Association of Ambulatory Blood Pressure with All-Cause and Cardiovascular Mortality in Hemodialysis Patients: Effects of Heart Failure and Atrial Fibrillation

Christopher C. Mayer,[1,2] Julia Matschkal,[3] Pantelis A. Sarafidis,[4] Stefan Hagmair,[1,2] Georg Lorenz,[3] Susanne Angermann,[3] Matthias C. Braunisch,[3] Marcus Baumann,[5] Uwe Heemann,[3] Siegfried Wassertheurer,[1,2] and Christoph Schmaderer[3]

Due to the number of contributing authors, the affiliations are listed at the end of this article.

ABSTRACT

Background Evidence on the utility of ambulatory BP monitoring for risk prediction has been scarce and inconclusive in patients on hemodialysis. In addition, in cardiac diseases such as heart failure and atrial fibrillation (common among patients on hemodialysis), studies have found that parameters such as systolic BP (SBP) and pulse pressure (PP) have inverse or nonlinear (U-shaped) associations with mortality.

Methods In total, 344 patients on hemodialysis (105 with atrial fibrillation, heart failure, or both) underwent ambulatory BP monitoring for 24 hours, starting before a dialysis session. The primary end point was all-cause mortality; the prespecified secondary end point was cardiovascular mortality. We performed linear and nonlinear Cox regression analyses for risk prediction to determine the associations between BP and study end points.

Results During the mean 37.6-month follow-up, 115 patients died (47 from a cardiovascular cause). SBP and PP showed a U-shaped association with all-cause and cardiovascular mortality in the cohort. In linear subgroup analysis, SBP and PP were independent risk predictors and showed a significant inverse relationship to all-cause and cardiovascular mortality in patients with atrial fibrillation or heart failure. In patients without these conditions, these associations were in the opposite direction. SBP and PP were significant independent risk predictors for cardiovascular mortality; PP was a significant independent risk predictor for all-cause mortality.

Conclusions This study provides evidence for the U-shaped association between peripheral ambulatory SBP or PP and mortality in patients on hemodialysis. Furthermore, it suggests that underlying cardiac disease can explain the opposite direction of associations.

J Am Soc Nephrol 29: 2409–2417, 2018. doi: https://doi.org/10.1681/ASN.2018010086

The elevated morbidity and mortality rates in patients with ESRD are mainly driven by the increased prevalence of cardiovascular disease.[1,2] Hypertension is also highly prevalent in patients with CKD patients, especially in those with ESRD, undergoing hemodialysis.[3,4] Although high BP is common in this population, hypertension control is often inadequate because of several issues, including the complex pathophysiology, the limitations for sodium and water removal caused by the intermittent nature of hemodialysis, the inappropriate use of antihypertensive drugs and others.[5]

Received January 23, 2018. Accepted July 3, 2018.

C.C.M. and J.M. contributed equally to this work.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Christopher Clemens Mayer, Center for Health and Bioresources, AIT Austrian Institute of Technology GmbH, Giefinggasse 4, 1210 Vienna, Austria, or Dr. Christoph Schmaderer, Department of Nephrology, Technical University of Munich, Klinkum rechts der Isar, Ismaninger Str. 22, 81675 Munich, Germany. E-mail: christopher.mayer@ait.ac.at or christoph.schmaderer@mri.tum.de

Hypertension guidelines suggest ambulatory BP monitoring (ABPM) as the gold standard for the diagnosis of hypertension[6,7]; this is also proposed in reviews and consensus statements for patients on dialysis.[5,8,9] As recently summarized,[5] evidence from prospective studies[10–12] suggests that the association of home or ambulatory interdialytic BP with mortality and cardiovascular events is clearer than that of pre- and postdialytic BP recordings. Nevertheless, the evidence on ambulatory BP and risk prediction is still scarce and results are not fully aligned, with more recent studies not confirming an independent association of ambulatory BP with outcomes.[13] Furthermore, one can mention various potential limitations of published studies, such as low number of patients,[11] results not adjusted,[12] different nonlinear associations,[10,13] and inclusion of only black patients.[10,12]

Another important issue in hypertension management and risk prediction in patients on hemodialysis is the number of associated comorbidities patients are suffering from, especially the effect of the complex pattern of cardiac systolic and diastolic dysfunction.[14–16] It is now well established that several hemodynamic parameters have a different predictive behavior in patients with heart failure. For example, pulse pressure has an inverse association with risk in patients with heart failure.[17–19] Such an inverse association is also documented for systolic BP (SBP) in patients with heart failure.[20–22] Furthermore, prevalence of atrial fibrillation (AF) is high and an important risk factor in the hemodialysis population.[23] There is limited evidence that there is a U-shaped association of BP and mortality in patients with AF.[24,25]

Thus, the primary objective of this study was to investigate the nonlinear association between ambulatory BP and mortality in a large cohort of patients on hemodialysis. Furthermore, this study attempted to assess a possible effect of cardiac disease on the nonlinear (*i.e.*, curvilinear, U-shaped) association of BP with survival, as we hypothesize that this is an important moderator that has not previously been taken into account.

Significance Statement

Evidence on the utility of ambulatory BP monitoring for risk prediction has been scarce in patients on hemodialysis, and findings are inconclusive. In addition, in cardiac diseases commonly found among patients on dialysis, such as heart failure and atrial fibrillation, some previous studies have found that systolic BP and pulse pressure have inverse or nonlinear (U-shaped) associations with mortality. This study provides evidence for the nonlinear (U-shaped) association between peripheral ambulatory systolic BP or pulse pressure and mortality in patients on hemodialysis. Furthermore, it suggests that the associations can be explained by underlying cardiac disease. These findings support the importance of considering the comorbidity of cardiac disease when treating hypertension in patients on hemodialysis.

METHODS

Study Population

All 24-hour BP recordings used in this study were from the rISk strAtification in end-stage Renal disease (ISAR) study (Clinicaltrials.gov identifier: NCT01152892), which is a prospective, longitudinal, observational cohort study aiming at improving cardiovascular risk stratification in patients with ESRD.[26] The study protocol was approved by the Ethics Committees of the Klinikum rechts der Isar of the Technical University Munich and of the Bavarian State Board of Physicians. The study adheres to the Declaration of Helsinki. Patients were recruited in 17 dialysis centers in Munich and the surrounding area.[26] All patients gave informed consent. Patients were recruited between September of 2010 and January of 2014. Inclusion criteria were age ≥18 years, dialysis vintage ≥90 days, willingness to participate in at least one technical examination (*e.g.*, 24-hour ABPM), and written informed consent.[26] Patients were excluded if an ongoing infection, pregnancy, malignant disease with a life expectancy of <24 months was present, or they were unwilling to participate.[26]

The ISAR cohort included in total 519 patients and 414 thereof agreed to undergo 24-hour ABPM including pulse wave analysis. In total, 344 recordings were included in data analysis after exclusion of patients with too few measurements or too short recording time (n=47), incomplete laboratory values (n=17), or insufficient data quality (n=6) (see Figure 1).

Ambulatory BP Measurement

All measurements were obtained with the Mobil-O-Graph 24h PWA Monitor (I.E.M. GmbH, Stolberg, Germany) using validated ARCSolver algorithms (Austrian Institute of Technology GmbH, Vienna, Austria)[27–29] within the ISAR hemodialysis study. The Mobil-O-Graph's brachial BP measurement unit is validated according to standard protocols.[30,31] Measurement using appropriate cuffs on the nonfistula arm started before the midweek dialysis session, where volume withdrawal was set according to clinical standard on the basis of the personal dry-weight, and lasted for 24 hours. The monitor was programmed to measure BP and pulse wave analysis parameters every 15 minutes at daytime (8:00 AM to 9:00 PM) and every 30 minutes at night (9:00 PM to 8:00 AM). BP data were averaged for 24 hours. There was no particular outlier detection and manual data cleaning performed.

Data Collection and Laboratory Measurements

Patients' clinical characteristics, including regular medical treatment with antihypertensive agents, statins, or oral anticoagulants, were obtained at the time of enrollment from dialysis protocols and medical records. Paroxysmal and permanent AF was determined on the basis of a Holter ECG, if available in the ISAR study, or medical record from dialysis centers. Diagnosis of heart failure was on the basis of medical records from dialysis centers, where information is mainly from echocardiography. Baseline comorbidities were determined by the ISAR Endpoint Committee, a panel of three physicians including a nephrologist and a cardiologist.[26]

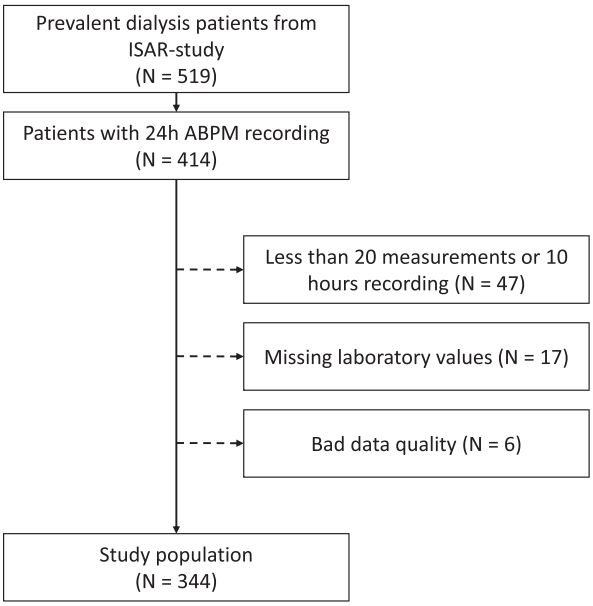

Figure 1. Flowchart of included patients.

Blood samples were obtained before starting ambulatory BP recording at baseline. High-resolution C-reactive protein was assayed with latex-enhanced reagents (Siemens), on a BN ProSpec analyzer (Siemens), following manufacturer's instructions. Other serum chemistry values were performed in International Organization for Standardization–certified laboratories in the different dialysis centers.

End points

Patients were followed up until death occurred and were censored after renal transplantation (per transplantation date). The latest follow-up took place between April and September of 2016. The primary end point of the study was all-cause mortality. Cardiovascular mortality (*i.e.*, death from sudden cardiac death, myocardial infarction, congestive heart failure, or stroke, or death after cardiovascular procedure) was a prespecified secondary end point.[26] Again, the ISAR Endpoint Committee independently adjudicated all end points on the basis of medical documentation or interviews with the physicians in the dialysis centers.[26]

Statistical Analyses

Statistical and computational evaluation was performed using Matlab R2014a (The MathWorks, Inc., Natick, MA) and R (version 3.1; R Foundation for Statistical Computing, Vienna, Austria). Continuous data are presented as mean (SD) or median (interquartile range [IQR]), according to the results of a Kolmogorov–Smirnov test for normality, with categorical data as *N* (percent). Between-group differences of continuous data were examined with a *t* test or Mann–Whitney *U* test, as appropriate. For proportions, we used the chi-squared test. In survival analysis, we first used Kaplan–Meier curves comparing quartiles to reveal possible violations of proportional hazard assumptions, thus identifying nonlinear (nonproportional) associations. Then, nonlinear, univariate, and multivariable Cox regression analyses were performed for determining the associations between variables and end points. According to the results of nonlinear and interaction analysis, patients were separated on the basis of the presence/absence of AF or heart failure in two groups to overcome interpretational limitations of nonlinear analysis. Subsequently, these two groups were analyzed with linear, univariate, and multivariable Cox models to correctly determine proportional hazard ratios (HRs) for risk prediction. Adjustment was done for age and sex (model 1), and model 1 plus diabetes mellitus and serum albumin (model 2). Additional adjustment models can be found in the Supplemental Material. Furthermore, interactions between risk predictors and the presence of AF or heart failure were tested using interaction terms in Cox regression analysis. Statistical significance was assumed at a 5% level.

RESULTS

Baseline Characteristics of Study Participants

The study population included 344 patients (234 men and 110 women; median, 69.3; IQR, 55.7–77.2 years of age). Sixty-nine (20%) patients had AF and 62 (18%) had heart failure; in total, 105 (30.5%) of patients had either one or both of the conditions (AF or heart failure group). The median dialysis vintage of all patients was 41.1 (IQR, 22.7–76.6) months. About 92% of all measurements contained a record duration of at least 20 hours. Prevalence of diabetes was 39% and of hypertension 95%, defined as either hypertensive BP values on the 24-hour BP recording or intake of an antihypertensive medication. There was a difference in age, presence of diabetes, smoking status, serum albumin, and use of anticoagulation medication for the two groups (AF or heart failure versus no AF or heart failure). Furthermore, there is a significance difference in systolic, mean, and diastolic BP (*e.g.*, SBP: mean 120 (17.5 SD) versus 125 (15.8 SD) mm Hg; P=0.003), but not pulse pressure, when comparing patients with AF and/or heart failure with patients without AF or heart failure. Detailed baseline characteristics can be found in Supplemental Table 1 and Table 1. Study population was mainly comparable with the excluded patients as defined in Figure 1 (see Supplemental Table 2).

The mean follow-up time for all patients was 37.6 (17.5 SD) months. During follow-up, 115 patients died (59 in AF or heart failure group), of whom 47 were due to cardiovascular reasons (20 in the AF or heart failure group). Reasons for cardiovascular death are presented in Supplemental Table 3. Patients were censored at renal transplantation (n=31), date of moving away (n=2), or loss to follow-up (n=5).

All-Cause Mortality

Kaplan–Meier plots suggest a nonlinear association between SBP/pulse pressure and all-cause mortality (Figure 2A). Figure 2B

Table 1. Baseline characteristics

Characteristic	AF or HF	No AF or HF	All	*P*-Value
N	105	239	344	
Age, yr	74.6 [68.4–80.9]	65.3 [50.1–75.2]	69.3 [55.7–77.2]	<0.001
Men, *n* (%)	76 (72%)	158 (66%)	234 (68%)	0.52
Body weight, kg	74.8 [66–86.6]	74 [65.4–84.9]	74.3 [65.5–85.5]	0.54
Height, m	1.71 (0.0893 SD)	1.71 (0.0837 SD)	1.71 (0.0853 SD)	0.93
Body mass index, kg/m^2	25.4 [22.5–29]	25.1 [22.8–28.6]	25.2 [22.8–28.7]	0.46
Dialysis vintage, mo	38 [21.2–77.6]	42.4 [23–75.6]	41.1 [22.7–76.6]	0.35
Calcium phosphate product, mmol^2/L^2	3.76 (1.07 SD)	3.88 (1.18 SD)	3.85 (1.15 SD)	0.38
Effective time of dialysis per session, h	4.22 [4–4.5]	4.25 [4–4.53]	4.23 [4–4.5]	0.33
UFV, ml	2366 (1190 SD)	2156 (1094 SD)	2220 (1127 SD)	0.11
UF rate, ml/h	539 (269 SD)	484 (237 SD)	501 (248 SD)	0.06
Kt/V (−)	1.45 (0.358 SD)	1.49 (0.402 SD)	1.48 (0.389 SD)	0.34
CVC/AVF, *n* (%)	11 (10%)/94 (90%)	10 (4%)/229 (96%)	21 (6%)/323 (94%)	0.08
Presence of diabetes, *n* (%)	54 (51%)	81 (34%)	135 (39%)	0.009
History of hypertension[a], *n* (%)	100 (95%)	226 (95%)	326 (95%)	0.97
Smokers, *n* (%)	15 (14%)	65 (27%)	80 (23%)	0.03
Hemoglobin, g/dl	11.7 (1.21 SD)	11.7 (1.18 SD)	11.7 (1.19 SD)	0.98
Total protein, g/dl	6.68 (0.529 SD)	6.57 (0.527 SD)	6.61 (0.529 SD)	0.17
Serum albumin, g/dl	3.89 (0.421 SD)	4.04 (0.404 SD)	3.99 (0.414 SD)	0.002
Total cholesterol, mg/dl	164 (39.1 SD)	182 (45.2 SD)	177 (44.2 SD)	0.001
High-sensitive CRP, mg/dl	0.712 [0.319–1.21]	0.377 [0.165–0.85]	0.47 [0.196–0.96]	<0.001
Use of statins, *n* (%)	52 (50%)	84 (35%)	136 (40%)	0.04
Use of anticoagulation medication, *n* (%)	28 (27%)	24 (10%)	52 (15%)	<0.001
Use of antihypertensive medication, *n* (%)	100 (95%)	214 (90%)	314 (91%)	0.23
SBP, mm Hg	120 (17.5 SD)	125 (15.8 SD)	124 (16.5 SD)	0.003
DBP, mm Hg	69.1 (11.6 SD)	75.6 (11.4 SD)	73.6 (11.8 SD)	<0.001
PP, mm Hg	50.6 (12.1 SD)	49.8 (11.4 SD)	50 (11.6 SD)	0.57
MBP, mm Hg	92.3 (13.3 SD)	98.4 (12.4 SD)	96.5 (13 SD)	<0.001
Heart rate, 1/min	71.3 (10.3 SD)	71.9 (10.2 SD)	71.7 (10.2 SD)	0.57
All-cause mortality, *n* (%)	59 (56%)	56 (23%)	115 (33%)	<0.001
Cardiovascular mortality, *n* (%)	20 (19%)	27 (11%)	47 (14%)	0.16

Results are presented as mean (SD) and median [IQR] for normally and non-normally distributed data, respectively; categorical data as total number (percentage). *P* values present the results of group-wise comparisons (AF or HF versus no AF or HF). HF, heart failure; UFV, ultrafiltration volume; UF, ultrafiltration; CVC, central venous catheter; AVF, arteriovenous fistula; CRP, C-reactive protein; DBP, diastolic BP; PP, pulse pressure; MBP, mean BP.
[a]History of hypertension was defined as either use of antihypertensive medication and/or 24-hour BP >140/90 mm Hg.

and Supplemental Figure 1, A–C depict the HRs for systolic/diastolic blood and pulse pressure related to the median value resulting from univariate nonlinear Cox regression analysis in the whole study population. Nonlinear Cox regression analysis revealed a nonlinear behavior for SBP and pulse pressure for all-cause mortality in the whole cohort, *i.e.*, significant nonlinear terms in univariate and multivariable analysis (Supplemental Table 4, Table 2). Diastolic BP turned out to be linearly but inversely associated with mortality.

Interaction analysis underpinned this behavior by significant interaction between predictors and absence of AF and/or heart failure for SBP ($P<0.001$) and pulse pressure ($P<0.001$), but not for diastolic pressure ($P=0.42$). Thus, data were analyzed in subgroups according to absence or presence of AF and/or heart failure. Results from nonlinear Cox regression analysis for the two study subgroups can be seen in Supplemental Figure 2 and Supplemental Tables 5 and 6. Nonlinear effects diminished in the two subgroups. As depicted in Figure 2, C and D, the nonlinear, U-shaped association of SBP and pulse pressure with all-cause mortality in the whole cohort could be the result of opposite associations presented in the two study subgroups.

In Table 3, the results from linear Cox regression analysis are presented for the study subgroups. SBP is an independent risk predictor for and inversely related to all-cause mortality in the AF or heart failure group (univariate HR, 0.97; 95% confidence interval [95% CI], 0.96 to 0.98; $P<0.001$; multivariable HR, 0.97; 95% CI, 0.96 to 0.99; $P\leq0.002$, independently of chosen adjustment model), but not associated to all-cause mortality in the no AF or heart failure subgroup. Positive association (although not significant) indicates an opposite behavior in the two subgroups. Diastolic BP is negatively associated to all-cause mortality in the whole cohort (HR, 0.95; 95% CI, 0.94 to 0.97; $P<0.001$), the AF or heart failure group (HR, 0.96; 95% CI, 0.94 to 0.98; $P<0.001$), and the no AF or heart failure group (HR, 0.97; 95% CI, 0.95 to 0.99; $P=0.007$), but after adjustment, was not predictive in the no AF or heart failure subgroup. Diastolic BP remains an

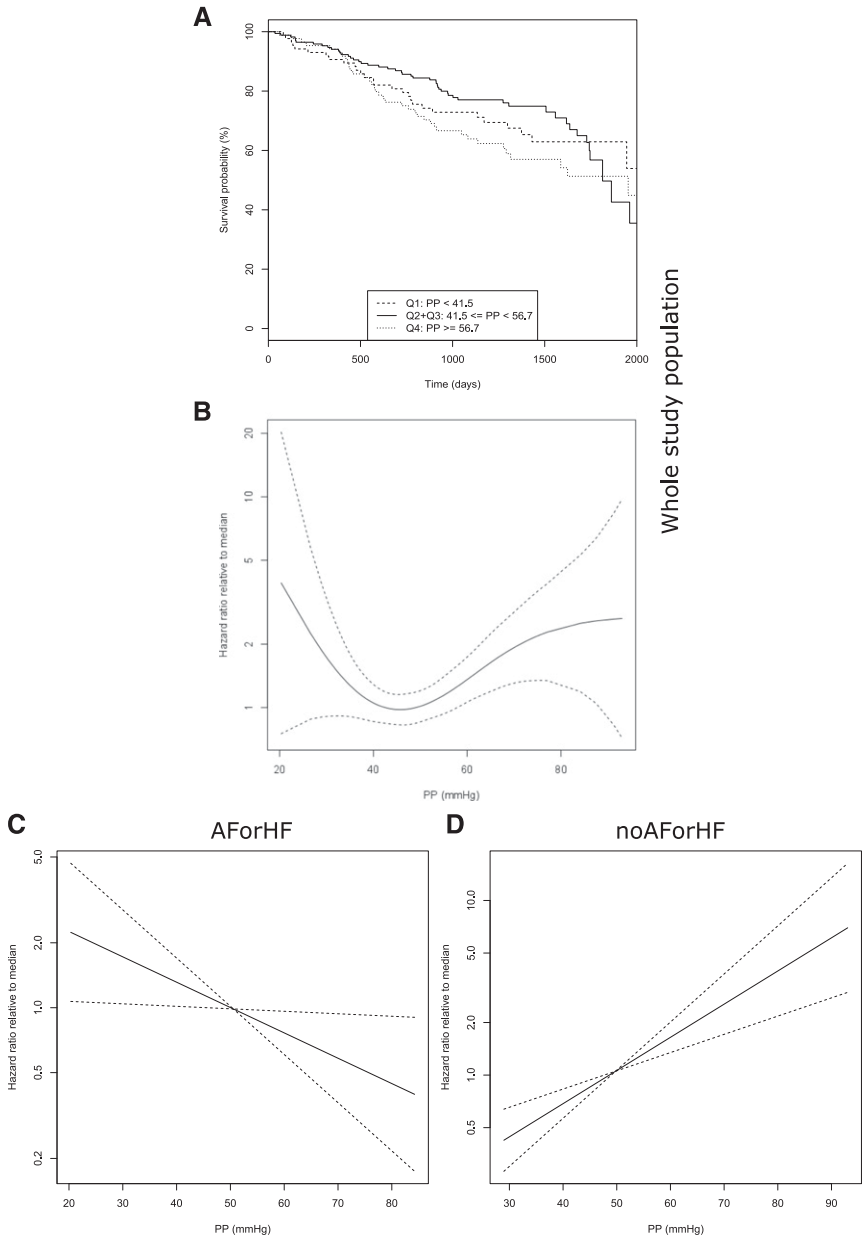

Figure 2. Nonlinear association of pulse pressure with all-cause mortality. Univariate association of pulse pressure with all-cause mortality in (A) Kaplan–Meier analysis, (B) nonlinear Cox regression analysis using penalized smoothing splines, and proportional hazard models for the (C) AF or HF group and (D) no AF or HF group. HF, heart failure; PP, pulse pressure; Q, quartile.

independent risk predictor in the whole cohort and the AF or heart failure subgroup no matter which adjustment model is chosen. Pulse pressure is negatively associated to all-cause mortality in the AF or heart failure group (HR, 0.97; 95% CI, 0.95 to 1.00; P=0.03) and positively in the no AF or heart failure group (HR, 1.04; 95% CI, 1.02 to 1.07; P<0.001). These associations are independent of other risk predictors. Further adjustment models can be found in Supplemental Table 7.

Cardiovascular Mortality

Kaplan–Meier plots suggest again a nonlinear association between systolic blood and pulse pressure and the study end point (Figure 3A). In Figure 3B and Supplemental Figure 1, D–F, one can see the univariate HRs for systolic/diastolic blood and pulse pressure related to the median value for cardiovascular mortality. The pattern for cardiovascular mortality is even more obvious than that of all-cause mortality. SBP and pulse pressure are nonlinearly associated with cardiovascular mortality in univariate and multivariable analysis (all P values for nonlinear term significant; for linear term nonsignificant; Supplemental Table 4, Table 2). Diastolic BP again turned out to be linearly and inversely associated with cardiovascular mortality. Interaction analysis revealed again interactions for SBP (P<0.001) and pulse pressure (P<0.001) with AF and/or heart failure, but not for diastolic BP (P=0.12). Results from nonlinear Cox regression analysis for the subgroups can be seen in in Supplemental Figure 3 and Supplemental Tables 5 and 6. Again, nonlinear effects diminished in the two subgroups anon. Furthermore, the U-shaped association for SBP and pulse pressure to cardiovascular mortality in the whole cohort can be explained by the opposite, and in each case, linear behavior in the two subgroups.

In Table 4, the results from linear Cox regression analysis are presented for the two subgroups. SBP is an independent risk predictor for and negatively related to all-cause mortality in the AF or heart failure group (HR, 0.95; 95% CI, 0.93 to 0.98; P<0.001) and positively associated in the no AF or heart failure subgroup (HR, 1.03; 95% CI, 1.00 to 1.05; P=0.02). SBP is an independent risk predictor for cardiovascular mortality independently of the chosen adjustment model. Pulse pressure behaves similarly (HR, 0.93; 95% CI, 0.88 to 0.97; P=0.003 in the AF or heart failure group and HR, 1.06; 95% CI, 1.03 to 1.09; P<0.001 in the no AF or heart failure subgroup). Risk prediction is independent of confounding factors (Supplemental Table 8, Table 4).

Summarized, results for all-cause and cardiovascular mortality are similar. Additional analyses such as Kaplan–Meier curves for different risk factors can be found in Supplemental Figures 4 and 5. Furthermore, incidence rates per person year are presented in Supplemental Table 9. As expected, these are

Table 2. *P* values for linear and nonlinear terms for univariate and adjusted nonlinear Cox regression analysis

Predictor	Linear Term		Nonlinear Term	
	P-Value (Univariate)	*P*-Value (Adjusted[a])	*P*-Value (Univariate)	*P*-Value (Adjusted[a])
All-cause mortality				
SBP	0.001	0.005; 0.06	0.04	0.02; 0.05
DBP	<0.001	<0.001; 0.01	0.86	0.84; 0.77
PP	0.05	0.85; 0.81	0.07	0.001; 0.002
Cardiovascular mortality				
SBP	0.09	0.22; 0.19	0.02	0.006; 0.004
DBP	0.001	0.05; 0.03	0.49	0.22; 0.25
PP	0.09	0.55; 0.54	0.07	0.005; 0.004

DBP, diastolic BP; PP, pulse pressure.
[a]Adjustment for age and sex (model 1), and model 1 plus diabetes mellitus and serum albumin (model 2).

significantly higher for patients with AF and/or heart failure for the whole follow-up period and especially in the first follow-up years.

DISCUSSION

In this study, the associations of ambulatory BP recordings and all-cause and cardiovascular mortality in patients on hemodialysis were evaluated. Furthermore, a possible effect of cardiac disease on the observed associations of SBP and pulse pressure with outcomes was examined. The main findings are a U-shaped association for ambulatory SBP and pulse pressure with all-cause and cardiovascular mortality in the whole cohort, which could be explained by the opposite associations, *i.e.*, linear but negative or positive, for patients with and without AF and/or heart failure. To our knowledge, this is the largest study to demonstrate the nonlinear association of ambulatory systolic BP and pulse pressure with all-cause and cardiovascular mortality, and to provide evidence for the explanation of these associations in white patients on hemodialysis. When comparing results from the study with previous evidence, one has to take into account that in contrast to most other studies, no exclusion criteria regarding heart function were defined in the ISAR study.[26] This allows us to study the association of ambulatory BP measurement and mortality in a representative sample of stable European patients on dialysis who are willing to undergo 24-hour APBM.

Table 3. Univariate and adjusted proportional HRs for all-cause mortality including 95% CIs for systolic/diastolic BP and pulse pressure per mm Hg increase

Predictor	AF or HF (*n*=105)		No AF or HF (*n*=239)	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
SBP	0.97 (0.96 to 0.98)	<0.001	1.01 (0.99 to 1.03)	0.30
SBP[a]	0.97 (0.96 to 0.99)	<0.001	1.01 (0.99 to 1.03)	0.30
SBP[b]	0.97 (0.96 to 0.99)	<0.001	1.01 (1.00 to 1.03)	0.12
DBP	0.96 (0.94 to 0.98)	<0.001	0.97 (0.95 to 0.99)	0.007
DBP[a]	0.96 (0.94 to 0.99)	0.001	0.98 (0.96 to 1.01)	0.21
DBP[b]	0.96 (0.94 to 0.99)	0.004	1.00 (0.97 to 1.02)	0.80
PP	0.97 (0.95 to 1.00)	0.03	1.04 (1.02 to 1.07)	<0.001
PP[a]	0.97 (0.95 to 1.00)	0.04	1.03 (1.01 to 1.06)	0.004
PP[b]	0.97 (0.94 to 1.00)	0.02	1.03 (1.01 to 1.05)	0.01

HF, heart failure; DBP, diastolic BP; PP, pulse pressure.
[a]Adjusted for age and sex (model 1).
[b]Adjusted for model 1 plus diabetes mellitus and serum albumin (model 2).

The results of this study are not in direct contrast with existing evidence from the literature. Amar *et al.*[11] showed the association of elevated 24-hour ambulatory pulse pressure with increased risk of cardiovascular mortality in a relatively small cohort (n=57 with ten cardiovascular events), which could have led to overadjustment. Besides, patients with significant cardiac valvular disease or congestive heart failure with low left ventricular ejection fraction (<40%) were excluded. Alborzi *et al.*[12] described an association between interdialytic ambulatory or home BP with mortality in 150 patients on hemodialysis, but no adjustment for any possible confounding factors was reported. Of note, patients with chronic AF were excluded from analysis. Presented HRs according to quartiles showed a weak U-shaped relationship and authors stated that 115–125 mm Hg by ambulatory BP were associated with the best prognosis. Agarwal[10] reported a nonlinear relationship for ambulatory and home SBP with all-cause mortality on the basis of a cohort of mainly black patients; patients with chronic AF were again excluded. Nonlinear analysis revealed a W-shaped curve for home and ambulatory BP, with best prognosis for systolic ambulatory BP between 110 and 120 mm Hg. Recently, Sarafidis *et al.*[13] showed, in a cohort of 170 patients on hemodialysis, that ambulatory pulse wave velocity is a stronger predictor for cardiovascular events and mortality than ambulatory systolic BP in a linear analysis, as SBP showed only a nonsignificant U-shaped trend when comparing quartiles. Chronic AF or other arrhythmia that could interfere with BP measurements and congestive heart failure class III and IV on the basis of the New York Heart Association classification were exclusion criteria in this study.

The results of our study underpin the fact that it is important to keep in mind that "the lower the better" paradigm does not apply to all patients,[32] especially when evaluating the association of ambulatory BP with outcomes in patients on hemodialysis. Within the BP in Dialysis pilot study, Miskulin *et al.*[33] reported possible safety issues when intensively treating BP in patients on dialysis, but nevertheless highlighted the need for a full-scale trial to assess intensive hypertension management. The presented results for patients with AF or heart failure confirm the inverse (negative) association between SBP and pulse pressure and mortality for patients with heart failure observed in other populations.[17–22] This is in contrast to the

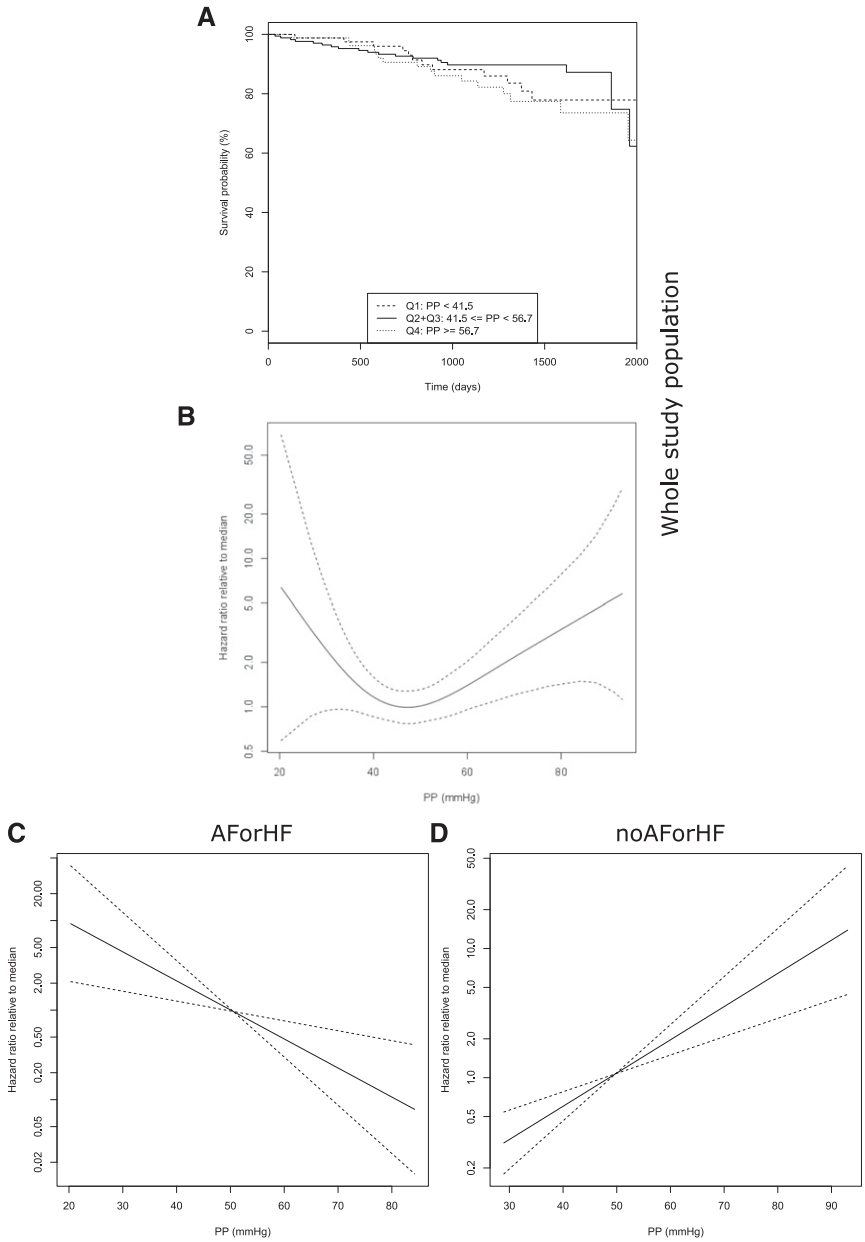

Figure 3. Nonlinear association of pulse pressure with cardiovascular mortality. Univariate association of pulse pressure with cardiovascular mortality in (A) Kaplan–Meier analysis, (B) nonlinear Cox regression analysis using penalized smoothing splines, and proportional hazard models for the (C) AF or HF group and (D) no AF or HF group. HF, heart failure; PP, pulse pressure; Q, quartile.

observed positive association between SBP and pulse pressure with outcome for patients without AF or heart failure reflecting evidence from the general population.[7,34,35] For patients with AF, Badheka *et al.*[24] reported a U-shaped association of SBP and mortality, whereas a statistically significant increase in mortality was seen for SBP <110 and >160 mm Hg. In this study, patients with AF had a mean SBP of 117 mm Hg (17.8 SD) and just one (1.5%) patient had an SBP >160 mm Hg and six (8.7%) had an SBP >140 mm Hg. Thus, the mortality increase for higher pressure is not reflected in the ISAR cohort.

The influence of the heart status delivers a possible explanation for the well known U-shaped associations in patients on hemodialysis found in the data and literature, especially for pre-, post-, or nadir-readings in a dialysis session.[5,10,36–38] So far, the origin of this phenomena is not completely understood. Overall, peri-dialytic BP recordings are characterized by poor validity and reproducibility, facts that can greatly interfere with the observed associations with outcome.[5] Foley *et al.*[39] stated that low BP is a marker of mortality in patients with ESRD and potentially for cardiac failure anteceding death. Other explanations include survival bias and the reverse epidemiology of other cardiovascular risk factors, *e.g.*, nutrition in patients on dialysis.[40,41] Bansal *et al.*[42] raised the hypothesis that it is a sign of relative health if patients on hemodialysis can react by increasing BP as a response to fluid accumulated between hemodialysis sessions. Agarwal[10] speculated about the unexpected W-shaped relationship for home and ambulatory BP and mortality to be caused by an updated hypertension treatment using antihypertensive medication or dry-weight reduction on the basis of high ambulatory readings, leading to a modification of the relationship. Our data further support the idea that measurement inadequacies during dialysis can be overcome by ambulatory recordings (either including dialysis session or not) and home recordings. In the ISAR cohort, results for ambulatory BP excluding the dialysis session (data not shown) are in line with and underpin the presented findings. Sarafidis *et al.*[5] summarized that the location (*i.e.*, home or ambulatory) and the timing of the BP recording (*i.e.*, out-of-dialysis unit) determine the strong prognostic significance of interdialytic ambulatory BP measurements observed in previous studies.

Strengths of this study include the sample size, follow-up time, and inclusion of patients with AF and heart failure, which enabled us to do the additional analyses. There was no further preselection of patients besides the mentioned exclusion criteria. An important limitation in this study is that recording was limited to 24 and not 48 hours, thus the dialysis-off day could not be incorporated into the analysis. Another issue could be that heart failure was defined only by medical record criteria; although echocardiography was

Table 4. Univariate and adjusted proportional HRs for cardiovascular mortality including 95% CIs for systolic/diastolic and pulse pressure per mm Hg increase

Predictor	AF or HF, *n*=105		No AF or HF, *n*=239	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
SBP	0.95 (0.93 to 0.98)	<0.001	1.03 (1.00 to 1.05)	0.02
SBP[a]	0.95 (0.93 to 0.98)	<0.001	1.03 (1.01 to 1.05)	0.01
SBP[b]	0.94 (0.91 to 0.97)	<0.001	1.03 (1.00 to 1.05)	0.02
DBP	0.95 (0.91 to 0.98)	0.005	0.98 (0.95 to 1.02)	0.32
DBP[a]	0.95 (0.91 to 0.99)	0.02	1.00 (0.97 to 1.04)	0.89
DBP[b]	0.95 (0.91 to 0.99)	0.01	1.00 (0.96 to 1.04)	0.90
PP	0.93 (0.88 to 0.97)	0.003	1.06 (1.03 to 1.09)	<0.001
PP[a]	0.93 (0.88 to 0.98)	0.006	1.06 (1.03 to 1.09)	<0.001
PP[b]	0.92 (0.87 to 0.97)	0.002	1.06 (1.03 to 1.10)	<0.001

HF, heart failure; DBP, diastolic BP; PP, pulse pressure.
[a]Adjusted for age and sex (model 1).
[b]Adjusted for model 1 plus diabetes mellitus and serum albumin (model 2).

performed in practically every patient with this diagnosis in the past as part of standard clinical care, it was not repeated at baseline for this specific study. Finally, because the study was limited to participants from centers in Munich and the suburban area (*i.e.*, a mainly white population), generalization of these results to other ethnic groups should be done with caution.

In conclusion, this study provides evidence for the U-shaped association between peripheral ambulatory SBP or pulse pressure and mortality in patients on hemodialysis as a whole. Furthermore, it suggests that the opposed associations can be explained by the underlying patients' cardiac diseases, as linear relationships were evident in both subgroups representing patients with and without AF or heart failure. Hence, proportional hazard models in subgroups overcome interpretational limitations of nonlinear analysis. The findings of this study therefore support the importance of considering existing cardiac diseases when treating hypertension in patients on hemodialysis.

ACKNOWLEDGMENTS

We acknowledge the support and assistance of all participating dialysis centers, hospitals, and patients for making this study possible.

Research idea and study design: C.C.M., S.W., P.A.S., M.B., and C.S.; data acquisition: J.M., S.A., G.L., and M.C.B.; data analysis/interpretation: C.C.M., S.H., J.M., P.A.S., and S.W.; statistical analysis: C.C.M. and S.W.; supervision or mentorship: C.S., S.W., and U.H. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

The direct costs of the rISk strAtification in end-stage Renal disease study at the Klinikum rechts der Isar are internally funded by university grants and by grants from the Else-Kröner-Fresenius Stiftung and Servier.

DISCLOSURES

S.W. and C.C.M. are the inventors (not holders) of a patent that is partly used in the ARCSolver algorithm in the Mobil-O-Graph 24h PWA Monitor. The remaining authors declare no conflicts of interest.

REFERENCES

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004
2. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al.: Chronic kidney disease and mortality risk: A systematic review. *J Am Soc Nephrol* 17: 2034–2047, 2006
3. Coresh J, Wei GL, McQuillan G, Brancati FL, Levey AS, Jones C, et al.: Prevalence of high blood pressure and elevated serum creatinine level in the United States: Findings from the third National Health and Nutrition Examination Survey (1988-1994). *Arch Intern Med* 161: 1207–1216, 2001
4. Agarwal R, Nissenson AR, Batlle D, Coyne DW, Trout JR, Warnock DG: Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. *Am J Med* 115: 291–297, 2003
5. Sarafidis PA, Persu A, Agarwal R, Burnier M, de Leeuw P, Ferro CJ, et al.: Hypertension in dialysis patients: A consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH). *Nephrol Dial Transplant* 32: 620–640, 2017
6. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, et al.: European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability: European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 32: 1359–1366, 2014
7. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al.: Task Force Members: 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 31: 1281–1357, 2013
8. Agarwal R, Flynn J, Pogue V, Rahman M, Reisin E, Weir MR: Assessment and management of hypertension in patients on dialysis. *J Am Soc Nephrol* 25: 1630–1646, 2014
9. Parati G, Ochoa JE, Bilo G, Agarwal R, Covic A, Dekker FW, et al.: European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association–European Dialysis Transplantation Association (ERA-EDTA): Hypertension in chronic kidney disease part 1: Out-of-office blood pressure monitoring: Methods, thresholds, and patterns. *Hypertension* 67: 1093–1101, 2016
10. Agarwal R: Blood pressure and mortality among hemodialysis patients. *Hypertension* 55: 762–768, 2010
11. Amar J, Vernier I, Rossignol E, Bongard V, Arnaud C, Conte JJ, et al.: Nocturnal blood pressure and 24-hour pulse pressure are potent indicators of mortality in hemodialysis patients. *Kidney Int* 57: 2485–2491, 2000
12. Alborzi P, Patel N, Agarwal R: Home blood pressures are of greater prognostic value than hemodialysis unit recordings. *Clin J Am Soc Nephrol* 2: 1228–1234, 2007
13. Sarafidis PA, Loutradis C, Karpetas A, Tzanis G, Piperidou A, Koutroumpas G, et al.: Ambulatory pulse wave velocity is a stronger predictor of cardiovascular events and all-cause mortality than office and ambulatory blood pressure in hemodialysis patients. *Hypertension* 70: 148–157, 2017
14. McIntyre CW: Effects of hemodialysis on cardiac function. *Kidney Int* 76: 371–375, 2009
15. Tsilonis K, Sarafidis PA, Kamperidis V, Loutradis C, Georgianos PI, Imprialos K, et al.: Echocardiographic parameters during long and short

interdialytic intervals in hemodialysis patients. *Am J Kidney Dis* 68: 772–781, 2016
16. Sarafidis PA, Kamperidis V, Loutradis C, Tsilonis K, Mpoutsiouki F, Saratzis A, et al.: Haemodialysis acutely deteriorates left and right diastolic function and myocardial performance: An effect related to high ultrafiltration volumes? *Nephrol Dial Transplant* 32: 1402–1409, 2017
17. Regnault V, Lagrange J, Pizard A, Safar ME, Fay R, Pitt B, et al.: Opposite predictive value of pulse pressure and aortic pulse wave velocity on heart failure with reduced left ventricular ejection fraction: Insights from an Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) substudy. *Hypertension* 63: 105–111, 2014
18. Aronson D, Burger AJ: Relation between pulse pressure and survival in patients with decompensated heart failure. *Am J Cardiol* 93: 785–788, 2004
19. Voors AA, Petrie CJ, Petrie MC, Charlesworth A, Hillege HL, Zijlstra F, et al.: Low pulse pressure is independently related to elevated natriuretic peptides and increased mortality in advanced chronic heart failure. *Eur Heart J* 26: 1759–1764, 2005
20. Raphael CE, Whinnett ZI, Davies JE, Fontana M, Ferenczi EA, Manisty CH, et al.: Quantifying the paradoxical effect of higher systolic blood pressure on mortality in chronic heart failure. *Heart* 95: 56–62, 2009
21. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al.: OPTIMIZE-HF Investigators and Coordinators: Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* 296: 2217–2226, 2006
22. Lee TT, Chen J, Cohen DJ, Tsao L: The association between blood pressure and mortality in patients with heart failure. *Am Heart J* 151: 76–83, 2006
23. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM: Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. *Nephrol Dial Transplant* 27: 3816–3822, 2012
24. Badheka AO, Patel NJ, Grover PM, Shah N, Patel N, Singh V, et al.: Optimal blood pressure in patients with atrial fibrillation (from the AFFIRM Trial). *Am J Cardiol* 114: 727–736, 2014
25. Tremblay-Gravel M, Khairy P, Roy D, Leduc H, Wyse DG, Cadrin-Tourigny J, et al.: Systolic blood pressure and mortality in patients with atrial fibrillation and heart failure: Insights from the AFFIRM and AF-CHF studies. *Eur J Heart Fail* 16: 1168–1174, 2014
26. Schmaderer C, Tholen S, Hasenau AL, Hauser C, Suttmann Y, Wassertheurer S, et al.: Rationale and study design of the prospective, longitudinal, observational cohort study "rISk strAtification in end-stage renal disease" (ISAR) study. *BMC Nephrol* 17: 161, 2016
27. Sarafidis PA, Georgianos PI, Karpetas A, Bikos A, Korelidou L, Tersi M, et al.: Evaluation of a novel brachial cuff-based oscillometric method for estimating central systolic pressure in hemodialysis patients. *Am J Nephrol* 40: 242–250, 2014
28. Weber T, Wassertheurer S, Rammer M, Maurer E, Hametner B, Mayer CC, et al.: Validation of a brachial cuff-based method for estimating central systolic blood pressure. *Hypertension* 58: 825–832, 2011
29. Salvadé I, Schätti-Stählin S, Violetti E, Schönholzer C, Cereghetti C, Zwahlen H, et al.: A prospective observational study comparing a non-operator dependent automatic PWV analyser to pulse pressure, in assessing arterial stiffness in hemodialysis. *BMC Nephrol* 16: 62, 2015
30. Franssen PM, Imholz BP: Evaluation of the Mobil-O-Graph new generation ABPM device using the ESH criteria. *Blood Press Monit* 15: 229–231, 2010
31. Wei W, Tölle M, Zidek W, van der Giet M: Validation of the mobil-O-Graph: 24 h-blood pressure measurement device. *Blood Press Monit* 15: 225–228, 2010
32. Böhm M, Schumacher H, Teo KK, Lonn EM, Mahfoud F, Mann JFE, et al.: Achieved blood pressure and cardiovascular outcomes in high-risk patients: Results from ONTARGET and TRANSCEND trials. *Lancet* 389: 2226–2237, 2017
33. Miskulin DC, Gassman J, Schrader R, Gul A, Jhamb M, Ploth DW, et al.: BP in dialysis: Results of a pilot study. *J Am Soc Nephrol* 29: 307–316, 2018
34. Benetos A, Rudnichi A, Safar M, Guize L: Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. *Hypertension* 32: 560–564, 1998
35. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetieère P, et al.: Pulse pressure: A predictor of long-term cardiovascular mortality in a French male population. *Hypertension* 30: 1410–1415, 1997
36. Foley RN, Herzog CA, Collins AJ: United States Renal Data System: Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. *Kidney Int* 62: 1784–1790, 2002
37. Conion PJ, Walshe JJ, Heinle SK, Minda S, Krucoff M, Schwab SJ: Predialysis systolic blood pressure correlates strongly with mean 24-hour systolic blood pressure and left ventricular mass in stable hemodialysis patients. *J Am Soc Nephrol* 7: 2658–2663, 1996
38. Merchant A, Wald R, Goldstein MB, Yuen D, Kirpalani A, Dacouris N, et al.: Relationship between different blood pressure measurements and left ventricular mass by cardiac magnetic resonance imaging in end-stage renal disease. *J Am Soc Hypertens* 9: 275–284, 2015
39. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE: Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Kidney Int* 49: 1379–1385, 1996
40. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD: Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 63: 793–808, 2003
41. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH: A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. *Am J Kidney Dis* 38: 1251–1263, 2001
42. Bansal N, McCulloch CE, Rahman M, Kusek JW, Anderson AH, Xie D, et al.: Blood pressure and risk of all-cause mortality in advanced chronic kidney disease and hemodialysis: The chronic renal insufficiency cohort study. *Hypertension* 65: 93–100, 2015

This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2018010086/-/DCSupplemental.

AFFILIATIONS

[1]Center for Health and Bioresources, Biomedical Systems, AIT Austrian Institute of Technology GmbH, Vienna, Austria; [2]Institute for Analysis and Scientific Computing, Vienna University of Technology, Vienna, Austria; [3]Department of Nephrology, Technical University of Munich, Klinkum rechts der Isar, Munich, Germany; [4]Department of Nephrology, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki, Greece; and [5]Internistische Fachklinik Dr. Steger, Nuremberg, Germany