?
    > 0,5 g/24h or g/g
    >1g/24h or g/g
    > 2g/24h or g/g
    >3g/24h or g/g

31. In front of a proteinuria > 3g/24h, do you use a dual blockade of the renine angiotensin system with ACE inhibitors an ARBs?
    Yes

No

32. In patients with true resistant hypertension, from which threshold of serum K+ would you accept to initiate an anti-aldosterone drugs (Aldactone)?
    4mmol/L
    4,5 mmol/L
    5 mmol/L using Kayexalate or a new potassium binder
    5,5 mmol/L using Kayexalate or a new potassium binder
    I would never initiate anti aldosterone drugs in renal transplant recipients

33. In patient with true resistant hypertension with normal serum potassium, from which threshold of eGFR would you accept to initiate an anti-aldosterone drugs (Aldactone)?
    90mL/min/1.73m2
    60 mL/min/1.73m2
    45 mL/min/1.73m2
    30 mL/min/1.73m2
    I would never initiate anti aldosterone drugs in renal transplantation recipients

34. Which recommendation do you use?
    KDIGO
    ESH-ESC
    JCN7
    Other

35. Do you have any comments?

Annex 2: Patient survey

Demographic data

What is your gender?
Male ☐ Female ☐

What is your age range?
18/30 ☐ 31/40 ☐ 41/50 ☐ 51/60 ☐ 61/70 ☐ 71/80 ☐ > 80 ☐

How long have you been transplanted?
< 6 months ☐ 6 to 12 months ☐ 1 to 2 years ☐ Over 2 years ☐

Do you have hypertension?
Yes ☐ No ☐

Do you take medication for hypertension?
Yes ☐ No ☐
If so, how many different drugs/molecules? |___| I don't know ☐

Questionnaire regarding your blood pressure (BP) measurement during your last transplant follow-up visit:

1. Before the blood pressure measurement, did the physician explain the procedure?
Yes ☐ No ☐

2. Before the last blood pressure measurement, were you at rest for at least 5 minutes?
Yes ☐ No ☐

3. Before measuring your blood pressure, did the physician ask you if, in the last hour, you had: Smoked? Eaten? Drank coffee? Had any physical activity or made any effort (e.g. climbing stairs)? Been anxious?
Yes ☐ No ☐

4. Is the blood pressure measurement done after the blood sample is taken?
Yes ☐ No ☐

5. Has the operator ever measured the circumference of your arm?
Yes ☐ No ☐

6. Has the operator ever taken blood pressure on both arms at least once?
Yes ☐ No ☐

7. Is the blood pressure measurement always performed in the same position?
Yes ☐ No ☐

8. Which one?
Sitting in the armchair ☐ Sitting on a chair ☐
Lying on the exam table ☐ Sitting at the edge of the examination table ☐

9. Does the operator measure the blood pressure only once, or does he repeat the measurement?
Only once ☐ Repeated measures ☐

10. During the blood pressure measurement, were you silent?
Yes ☐ No ☐

11. During the blood pressure measurement, was your back supported by the examination chair or table?
Yes ☐ No ☐

12. During the blood pressure measurement, was your arm supported?
(e.g., by a table if you were sitting or resting on the examination table)
Yes ☐ No ☐

13. During the blood pressure measurement, was the cuff at the same height as your heart?
Yes ☐ No ☐

14. During the blood pressure measurement, was the cuff placed over your clothing?
Yes ☐ No ☐

15. Has the blood pressure measurement ever been performed anywhere other than on your arm?
Yes ☐ No ☐

16. Have you ever measured your blood pressure at home?
Yes ☐ No ☐
If yes, did you do a 3-day collection of 3 measurements morning and evening?
Yes ☐ No ☐

17. Has your blood pressure ever been measured over 24 hours?
Yes ☐ No ☐

18. Do you know your blood pressure objective?
Yes ☐ No ☐
If so, what is it? |_____| / |_____| **mmHg**

19. Do you think your blood pressure monitoring is adequate?
Yes ☐ No ☐

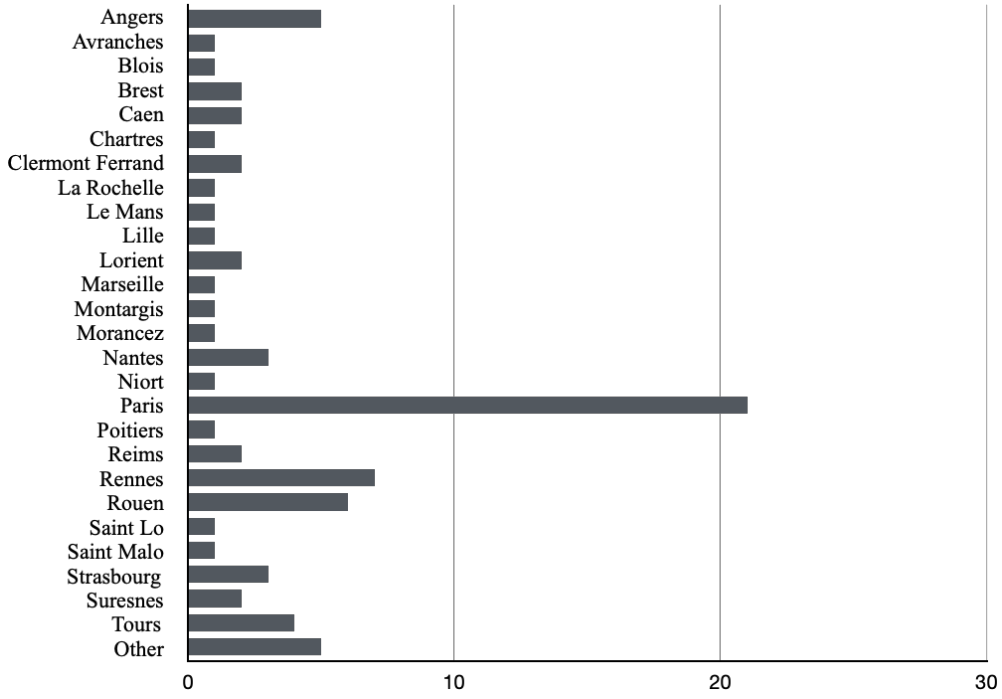
20. Do you think your treatment for hypertension is improving your quality of life?
Yes ☐ No ☐

21. Do you think your treatment for hypertension is too restrictive?
Yes ☐ No ☐

22. Do you think you are compliant with your treatment for hypertension?
Yes ☐ No ☐

23. Do you have any comments?

Figure S1: Distribution by city of nephrologists who participated in the study



Vu, le Directeur de Thèse

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Par FILLON Alexandre

Nombre de pages : 44
Nombre de tableau : 2
Nombre de figure : 9

Abstract

Context: Cardiovascular mortality is the leading cause of death in kidney transplant recipients. Hypertension, whose prevalence is close to 80% in these patients, is the first modifiable cardiovascular risk factor. Practices for the management of hypertension in kidney transplant recipients are diverse and scientific data are missing. The objective of this study is to describe the practices concerning the measurement of hypertension and its pharmacological management by healthcare professionalś and to compare the results with data collected from kidney transplant recipients.

Material and method: A survey was distributed to French nephrologists and kidney transplant recipients. The questions concerned blood pressure (BP) measurement, its therapeutic management, and compliance.

Results: We received responses from 78 nephrologists and 86 patients. For the therapeutic drug management of hypertension, healthcare professionals introduced calcium channel blockers followed by renin angiotensin system inhibitors as first-line therapy (58% and 37%). Once triple antihypertensive therapy is required, nephrologists introduce non-potassium-sparing diuretics in more than half of the cases (51%), in the absence of proteinuria. Regarding BP measurement, practitioner and patient responses were similar for 8 questions, but 8 questions had significant differences, particularly regarding ambulatory BP measurements. A majority of patients felt an improvement in their quality of life related to the treatment of hypertension (80%), and 71% reported being compliant.

Conclusion: Therapeutic management of hypertension is mostly done in accordance with the KDIGO recommendations. Ambulatory and home BP measurement is insufficient and yet indispensable in this population at high risk of resistant hypertension, masked hypertension and nocturnal hypertension. Interventional studies on the use of ambulatory and home BP measurement in kidney transplant patients seem indispensable.

Key words: Nephrology, Transplantation, Blood Pressure, Cardiovascular, Hypertension, Risk factor, Monitoring, Pharmacology, Compliance

Jury:

Président du Jury : Professeur HALIMI Jean Michel

Directeur de thèse : Docteur SAUTENET Bénédicte

Membre du Jury : Professeur BUCHLER Mathias

Professeur GATAULT Philippe

Docteur BARBET Christelle

Date de la soutenance : Le 22 octobre 2021