Optimizing hypertension management in renal transplantation: a call to action*

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INTRODUCTION

Cardiovascular events represent a major cause of death in renal transplant patients [1,2]. Renal transplant recipients also constitute a population at very high risk for progressive graft loss and renal events. Although immunological risk factors play an important role in renal survival, it is less recognized that hypertension is probably the major nonimmunological risk factor for graft loss [2]. Accurate diagnosis of hypertension and adequate control of blood pressure (BP) is considered as a fundamental goal in the management of renal transplant patients to lower their cardiovascular and renal risk. However, diagnosis, treatment and monitoring of hypertension remain suboptimal in most renal transplant patients [3]. This editorial is a call for action aiming at improving hypertension control in the transplant population.

BLOOD PRESSURE CONTROL AND THE RISK OF GRAFT LOSS AND CARDIOVASCULAR DEATH

Most renal transplant recipients exhibit high BP (Fig. 1). However, the prevalence of true hypertension is not clearly known and seems to vary widely with duration of transplantation, renal function and probably many other parameters. In a recent study, in hypertensive renal transplant recipients in France, 89.5% patients were hypertensive patients; among them, only 45.5% had controlled hypertension [using office BP measurements and the 130/80 mmHg Kidney Disease Improving Global Outcomes (KDIGO) cutoff value]; resistant hypertension (high BP values despite three or more antihypertensive medications) was present in 17.5% of patients [4]. It can be argued that the use of 130/80-mmHg cutoff may overestimate the prevalence of uncontrolled hypertension; however, *unattended* BP measurements were used in this study, and therefore, the prevalence of uncontrolled hypertension was probably *underestimated*. In another study, resistant hypertension was reported in 23.5% of cases [5]. Whether comparable findings are observed in other centers is presently unknown. Of note, hypertension and uncontrolled hypertension seem more frequent in renal transplantation than in heart, liver or lung transplantation from centers in Switzerland (Fig. 1).

Ambulatory BP monitoring (ABPM) is not commonly used in the transplantation field. However, ABPM is especially useful in this population. Recent data indicate that the prevalence of nocturnal hypertension exceeds the prevalence of hypertension using office BP or daytime ABPM, and is associated with markers of vascular damage [6]. A study from Spain has found that the prevalence of white-coat hypertension (WCH) is 23%, whereas the prevalence of masked hypertension is 20% among 868 hypertensive renal transplant recipients, when using the cutoff value of 130/80 mmHg average 24-h ABPM [5]. In another study, the respective figures for WCH and masked hypertension were 3 and 56%, respectively [7].

Many factors have been identified as potential causes for the development of hypertension in renal transplant patients. This includes chronic allograft nephropathy, the use of calcineurin inhibitors and steroids, the recurrence of glomerulonephritis and diseased native kidneys [1]. Secondary causes of hypertension may also exist in this population.

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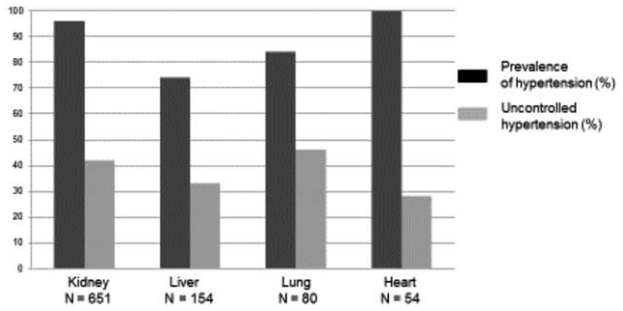

FIGURE 1 Prevalence of hypertension and uncontrolled hypertension in solid organ transplantation [24].

Secondary hypertension was suspected in 14 of 1008 (1.4%) patients initially recruited in the study of Arias-Rodríguez *et al.* [5]. In the current literature, it remains however unclear whether a systematic assessment of the cause of hypertension would result in similar figures. Of note, the incidence of transplant renal artery stenosis is highly variable (1–16%) and the reasons for this variability are unclear [8].

Observational studies usually show that high BP is associated with worse renal and cardiovascular outcomes [8,9]. Indeed, in the European transplant registry, Opelz *et al.* have reported a stepwise improvement in both graft and patient survival with lower BP, without evidence of a *J*-curve effect [9]. Moreover, in a post-hoc analysis of the FAVORIT trial, Carpenter *et al.* [10] assessed the associations of BP with cardiovascular disease and mortality in 3474 kidney transplant recipients; after multiple adjustments, each 20-mmHg increase in SBP was associated with a 32% increase in the risk for cardiovascular events, whereas each 10-mmHg decrease in DBP below the 70-mmHg level was associated with a 31% increase in cardiovascular risk, whereas no such an association emerged for levels above 70 mmHg. As this post-hoc analysis was observational in nature, the link between DBP and cardiovascular risk may result from reverse causality and/or be seen as an expression of arterial stiffening and wide pulse pressure (PP). In this respect, it should be noted that wide PP is an important risk modifier for the adverse effect of low DBP [11].

CURRENT GUIDELINES: WHAT IS RECOMMENDED, WHAT WE DO KNOW AND WHAT WE DON'T

The BP target in renal transplant patients remains unclear. Of note, there are no recommendations for BP targets in renal transplant recipients in the latest european society of hypertension/european society of cardiology (ESH/ESC) guidelines [12]. The KDIGO guidelines suggest to lower BP less than 130/80 mmHg in renal transplant recipients [13]. However, this recommendation is not based on randomized clinical trials (RCTs) but rather on observational studies and extrapolations from other populations (this recommendation is graded two-dimensional).

According to the ESH/ESC guidelines, physicians should assess the presence of target organ damage in all hypertensive patients to improve the assessment of the patients' cardiovascular risk [12]. Thus, an evaluation of left ventricular hypertrophy and function and an assessment of large artery function, including PP, central aortic pressure and carotid–femoral pulse wave velocity are recommended to detect large artery stiffness and hypertensive heart disease in patients with hypertension [13]. Today, it is unknown whether these cardiac and vascular evaluations are performed, and whether treatment protocols considering these investigations improve the outcome of renal transplant patients.

Hypertension in renal transplantation is often difficult to manage. Over the last decade, special attention has been given to the diagnosis and management of resistant hypertension in chronic kidney disease (CKD) and hypertensive populations [14]. However, the prevalence, the diagnosis (using ABPM) and the management of resistant hypertension in renal transplantation remain an underinvestigated area [5,7]. This clearly reflects that not only the insufficient application of ABPM or home BP in renal transplant patients but also scarce clinical research on the management and diagnosis of resistant hypertension in this population.

There are still controversies regarding the choice of the antihypertensive medications in transplant patients. For instance, some studies claimed that the use of renin–angiotensin system (RAS) blockers results in prolonged graft and patient survival [15], whereas others did not find any renal protection by these agents [16]. A Cochrane systematic review published in 2009 found that placebo-controlled studies testing angiotensin-converting enzyme inhibitors (ACEis) in renal transplant patients were inconclusive [17]. This meta-analysis showed that ACEi may expose transplant recipients to a higher risk of hyperkaliemia and anemia as compared with other agents, and that calcium-channel blockers may be associated with better renal protection in hypertensive kidney transplant recipients [17]. The conclusion was that 'more high quality studies reporting patient centered outcomes are required'. Since then, other RCTs [18,19] were published, but they were underpowered and inconclusive. In renal transplant recipients with proteinuria, the use of RAS blockers is advocated as they may provide renal protection [15,20]. However, ramipril was not superior to placebo on hard endpoints in a recent – although underpowered – RCT in proteinuric renal transplant recipients [21]. Of note, median proteinuria in this trial was only 0.4 g/day, that is well below the 1 g/day threshold in which RAS blockade has shown its beneficial renal effects in the general and in the CKD populations. A recent meta-analysis reconsidering the effect of ACE inhibition and angiotensin II antagonism on renal outcomes in transplant patients did not provide a definitive response to this issue [22]. A trial enrolling over 10 000 patients would be needed to definitively answer the question whether interference with the RAS may mitigate transplant loss in this population [22]. Given the dimension of the trial, it seems unlikely that such a trial will be performed in the foreseeable future. Comparative effectiveness studies based on analyses in large international databases seem to be a more realistic alternative to further investigate this issue.

THE CURRENT INVOLVEMENT OF THE SCIENTIFIC COMMUNITY IS INSUFFICIENT

It is obviously hard to evaluate the contribution of scientists in a specific area, and it is even harder to estimate the

TABLE 1. Scientific communications related to hypertension in renal transplantation in most recent international meetings

	Number of oral communications
International meetings	
Transplantation	
Europe (Brussels, ESOT, 2015)	0
USA (Chicago, ATC, 2017)	3
Nephrology	
Europe (Madrid, EDTA-ERA, 2017)	7
USA (ASN, Chicago, 2016)	1
Hypertension	
Europe (Milano, ESH, 2017)	2
USA (New-York, ASH, 2016)	0

relative weight of research in a specific area in relation to the clinical needs. Studies indicate that hypertension is a modifiable factor associated with reduced long-term graft survival and a higher risk of cardiovascular events and mortality. This should prompt initiation of a large number of studies dedicated to these issues. One way to assess the real interest for these topics is to estimate the number of scientific communications in large meetings or publications. Actually, the number of abstracts focused on hypertension in renal transplantation presented in the most recent major European and American scientific meetings in nephrology, transplantation and hypertension is very small indeed, and sometimes this topic was not even included in the program of these meetings (Table 1). This lack of focus on a major clinical problem in a high-risk population like transplant patients is concerning, because hypertension control remains a largely unmet clinical need in these patients. The scarce focus on hypertension control within the community of renal transplant physicians may perhaps be explained by the fact that the main focus of researchers and clinicians involved in renal transplantation is the prevention and management of acute and chronic rejection, nonimmunological factors such as hypertension and proteinuria being considered of minor relevance for the long-term outcome of renal transplant patients [20].

A CALL TO ACTION

Hypertension management still relies on expert opinion rather than on hard evidence, and essential data are lacking. A definition of what should be an adequate hypertension management needs to be proposed based on data regarding pathophysiology, specific BP targets, real-life high BP prevalence, BP control, RCTs demonstrating the clinical benefits of BP lowering in terms of renal and major cardiovascular events and an appropriate use of antihypertensive drugs.

Surveys aimed at assessing the prevalence of hypertension (including white-coat and masked hypertension) and feasible RCTs in this patients' population are urgently needed. As representatives of scientific societies, we commit ourselves to promote efforts to provide systemic reviews on specific topics such as the prevalence of resistant hypertension, the association of BP levels and renal and cardiovascular outcomes, and the effect of antihypertensive drugs in well designed RCTs [23]. We believe that these data will stimulate our community to provide innovative research programs in hypertension in renal transplantation for the benefit of renal transplant patients.

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Conflicts of interest

There are no conflicts of interest.

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