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Blood Pressure Goals and Outcomes in Kidney Transplant Recipients in an Analysis of the Collaborative Transplant Study

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Introduction: Hypertension is an independent risk factor for cardiovascular disease, the leading cause of death in kidney transplant recipients. However, optimal blood pressure targets posttransplant remain uncertain. We investigated the impact of different American College of Cardiology and the American Heart Association (ACC/AHA) blood pressure categories on graft survival and patient mortality, and analyzed subgroup-specific effects.

Methods: This large-scale retrospective study included 1-year blood pressure data from 62,556 kidney transplant recipients across 209 centers in 39 countries, using the collaborative transplant study (CTS) database. Primary outcomes were death-censored graft failure and patient mortality during first 6 years posttransplantation. Multivariable Cox regression analysis controlled for multiple immunological and nonimmunological confounders.

Results: At 1 year posttransplant, 77% of kidney transplant recipients had hypertension. We did not find a significant difference in death-censored graft failure and patient mortality between patients with normal blood pressure ($<$ 120/$<$ 80 mm Hg) and those with elevated blood pressure (120–129/$<$ 80 mm Hg). Hypertension stages 1 (130–139/80–89 mm Hg) and 2 ($\geq$ 140/$\geq$ 90 mm Hg) were associated with an 11% and 55% increased risk of death-censored graft failure, respectively. Patient mortality was only significantly increased in those with hypertension stage 2. Kidney transplant recipients with hypertension stage 2 continued to have an increased risk of graft failure, even when they achieved normal blood pressure in the second year posttransplant. Certain subgroups of patients were at particularly high risk of detrimental effects of high blood pressure.

Conclusion: This study highlights the negative impact of hypertension early after kidney transplantation and emphasizes the importance of effective treatment to improve long-term graft and patient survival.

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The systolic blood pressure intervention trial led to a reconsideration of blood pressure targets after a systolic blood pressure (SBP) of $<$ 130 mm Hg had been shown to significantly reduce cardiovascular and all-cause mortality compared with liberal blood pressure management in a high-risk cardiovascular population.[1] Accordingly, in 2017, the ACC/AHA in partnership with 9 other professional societies adjusted its blood pressure targets for adults and recommended an SBP of $\geq$ 130 mm Hg or diastolic blood pressure (DBP) $\geq$ 80 mm Hg to identify hypertension, which is contrary to European guidelines that defined hypertension as levels $\geq$ 140/90 mm Hg.[2,3] The ACC/AHA hypertension guidelines further proposed a blood pressure classification with categories for normal blood pressure (SBP $<$

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120 and DBP <80 mm Hg), elevated blood pressure (SBP 120–129 and DBP < 80 mm Hg), hypertension stage 1 (SBP 130–139 or DBP 80–89 mm Hg), and stage 2 (SBP ≥ 140 or DBP ≥ 90 mm Hg) based on observations of how hypertension relates to cardiovascular disease and the advantages of reducing blood pressure in clinical trials.[2] In their recent update, the 2024 European Society of Cardiology guidelines retain the definition of "hypertension" as blood pressure ≥ 140/90 mm Hg but introduce a new "elevated BP" category (120–139/70–89 mm Hg) to support more intensive treatment targets for those at higher risk of cardiovascular disease.[4]

Similar to the general population, hypertension is an independent risk factor for cardiovascular disease, which constitutes the leading cause of death in kidney transplant recipients.[5,6] In addition, hypertension with over 80% prevalence in kidney transplant recipients significantly influences death-censored graft failure.[7,8] However, the optimal blood pressure targets and the suitable guideline recommendations for kidney transplant recipients remain unclear. The Kidney Disease: Improving Global Outcomes 2021 Clinical practice guideline recommendation to treat adult kidney transplant recipients for blood pressure values < 130/80 mm Hg is still based on expert opinions, because there are no randomized controlled trials investigating different blood pressure targets in relation to graft survival, cardiovascular events, or mortality.[9,10]

Although we and others showed that an SBP ≥ 140 mm Hg significantly reduces kidney graft and patient survival, the extent to which blood pressure levels should be lowered is not known.[11,12] Observations from the Systolic blood pressure intervention trial indicated that, compared with the standard SBP target of < 140 mm Hg, individuals in the intensive treatment arm (SBP < 120 mm Hg) had higher rates of mild acute kidney injury, incidence of chronic kidney disease, and loss of estimated glomerular filtration rate.[13,14] Therefore, the Kidney Disease: Improving Global Outcomes Working Group hypothesized that a lower SBP target, such as < 120 mm Hg, may not be appropriate for kidney transplant recipients without further data on risks and benefits.[10]

Because there is no "one size fits all" approach to blood pressure targets, particularly in the heterogenous group of kidney transplant recipients, identification of subgroup-specific targets, considering factors such as age and sex, may be appropriate.

In the present large-scale retrospective analysis including more than 60,000 kidney transplant recipients reported to the international CTS, we addressed these issues and examined the effects of different blood pressure targets according to ACC/AHA hypertension categories on death-censored graft survival and patient mortality. In addition, we performed multivariable Cox analyses to identify individualized blood pressure targets for different subpopulations of transplant recipients.

METHODS

Since its initiation in 1982, the CTS has accumulated data from over 500,000 kidney, liver, heart, lung, and pancreas transplants (https://www.ctstransplant.org).[15] The CTS asks participating centers to provide data on posttransplant SBP and DBP in an extended follow-up questionnaire (Supplementary Methods). The first request for information on blood pressure is made at 1 year posttransplant for patients with a functioning graft and then at years 2, 3, 5, and 10. This study included all kidney transplant patients with available 1-year SBP and DBP values from 2000 to 2021, who were adults at the time of blood pressure measurement. Multiorgan transplants, transplants with pediatric recipient or donor, unknown recipient sex, transplant number, or donor relationship were excluded. The work of the CTS is approved by the ethics committee of the Medical Faculty of Heidelberg University (No. 083/2005) and performed in accordance with the Declaration of Helsinki.

According to the 2017 ACC/AHA hypertension guidelines for adult patients, blood pressure values were classified as normal (SBP < 120 mm Hg and DBP < 80 mm Hg), elevated (SBP 120–129 mm Hg and DBP < 80 mm Hg), hypertension stage 1 (SBP 130–139 mm Hgor DBP 80–89 mm Hg), and hypertension stage 2 (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg). Because of the high proportion of patients with hypertension stage 2 in our study cohort and the known influence of blood pressure on graft function, we further subdivided hypertension stage 2 into hypertension stage 2a (SBP 140–159 mm Hg or DBP 90–99 mm Hg) and 2b (SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg) as per the previous guidelines.[16]

The primary outcomes were death-censored graft failure and patient mortality after the first-year posttransplant, up to year 6 posttransplant. To control for confounding factors, the following variables were considered confounders in all multivariable Cox regression analyses: geographical region, year of transplantation, graft number, recipient age, sex and race, pretransplant panel-reactive antibodies, number of human leukocyte antigen (HLA) − A + B + DR mismatches, time on dialysis, cause of end-stage kidney

disease, modality of transplant (living vs. deceased), donor age, cause of donor death, donor history of hypertension, induction therapy, and also the following variables at 1 year posttransplant: treatment for diabetes, immunosuppressive regimen, body mass index, serum cholesterol, administration of statins, and antihypertensive medication. As sensitivity analyses, Cox regressions were performed in key demographic subgroups, taking all confounders into consideration. Interaction terms between the confounders and hypertension were included in supplementary Cox regression analyses. Cox regression results are indicated as hazard ratio (HR) and 95% confidence interval (CI). The software package IBM SPSS Statistics 29 (SPSS Inc, Chicago, IL) was used.

RESULTS

Study Population and Prevalence of Different Hypertension Stages in Kidney Transplant Recipients According to the ACC/AHA Hypertension Guidelines

A total of 62,556 kidney transplant recipients who met the inclusion criteria, reported to the CTS from 209 centers in 39 countries. Only 45 patients (0.07%) had to be excluded because of missing information on recipient gender, transplant number, or donor relationship. The main patient characteristics are shown in Table 1 and extended data are shown in Supplementary Table S1. The median (interquartile range) age at the time of blood pressure measurement was 49 (37–58) years, and 38% of the recipients were female. The majority of patients (89%) had received their first kidney transplant, 69% were kidney recipients from deceased donors, and 81% had no detectable human leukocyte antigen antibodies before transplantation. The cause of end-stage kidney disease and the respective prevalence of stage 1 and stage 2 hypertension are shown in Supplementary Table S2.

At year 1 posttransplant, more than three-quarters of kidney transplant recipients (77%) had SBP levels $\geq$ 130/80 mm Hg and therefore met the diagnosis criteria for hypertension by the 2017 ACC/AHA hypertension guidelines. The distribution of hypertension stages of study patients by recipient age at 1 year posttransplant is shown in Figure 1. The prevalence of hypertension gradually increased with age at transplantation, with approximately 80% of recipients aged $\geq$ 50 years being diagnosed with hypertension. However, even among the individuals in the age group of 18 to 24years, 66% were found to have hypertension, of whom 27% were classified as stage 2 hypertension (Figure 1).

Risk for Death-Censored Graft Failure and Patient Mortality in Correlation With Hypertension Based on 1-Year Blood Pressure Value

Based on blood pressure measured at year 1 follow-up, we determined the risk for death-censored graft failure and patient mortality during the subsequent 5 years posttransplant. Patients with blood pressure level of 120–129/< 80 mm Hg (classified as "elevated" according to ACC/AHA classification) served as reference. Normal blood pressure levels 1 year after transplantation (< 120/< 80 mm Hg) were not associated with a decreased risk for death-censored graft failure during the subsequent 5 years of follow-up. However, the risk for death-censored graft failure was significantly higher in recipients with hypertension (Figure 2). Patient mortality was only significantly increased in those with hypertension stage 2 (HR = 1.13, 95% CI: 1.05–1.22; $P = 0.002$). All detailed HRs with 95% CIs and P values of multivariable Cox regression for the influence of 1-year blood pressure (hypertension stage 2 split into 2a and 2b for more in depth-results) on death-censored graft failure and mortality during the following 5 years posttransplant are shown in Supplementary Table S3.

Because we observed no statistically relevant differences in the risk for death-censored graft failure and mortality in recipients with normal and elevated blood pressure, we combined these 2 groups as the "no hypertension group" (blood pressure values < 130/80 mm Hg) and performed the subsequent analyses on the effects of stage 1 and stage 2 hypertension using the "no hypertension group" as reference. For death-censored graft failure, these aggregations showed HRs of 1.11 (95% CI: 1.02–1.20; $P = 0.018$) for hypertension stage 1 and 1.55 (95% CI: 1.43–1.68; $P < 0.001$) for stage 2 (Table 2).

We conducted a subanalysis to explore how antihypertensive therapy impacts death-censored graft survival among recipients classified as no hypertension, stage 1, or stage 2 hypertension (Supplementary Figure S1). There were no statistically significant differences observed between patients on antihypertensive therapy and those without, for all 3 subgroups, pointing to the relevance of the actual blood pressure value itself as a risk factor, which was obviously not sufficiently controlled by antihypertensive medication in a proportion of patients.

Influence of Hypertension on Death-Censored Graft Failure, Stratified According to Good and Poor Graft Outcome Evaluated at 1-Year Posttransplant

Asking whether hypertension may be particularly relevant in patients with posttransplant immunological complications or impaired graft function, we

Table 1. Demographical, immunological, and clinical data of the study population

Characteristics	Unkn. (%)	Patients *n* (%)	Hypertension (%)			
			No	Stage 1	Stage 2	*P* value
Geographical region	–					< 0.001
Europe		32,260 (51.6)	21.8	34.3	43.9	
North America		3715 (5.9)	31.5	31.6	36.9	
Latin America		18 948 (30.3)	19.1	41.0	39.8	
Australia/New Zealand		3273 (5.2)	28.4	35.3	36.3	
Other		4360 (7.0)	32.5	34.9	32.5	
Year of BP measurement	–					< 0.001
2000–2010		37,274 (59.6)	22.2	34.8	42.9	
2011–2021		25,282 (40.4)	23.2	38.4	38.3	
Graft number	–					< 0.001
First transplant		55,875 (89.3)	22.2	36.2	41.5	
Retransplant		6681 (10.7)	26.0	36.5	37.5	
Recipients sex	–					< 0.001
Female		23,506 (37.6)	26.0	36.0	38.0	
Male		39,050 (62.4)	20.6	36.4	42.9	
Recipient age (yrs)[a]	–					< 0.001
18–39		17,937 (28.7)	27.2	39.6	33.2	
40–59		29,982 (47.9)	21.3	36.9	41.7	
≥60		14,637 (23.4)	19.8	30.8	49.4	
Donor relationship	–					< 0.001
Deceased		43,094 (68.9)	21.4	35.4	43.2	
Living		19,462 (31.1)	25.4	38.3	36.3	
Donor age (yrs)	–					< 0.001
18–59		50,266 (80.4)	23.7	37.3	39.0	
≥60		12,290 (19.6)	18.4	32.0	49.6	
Pretransplant HLA AB	19.3					0.23
negative		40 743 (80.7)	22.2	36.8	41.0	
positive		9 730 (19.3)	22.7	37.2	40.1	
Induction treatment	0.9					< 0.001
No		26 311 (42.4)	22.3	35.4	42.2	
Yes		35 683 (57.6)	22.9	36.9	40.2	
1-year medication[b]	–					
With CNI		59 035 (94.4)	22.6	36.4	41.0	0.011
With antimetabolites		53 387 (85.4)	23.2	36.4	40.4	< 0.001
With steroids		54 380 (86.9)	21.8	36.6	41.6	< 0.001
With antihypertensives		47 850 (76.5)	19.9	35.4	44.7	< 0.001

AB, antibodies; BP, blood pressures; CNI, calcineurin inhibitors; HLA, human leukocyte antigen; Unkn., unknown.
Demographics of 62,556 study patients, *n* (%) and prevalence of hypertension. *P* values of χ^2-tests for hypertension (no, stage 1, stage 2) between categories of characteristic are shown.
[a]At time of blood pressure measurement (1 year posttransplant).
[b]*P* value of χ^2-test between with and without corresponding medication.

categorized kidney transplant recipients into patients with "good outcome" ($n = 31{,}090$) and patients with "poor outcome" ($n = 31{,}466$), the latter defined as the need for antirejection treatment or a serum creatinine ≥ 130 μmol/l at 1 year posttransplant. Serum creatinine was used for stratification because it has the strongest predictive power for the subsequent outcome than all confounders considered;[17] however, it must not be used as a confounder because it correlates with 1-year blood pressure.

In Figure 3, we show the influence of different hypertension stages on death-censored graft failure during the subsequent 5 years posttransplant. Multivariable Cox regression analyses adjusting for confounders in both groups confirmed these results. Among patients with "good outcome", those with hypertension stage 1 did not have an increased risk of death-censored graft failure (HR = 0.99, 95% CI: 0.88–1.11; $P = 0.82$), whereas those with hypertension stage 2 had a significantly increased risk (HR = 1.22; 95% CI: 1.09–1.37; $P < 0.001$) compared with recipients without hypertension. In contrast, kidney transplant recipients with "poor outcome" showed a strong and progressive risk of death-censored graft failure with an HR of 1.12 (95% CI: 1.04–1.21; $P = 0.004$) at hypertension stage 1 and an HR of 1.43 (95% CI: 1.33–1.54; $P < 0.001$) at hypertension stage 2 compared with patients without hypertension.

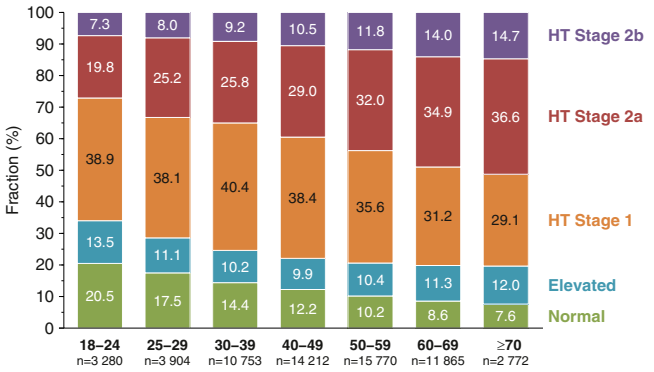

Figure 1. Distribution of hypertension stages at 1-year posttransplant by recipient age in the study cohort. The prevalence of hypertension increases with age at transplantation. Each bar represents a different age group as listed on the x-axis in bold, with the corresponding number of patients given below. The y-axis displays the percentage of patients in different blood pressure categories: normal (< 120/80 mm Hg; green), elevated (systolic blood pressure 120–129 mm Hg and diastolic blood pressure < 80 mmHg; blue), hypertension (HT) stage 1 (130–139/80–89 mm Hg; orange), 2a (140–159/90–99 mm Hg; red), and 2b (≥ 160/≥ 100 mm Hg; purple).

Impact of Hypertension on Death-Censored Graft Failure in Different Subpopulations

We further investigated the risk of hypertension on death-censored graft failure for different subpopulations of kidney transplant recipients (Table 2).

Regarding recipient sex, death-censored graft failure was associated with higher blood pressure particularly in female recipients, with an HR of 1.20 (95% CI: 1.05–1.37; $P = 0.007$) at stage 1 and an HR of 1.67 (95% CI: 1.47–1.90; $P < 0.001$) at stage 2 hypertension. In contrast, male recipients had an increased risk of death-censored graft failure only at stage 2 hypertension, showing an HR of 1.48 (95% CI: 1.33–1.64; $P < 0.001$), whereas no significant adverse effect on death-censored graft failure was observed at stage 1 hypertension.

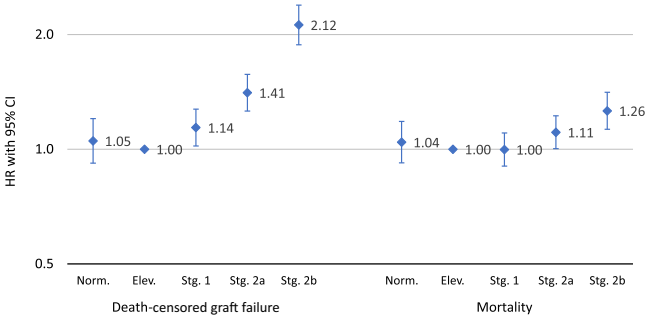

Figure 2. Risk associated with blood pressure levels recorded at 1-yr for death-censored graft failure and patient mortality during the following 5 yrs posttransplant. The risk for death-censored graft failure (left panel) and patient mortality (right panel) during the subsequent 5 yrs posttransplant were assessed using blood pressure measurements obtained at the year 1 follow-up. Hazard ratios (HR) with 95% confidence interval (CI) of multivariable Cox regression with all mentioned confounders are shown. Patients with blood pressure of 120–129/< 80 mm Hg serve as reference (HR = 1.0). The exact values of the 95% CI with the corresponding *P* values are given in Supplementary Table S3.

Regarding recipient age, the negative impact of higher blood pressure levels on death-censored graft survival was more pronounced in younger recipients. Recipients aged 18 to 39 years and 40 to 59 years with stage 1 hypertension, showed an increased risk for death-censored graft survival with HRs of 1.16 (95% CI: 1.02–1.32; $P = 0.025$) and 1.14 (95% CI: 1.00–1.31; $P = 0.054$), respectively; and the HRs increased to 1.71 (95% CI: 1.50–1.94; $P < 0.001$) and 1.67 (95% CI: 1.47–1.90; $P < 0.001$), respectively, in stage 2 hypertension. In recipients aged ≥ 60 years, a marked increased risk of death-censored graft failure was observed only in those with stage 2 hypertension, with an HR of 1.25 (95% CI: 1.05–1.49; $P = 0.011$). Similar results were obtained for donor age, with the risk of death-censored graft failure in both stage 1 and stage 2 hypertension being significantly increased in recipients who had received kidneys from donors aged < 60 years (Table 2).

Retransplanted kidney recipients exhibited an increased HR of 1.85 (95% CI: 1.52–2.26; $P < 0.001$) for death-censored graft survival at stage 2 hypertension, whereasa somewhat lower, albeit still significant HR of 1.50 (95% CI: 1.37–1.64; $P < 0.001$) was detected in first-transplant recipients, at stage 2 hypertension. Notably, in retransplanted patients, a trend toward worse death-censored graft survival was already detected at stage 1 hypertension (HR = 1.21, 95% CI: 0.98–1.49; $P = 0.069$) (Table 2).

Kidney transplant recipients with pretransplant human leukocyte antigenantibodies had a significantly higher risk of death-censored graft failure already at stage 1 hypertension. Specifically, patients with pretransplant human leukocyte antigenantibodies had an HR of 1.26 (95% CI: 1.04–1.52; $P = 0.018$) at stage 1 and an HR of 1.66 (95% CI: 1.39–2.00; $P < 0.001$) at stage 2 hypertension, compared with nonsensitized patients with HRs of 1.09 (95% CI: 0.98–1.22, $P = 0.11$) and 1.51 (95% CI: 1.36–1.67, $P < 0.001$) at stage 1 and 2 hypertension, respectively.

Furthermore, we performed interaction statistics, looking at interaction terms of variables considered in Table 2 and blood pressure in multivariable Cox regression for death-censored graft survival (Supplementary Table S4). The result showed that the effect of hypertension was significantly stronger in patients with hypertension stage 2 who remained hypertensive despite antihypertensive therapy compared with those without antihypertensive medication.

Table 2. The influence of hypertension stage 1 and stage 2 on death-censored graft failure during the subsequent 5 years posttransplant in all patients and in subgroup analyses

		HT stage 1			HT stage 2		
Subpopulation	***N***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
All patients	62,556	1.11	1.02–1.20	0.018	1.55	1.43–1.68	< 0.001
Recipient sex							
Female	23,506	1.20	1.05–1.37	0.007	1.67	1.47–1.90	< 0.001
Male	39,050	1.05	0.94–1.17	0.39	1.48	1.33–1.64	< 0.001
Recipient age, yr[a]							
18–39	17,937	1.16	1.02–1.32	0.025	1.71	1.50–1.94	< 0.001
40–59	29,982	1.14	1.00–1.31	0.054	1.67	1.47–1.90	< 0.001
≥60	14,637	1.04	0.86–1.26	0.69	1.25	1.05–1.49	0.011
Graft number							
First transplant	55,875	1.09	0.99–1.19	0.076	1.50	1.37–1.64	< 0.001
Retransplant	6681	1.21	0.98–1.49	0.069	1.85	1.52–2.26	< 0.001
Pretransplant HLA antibodies							
Negative	40,743	1.09	0.98–1.22	0.11	1.51	1.36–1.67	< 0.001
Positive	9730	1.26	1.04–1.52	0.018	1.66	1.39–2.00	< 0.001
Donor relationship							
Deceased	43,094	1.08	0.98–1.19	0.12	1.49	1.36–1.63	< 0.001
Living	19,462	1.22	1.03–1.44	0.020	1.78	1.52–2.10	< 0.001
Donor Age, yr							
<60	50,266	1.13	1.02–1.24	0.014	1.58	1.44–1.73	< 0.001
≥60	12,290	1.12	0.94–1.33	0.22	1.56	1.33–1.83	< 0.001
Antihypertensive drugs							
No	14,706	1.03	0.88–1.20	0.69	1.32	1.13–1.54	< 0.001
Yes	47,850	1.15	1.04–1.28	0.005	1.64	1.50–1.81	< 0.001

CI, confidence interval; HLA, human leukocyte antigen; HR, hazard ratio; HT, hypertension.
[a]At time of blood pressure measurement (1 yr after transplantation).
Results of multivariable Cox regression with all mentioned confounders for the influence of hypertension stage 1 and stage 2 recorded at year 1 posttransplant on death-censored graft failure during the subsequent 5 yrs posttransplant in all patients and in subgroups. Hazard ratios with 95% confidence interval (CI) and *P* values are shown. Patients with blood pressure <130/80 mm Hg serve as reference ("no hypertension" = normal and elevated blood pressure).

Early Blood Pressure Control Posttransplantation Influences Long-Term Transplant Outcomes

We investigated how blood pressure control in the firstand secondyear posttransplant influenced death-censored graft failure during the subsequent 5 years posttransplant (Table 3). Multivariate Cox regression analysis confirmed that particularly recipients afflicted with stage 2 hypertension at 1 year posttransplant were at increased risk of death-censored graft failure later on (Table 3). Remarkably, even if recipients who were diagnosed with stage 2 hypertension at 1 year post transplantation managed to achieve controlled blood pressure levels 1 year later, the risk of death-censored graft failure remained significantly elevated compared with individuals with no hypertension, 1 year post-transplant (Table 3).

DISCUSSION

In this large multicenter study of 62,556 kidney transplant recipients from the CTS database, hypertension, classified according to the 2017 ACC/AHA guidelines, was highly prevalent at 77% 1 year post-transplant, even among recipients aged 18 to 24 years at 66%. Wangueu *et al*. recently published data of a French multicenter study including more than 2000 kidney transplant recipients and found a higher prevalence (88%) of hypertensive kidney transplant recipients; however, the authors defined hypertension as the use of 1 or more antihypertensive medications at 12 months.[18] The authors also reported that there was no significant improvement in blood pressure control during the period between 2001 and 2020. This is in line with our observation that the prevalence of hypertension (stage 1 and 2) between the 2 time periods (2000–2010 vs. 2011–2021) was comparable (77.7% vs. 76.7%) (Table 1). Therefore, our results confirm the notion that blood pressure is still not satisfactorily controlled in a large proportion of kidney transplant recipients.

Although the deleterious effects of hypertension on cardiovascular mortality and graft survival in kidney transplanted patients are well known, there is still a lack of defined optimal blood pressure targets for kidney transplant recipients, particularly for the lower range of blood pressure values.[5–8] In our current study, we show that normal blood pressure (< 120/< 80 mm Hg) registered at 1 year after transplantation was not associated with a decreased risk for death-censored

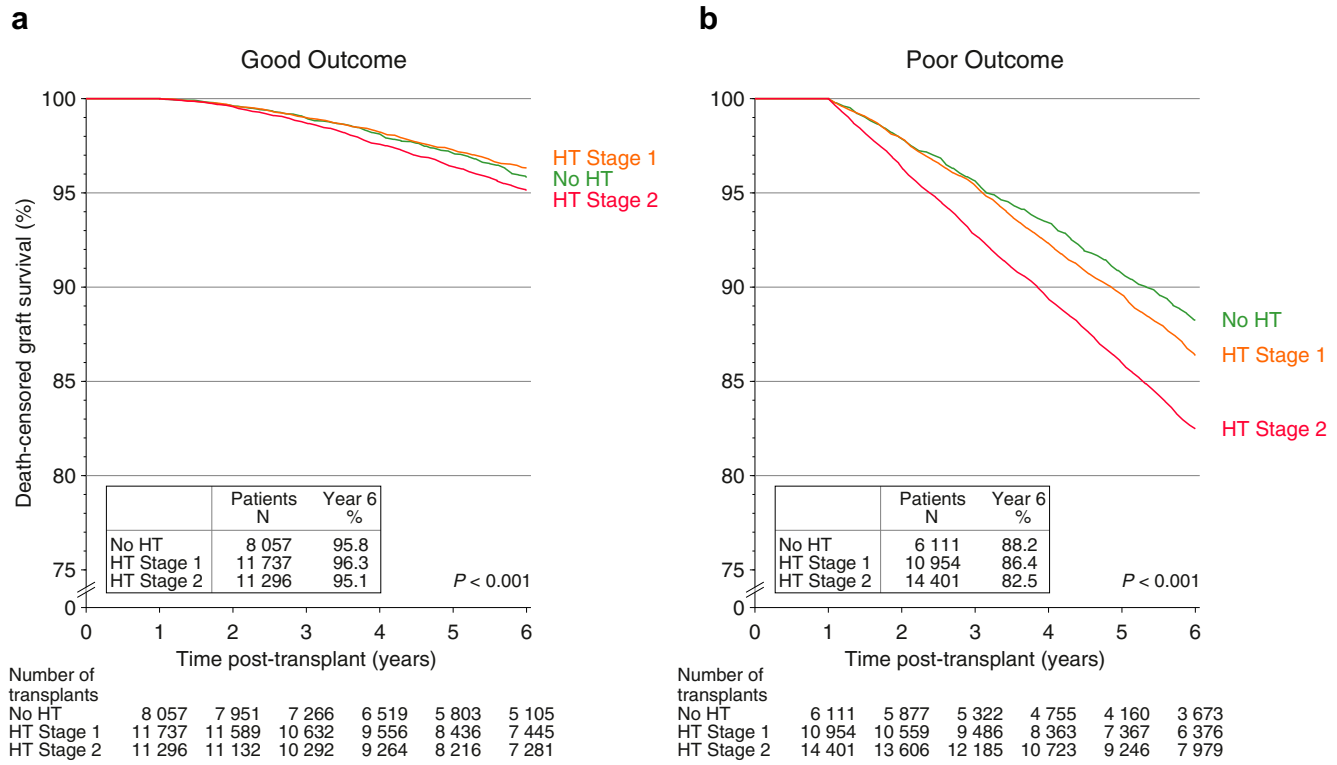

Figure 3. Influence of 1-year hypertension (HT stage 1 or 2) on death-censored graft failure during the following 5 years posttransplant according to graft outcome at year 1 posttransplant. Exploring the potential significance of hypertension in individuals with posttransplant immunological complications or compromised graft function, kidney transplant recipients were classified into those with a "good outcome" ($n =$ 31,090) and those with a "poor outcome" ($n =$ 31,466). The latter was defined by the requirement for antirejection treatment or a serum creatinine level ≥ 130 μmol/l at 1-year posttransplant. Log rank *P* values of Kaplan-Meier analyses are shown.

graft failure compared with elevated blood pressure (120–129/< 80 mm Hg) (Figure 2 and Supplementary Table S3). Patients with hypertension stage 1 (130–139/80–89 mm Hg) and stage 2 (≥ 140/≥ 90 mm Hg), however, have an 11% and 55% higher risk of death-censored graft failure compared with lower blood pressure, respectively (Table 2).

Our data are consistent with other studies in kidney transplant recipients showing a stepwise increased risk of graft failure starting at blood pressure levels of ≥ 130/80 mm Hg.[18-21] Opelz *et al.* have already shown in 1998 that high blood pressure after transplantation had a deleterious effect on graft survival, which was significantly impacted by SBP values ≥ 140 mm Hg or DBP values ≥ 90 mm Hg.[22] In our present study, we did not examine DBP and SBP values individually, but investigated the impact of different ACC/AHA blood pressure categories on graft and patient survival. Nevertheless, we confirmed the significant influence from hypertension stage 2 (≥ 140/≥ 90 mm Hg) on death-censored graft survival. Data on the effect of blood pressure targets below 130 mm Hg systolic and 80 mm Hg diastolic on long-term graft survival are still limited and inconclusive.[21,23,24] Dasgupta *et al.* reviewed that the Kidney Disease: Improving Global Outcomes recommendation of an SBP < 120 mm Hg is controversial, relying primarily on limited evidence from the Systolic Blood Pressure Intervention Trialand its chronic kidney disease subgroup analysis.[25] They suggested that the target is not widely applicable to

Table 3. The influence of hypertension stage 1 and 2 at year 1 and year 2 posttransplant on death-censored graft failure

Year 1 \ Year 2	No HT	HT stage 1	HT stage 2
No HT	Ref. $n = 4494$	1.05 (0.88–1.26) $n = 3737$; $P = 0.59$	1.71 (1.42–2.05) $n = 2338$; $P<0.001$
HT stage 1	1.10 (0.92–1.32) $n = 3762$; $P = 0.31$	1.11 (0.95–1.30) $n = 7874$; $P = 0.18$	1.75 (1.50–2.04) $n = 5672$; $P<0.001$
HT stage 2	1.36 (1.12–1.64) $n = 2522$; $P = 0.002$	1.41 (1.20–1.65) $n = 5993$; $P<0.001$	2.02 (1.75–2.33) $n = 10,991$; $P<0.001$

Results of multivariable Cox regression with all mentioned confounders for the influence of hypertension (HT) stage 1 and 2 at year 1 and year 2 posttransplant ($n =$ 47,383) on death-censored graft failure during the following 5 yrs posttransplant. Hazard ratios with 95% confidence interval are shown. Significant hazard ratios are printed in bold.

chronic kidney disease populations and may even increase the risk of adverse outcomes, especially among frail patients with chronic kidney disease. Notably, in our study, lower blood pressure levels (< 120/80 mm Hg) were not associated with a significantly higher risk of death-censored graft failure than SBP values between 120 and 129 mm Hg and DBP < 80 mm Hg ("elevated" blood pressure). However, because the CTS did not gather data on other adverse events in patients with lower blood pressure, we would refrain from recommending blood pressure targets < 120 mm Hg. Therefore, in view of the current evidence of the literature, including our own findings, and the lack of randomized controlled trials, it is still not possible to recommend lowering blood pressure below 130/80 mm Hg in kidney transplant recipients.

Notably, the average blood pressure in healthy adult females is generally lower than that of males.[26,27] Several studies have shown that females exhibit increased cardiovascular risk at even lower blood pressure levels than males in a nontransplanted population.[27-29] There have been no data directly comparing blood pressure targets for male and female kidney transplant recipients. In this large scale-study, we clearly demonstrate a significantly increased risk of death-censored graft failure in female recipients starting at stage 1 hypertension (130–139/80–89 mm Hg). In contrast, male recipients acquired an increased risk of death-censored graft failure only at stage 2 hypertension (≥ 140/90 mm Hg), indicating the importance of close monitoring and timely initiation of hypertension treatment in female kidney transplant recipients.

Previous research has demonstrated that blood pressure patterns evolve with age in the nontransplanted population.[26,30-32] In the Framingham Offspring Study, Cheng *et al*. showed that SBP increases stepwise with advancing age in both sexes.[32] Therefore, it seems to be especially important for younger kidney transplant recipients to maintain a well-controlled hypertension over time. This was confirmed by our data with a significantly higher risk of death-censored graft failure in recipients aged < 60 years with stage 1 hypertension (130–139/80–89 mm Hg) compared with older recipients. Consistent with this, individuals receiving grafts from donors younger than 60 years had hypertension-associated risks and should proactively control their hypertension to protect the graft.

Interestingly, we also found a particularly high risk of death-censored graft failure in re-transplanted patients and in recipients with pre-transplant human leukocyte antigen antibodies with stage 1 hypertension (130–139/80–89 mm Hg). Sensitized patients are known to have poorer graft outcomes compared with nonsensitized patients,[33] and we assume that grafts exposed to heightened alloimmunity could be more susceptible to additional burdens caused by , for example, a high blood pressure. In line with those findings, we showed that patients who needed antirejection treatment or presented with impaired graft function (characterized by a serum creatinine level of ≥ 130 μmol/l 1 year posttransplant) had a 22% higher risk of death-censored graft failure at stage 1 hypertension (130–139/80–89 mm Hg) and a 43% increased risk at stage 2 hypertension (≥ 140/90 mm Hg), compared with patients without hypertension. However, these results should be interpreted with caution, because it is likely that both hypertension and treatment for rejection with high-dose corticosteroids may have contributed to higher serum creatinine values.[34]

Strikingly, we demonstrated that the risk of death-censored graft failure continued to be higher in recipients who were affected by stage 2 hypertension at 1 year posttransplant than in those without hypertension, even if the high blood pressure was lowered to a normal level or to stage 1 hypertension during the second year. Our observations are in line with Mange *et al*. who showed that both SBP and DBP 1 year posttransplant were independent predictors of long-term allograft survival.[19] Although our data support that antihypertensive treatment effectively lowers blood pressure (Supplementary Figure S2), the nature of the data reported to the CTS does not allow us to establish definitive causality between different medical interventions, including blood pressure treatment and transplant outcomes.

Another recent study by Kim *et al*. compared kidney transplant recipients on antihypertensive medications with recipients with incident hypertension without antihypertensive medications.[21] In addition, recipients on antihypertensive medications were further subdivided into controlled (< 130/80 mm Hg) and uncontrolled (≥ 130/80 mm Hg) hypertension. As compared with recipients with normal blood pressure, the HRs of recipients with incident hypertension, controlled hypertension, and uncontrolled hypertension were significantly increased with 1.46, 1.59, and 2.13, respectively. In our study, however, we investigated the use of antihypertensive medication 1 year posttransplant as a possible confounding factor and, like the observation made by Opelz *et al*.,[22]found that if hypertension persists despite medical intervention, the patient would likely suffer from higher graft loss and mortality in the subsequent years. This disadvantage is, as shown in our interaction statistics, especially pronounced in recipients with uncontrolled hypertension under antihypertensive therapy.

The strength of our study lies in the extensive volume of data analyzed, which enhances the study's validity and reproducibility. The current study is the largest study investigating the effect of blood pressure on kidney graft survival that has been performed so far. However, there are important limitations. First, the study design is retrospective, and we used a single office blood pressure measurement, including neither 24-h ambulatory nor home blood pressure measurements that are known to provide more accurate insights into blood pressure variations.[25] Documentation regarding the specific methods individual centers used to measure blood pressure is not provided within the CTS dataset. In addition, our analysis employs a cross-sectional approach, relying on a single blood pressure measurement at year 1 posttransplantation without incorporating interim measurements, which may not accurately reflect long-term blood pressure control or changes over time. These factors may have biased the correct classification of blood pressure levels.[35] Furthermore, the retrospective nature of our study lacking information on continuous monitoring of potential side effects, prevents us from making a statement regarding the lowest possible blood pressure for optimizing graft function. Despite extensive efforts to account for various factors influencing graft function through multivariable analyses, inherent biases and residual confounders typical of retrospective studies may still be present. Unmeasured variables such as adherence to antihypertensive therapy or lifestyle factors may also affect outcomes and were not assessed in our study. We stratified for "good" and "poor" transplant outcomes using serum creatinine values rather than estimated glomerular filtration ratevalues based on the structure of the CTS data collection. Although estimated glomerular filtration ratewould have been the more accurate parameter, we used serum creatinine values for stratification because individual values are only available in less than 50% of the patients. In addition, we did not have enough data on proteinuria in our study cohort to be included in the analysis.

In summary, this study shows that a substantial proportion of transplant recipients suffer from hypertension, which poses a significant risk factor for worse transplant outcomes. The results also highlight the importance of sufficient blood pressure control to improve long-term graft and patient survival.

APPENDIX

List of the Members of the Collaborative Transplant Study

See Acknowledgements in the Supplementary Material for the list of the transplant centers that provided data for this study of the Collaborative Transplant Study.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

Data generated or analyzed during the study are available from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

Study conceptualization was done by CS, LB, MZ, and BD. Study management and administration was by CS, LB, MZ, NF, GO, and BD. Design of methodology was done by BD. Data collection and cleaning was done by LB, CM, HT, and BD. Data analyses was done by BD. Drafting of the manuscript was done by CS, LB, and BD). All the authors did the final revisions. All the authors were not precluded from having full access to all the data collected in the present study and accepted responsibility to the current submission.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods. CTS questionnaire.

Supplementary Acknowledgements.

Figure S1. Influence of no hypertension (A), hypertension stage 1 (B), and hypertension stage 2 (C) 1 year after transplantation on death-censored graft survival during the following 5 years posttransplant in kidney transplant recipients, with and without antihypertensive therapy.

Figure S2. Effect of administered (+) or omitted (−) antihypertensive medication (AHY) on the level of systolic blood pressure at 1-year and 2-year mark posttransplant.

Table S1. Demographic, immunologic, and clinical data of the study population (continued).

Table S2. End-stage kidney disease of study patients and prevalence of hypertension (HT) stage 1 and 2.

Table S3. Results of multivariable Cox regression for the influence of blood pressure known at 1-year posttransplant on death-censored graft failure and mortality during the subsequent 5 years posttransplant.

Table S4. Hazard ratios (HR), 95% confidence intervals (CI) and *P* values of interaction terms of variables considered in Table 2 and hypertension (HT; no, stage 1, stage 2) in multivariable Cox regression for death-censored graft survival.

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