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Blood pressure and Mortality in the 4D Study

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ABSTRACT

Introduction: Systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP) are risk factors for cardiovascular mortality (CVM). Pulse pressure (PP) is an easily available parameter of vascular stiffness, but its impact on CVM in chronic dialysis patients with diabetes is unclear.

Methods: Therefore, we have examined the predictive value of baseline, predialytic PP, SBP, DBP and MAP in the German Diabetes and Dialysis (4D) study, a prospective, randomized, double-blind trial enrolling 1255 patients with type 2 diabetes on hemodialysis in 178 German dialysis centers.

Results: Mean age was 66.3 years, mean blood pressure 146/76 mmHg, mean time suffering from diabetes 18.1 years and mean time on maintenance dialysis 8.3 months. Considered as continuous variables, PP, MAP, SBP and DBP could not provide a significant mortality prediction for either cardiovascular or all-cause mortality. After dividing the cohort into corresponding tertiles, we did also not detect any significant mortality prediction for PP, SBP, DBP or MAP, both for all-cause mortality and CVM after adjusting for age and sex. Nevertheless, when comparing the HR plots of the corresponding blood pressure parameters, a pronounced U-curve was seen for PP for both all-cause mortality and CVM, with the trough range being 70-80 mmHg.

Discussion: In patients with end-stage renal disease and long-lasting diabetes mellitus predialytic blood pressure parameters at study entry are not predictive for mortality, presumably because there is a very high rate of competing mortality risk factors, resulting in overall very high rates of all-cause and cardiovascular mortality, that may no longer be significantly modulated by blood pressure control.

Key Learning Points

What is already known

- Interdialytic automatic blood pressure measurement (ABPM) is considered the most reproducible and accurate method to assess blood pressure in hemodialysis patients, but it is laborious and not well suited for day-to-day management of blood pressure.
- Home blood pressure measurements have also been shown to be similarly predictive for outcome than ABPM and are easily available in most hemodialysis patients.
- So far, mostly SBP and DBP measured during the dialysis session are routinely used in most dialysis units to judge blood pressure control, despite not being clearly predictive of outcome, whereas a possible predictive value of pulse pressure has hardly been studied until now.

What this study adds

- The blood pressure measured before the start of dialysis does not provide any significant cardiovascular or all-cause mortality prediction with any of its components: neither systolic, nor diastolic, nor mean arterial blood pressure, nor pulse pressure.
- However, a U-curve was found for PP for both all-cause mortality and CVM, with the trough range being 70-80 mmHg as well as a flatter U-curve for SBP with the trough range between 130 and 150 mmHg, suggesting, though with low evidence, that these blood pressure ranges may be optimal.

What impact this may have on practice or policy

- The use of predialytic SBP, DBP, MAP, and PP to predict cardiovascular and all-cause mortality risk in hemodialysis patients as well as to determine blood pressure target levels is discouraged.
- Home blood pressure measurements by the patient or a health care provider need to be implemented as diagnostic routine in all hemodialysis patients.

INTRODUCTION

Pulse pressure (PP) is defined as the difference between systolic (SBP) and diastolic blood pressure (DBP) and is easily determinable and available. It is clinically well known as a surrogate parameter of vascular stiffness.

The Framingham Heart Study was able to demonstrate in a collective of 1924 patients without antihypertensive therapy at baseline that PP is an important risk factor with regard to coronary artery disease (CAD) development in a 20-year follow-up. Furthermore, neither SBP nor DBP were superior to PP in predicting CAD risk [1]. In a large community-based population with 169 613 participants, PP independently predicted cardiovascular (CV) disease and mortality [2].

Furthermore, we have recently shown that PP and double product (DP, product of SBP and heart rate) are powerful predictors of cardiovascular mortality (CVM) and all-cause mortality in a cardiovascular medium- to high-risk population, i.e. in patients with CAD and heart failure (HF) [3]. While DP proved to be an independent predictor of CV and all-cause mortality also in a multivariate analysis adjusted for sex, BMI, diabetes, eGFR, PP was not an independent predictor in our cohort with widespread antihypertensive treatment (>85%) after additional adjustment for age [3]. PP is associated with age, presence of diabetes, obesity, and impaired renal function [3]. In addition, we have recently shown that catecholamines, but not renin, are associated with rising PP [4].

In an analysis of 43 006 renal transplant recipients, we have shown that higher PP 1-year posttransplant is associated with inferior patient and death-censored graft survival. The combined analysis of PP and SBP provided additional predictive information for patient survival beyond that derived from analysis of SBP alone [5]. Regarding hemodialysis patients, predialysis extracellular water/total body water, measured by bioimpedance, was significantly correlated only with PP and not with SBP or DBP, so PP may prove useful in estimating hydration status before hemodialysis [6].

The way and optimal timing to measure blood pressure in hemodialysis patients has previously been discussed in the literature. An interdialytic automatic blood pressure measurement (ABPM) is the most reproducible and accurate method and is thought to best represent blood pressure in hemodialysis patients [7] [8]. But ABPM is laborious and not well suited for daily management of hypertension. Alternatively, self-recorded home blood pressure measurements are easily available, and correlate with ABPM and outcomes [9] [10] [11] [12] [13] [14]. In two large observational studies from the USA predialysis blood pressure was overall a poor predictor of outcome, and a U type association with mortality was suggested [15] [16]. So far, it has mainly been investigated whether SBP or DBP measured in the dialysis unit or at home have a better predictive value. Since in a study the predialytic hydration status only correlated significantly with predialytic PP and not with SBP or DBP [6], the question arose whether PP measured before dialysis may provide a significant mortality prediction. We were therefore interested in clarifying whether PP in addition to SBP, DBP, and MAP is a predictive parameter with regard to CV mortality and morbidity in a prospective, randomized, controlled trial of patients with type 2 diabetes end-stage renal disease requiring maintenance dialysis.

METHODS

Patients with type 2 diabetes mellitus, aged 18 to 80 years, who had received maintenance hemodialysis for less than two years were included by 178 dialysis centers in Germany into the 4 D study (Die Deutsche Diabetes Dialyse Studie/German Diabetes and Dialysis Study). Exclusion criteria were: triglyceride levels greater than 1000 mg/dl (11.3 mmol/l), fasting serum low-density lipoprotein (LDL) cholesterol lower than 80 mg/dl (2.1 mmol/l) or more than 190 mg/dl (4.9 mmol/l); liver-function values more than three times the upper limit of normal or equal to those in patients with symptomatic hepatobiliary cholestatic disease; hematopoietic disease or systemic disease unconnected to end-stage renal disease; vascular intervention, congestive heart failure, or myocardial infarction within the three months before enrollment; unsuccessful kidney transplantation; and uncontrolled hypertension (i.e., SBP continuously greater than 200 mmHg or DBP greater than 110 mm Hg).

Blood pressure was measured in supine position after 5 minutes of rest but before taking blood and starting dialysis sessions. Furthermore, patients were monitored for blood pressure at the following time points: -4, -2, -1 week (i.e., in the run-in phase), and on day 0, i.e., on the day of randomization = baseline blood pressure [17].

Preexisting lipid-lowering therapies were stopped and replaced by a placebo during a four-week run-in phase of the study. Then eligible patients were randomized to receive double-blind treatment with atorvastatin 20 mg once daily or a matched placebo. Data were recorded after four weeks and then every six months. The protocol was approved by the Coordination Center Ethics Committee and the 29 regional institutional review boards. Written informed consent was obtained from all patients.

Each endpoint was assessed by three members of the endpoint committee based on predefined criteria that were part of the study protocol. All analyzes of the primary and secondary endpoints were based on the Endpoints Committee's grading, which was found by consensus or majority vote.

The primary endpoint included the following events: death from cardiac causes, nonfatal myocardial infarction, fatal stroke, or nonfatal stroke, whichever occurred first. Only one event per person was included in the analysis. A neurological deficit lasting more than 24 hours was classified as a stroke. Cerebral magnetic resonance imaging (MRI) or computed tomography (CT) was advised and available in all but 16 cases.

The diagnosis of myocardial infarction was made when two of the following criteria were met:

Typical angina pectoris symptoms, or elevated cardiac biomarkers (i.e., a level of creatine kinase MB above 5 % of the total level of creatine kinase, a level of lactic dehydrogenase 1.5 times the upper limit of normal, or a level of troponin T greater than 2 ng/ml), or typical changes in the electrocardiogram (ECG). Therefore, a resting ECG was performed every 6 months and interpreted by an independent cardiologist according to the Minnesota classification system. If an ECG documented a silent myocardial infarction, this was considered evidence of a primary endpoint. Death from cardiac causes included death from congestive heart failure, death within 28 days after a myocardial infarction, sudden death, death from coronary artery disease during or within 28 days after an intervention, and all other deaths related to coronary artery disease. Sudden cardiac death was defined as patients who died unexpectedly and did not have a potassium level of more than 7.5 mmol/l before the start of the last three hemodialysis sessions.

Secondary endpoints were death from all causes, all cardiac and all cerebrovascular events combined. Death from any cause other than cardiac or cerebrovascular disease was treated as a competing risk factor. The study design has been described in detail previously [18].

Statistical analysis

Continuous data are shown as the mean and standard deviation (SD) when normally distributed or as the median and 25th and 75th percentile for non-normally distributed variables. Statistical differences between groups and continuous variables were determined using analysis of variance. Non-normally distributed variables were log-transformed before entering analysis. The chi-square test was used for categorical variables. Hazard ratios (HRs) were calculated by Cox proportional hazards regression. We performed multivariate analysis with adjustments for age and sex. All tests were two-sided and a P value < 0.05 was considered statistically significant. R version 4.1.2 (R Core Team (2022). R: A language and environment for statistical computing. Available at: URL https://www.R-project.org/) was used for all analyses. Hazard ratio plots were created with the R package rms version 6.2-0. Restricted cubic splines were calculated using the rcs function of the rms package. The function sets knots automatically at 10th, 50th and 90th percentiles. Forest plots were drawn using the R package forestplot version 2.0.1.

RESULTS

A total of 1255 patients were recruited for the study, with 54% being male and 46% female. Mean age was 66.3 years, mean BMI 27.6 kg/m², mean predialytic blood pressure at baseline 146/76 mmHg, mean duration of diabetes 18.1 years and mean time since onset of dialysis 8.3 months at baseline (Table 1).

After dividing the total cohort into PP tertiles, there were no significant differences between the newly created patient groups with regard to age, gender, BMI, LDL or HDL cholesterol, fasting blood sugar CAD, heart failure, smoking status, duration of diabetes or time since the start of dialysis therapy. However, there was a significant increase in SBP with roughly the same DBP, so that the increasing PP resulted from the increase in SBP (Table 1).

PP, MAP, SBP and DBP, considered as continuous variables, could not provide a significant prediction for either CV or all-cause mortality (Figure 1), so we continued our analysis by grouping blood pressure parameters into tertiles. There was no significant mortality prediction in any tertile for PP, SBP, DBP and MAP, both for all-cause mortality and CVM, each adjusted for age and sex (Figure 2).

Nevertheless, we complemented our statistical investigations using HR plots for these blood pressure parameters. Interestingly, a U-curve was found for PP for both all-cause mortality and CVM, with the trough range being 70-80 mmHg (Figure 3). A U-curve was also registered for SBP, but much flatter than for PP. The trough range here was between 130 and 150 mmHg (Figure 4).

With regard to DBP, CVM showed an initially flat mortality line between 50 and 75 mmHg and a clear increase in HR from 75 mmHg onwards. The all-cause mortality analysis showed a very flat U-curve with a trough of 75-85mmHg (Figure 5). The HR plot for MAP regarding CVM followed a straight line with no slope up to 100 mmHg and rose thereafter. There is an HR plot for all-cause mortality, which is reminiscent of a flat U-curve with a valley of 90-100 mmHg (Figure 6).

In order to identify any clinical subgroup in which different hemodynamic blood pressure parameters have a significant predictive value, we divided the patient cohort into placebo vs. atorvastatin group, dialysis duration ≤ 5.95 months vs. dialysis duration >5.95 months, male vs. female, age ≤ 66.93 vs. age > 66.93 years, CAD present vs. CAD absent, smoker or ex-smoker vs. non-smoker. We divided the patients into roughly equal subgroups, so we used the median age of 66.93 years and median dialysis duration of 5.95 years.

In the comparison of placebo vs. verum, gender, age and smoking status, there was no significant prediction by PP, MAP, SBP, DBP (Supplementary Figures 1-4). For patients who have been on dialysis for more than 5.95 months, there was a significant HR of 1.32 for MAP in the 3rd tertile and a HR of 1.56 for DBP in the 3rd tertile with regard to all-cause mortality (Supplementary Figure 5). In the CAD group, there was a significant HR of 1.75 for all-cause mortality in the 3rd tertile of DBP (Supplementary Figure 6).

DISCUSSION

In the analysis of the 4 D dataset we did not detect a significant mortality prediction from baseline PP, SBP, DBP and MAP, both for all-cause mortality and CVM after adjusting for age and sex in diabetic patients on maintenance dialysis. Nevertheless, when comparing the HR plots of the corresponding blood pressure parameters, a pronounced

U-curve was seen for PP for both all-cause mortality and CVM, with a trough range of 70-80 mmHg for lowest mortality, and less so for SBP with a trough range of 130-150 mmHg with lowest mortality. It is unexpected, that overall neither SBP, DBP, nor PP provide a significant mortality prediction in diabetics with end-stage renal disease in the 4D cohort, given the well-known mortality prediction in the normal population, in CV risk patients and in patients with chronic kidney disease [1, 19, 20] [3, 21] [22, 23]. Multiple underlying reasons may account for our inability to detect a relevant mortality prediction by blood pressure parameters.

1. Baseline blood pressure before the start of hemodialysis may not be representative of blood pressure on non-dialysis days and for longterm (24h) ambulatory blood pressure regulation. Situative effects on blood pressure that are known as white-coat hypertension or masked hypertension may be amplified or modified in an unpredictable manner in the hemodialysis setting. Furthermore, during hemodialysis, blood pressure may increase or decrease to varying degrees with changes in ultrafiltration, refilling, vascular resistance, venous tone, autonomous neuropathy, thermoregulatory response, electrolyte changes, dialyzable antihypertensive medication, myocardial contractility, dialysate/room temperature and food intake [24, 25]. It is known that intradialytic blood pressure variability is a predictor for CVM and CV hospitalization in a hemodialysis population [26]. We could not take this effect into account in our analysis since only baseline blood pressure measurements were available. Therefore, we could not identify patients with intradialytic hypertension, where an increase in blood pressure from pre- to post-hemodialysis occurs. Intradialytic blood pressure rise is not rare. In a study of 1,748 patients, 12.2% had an increase in SBP >10 mmHg during hemodialysis [27]. This condition has been identified as an independent risk factor of mortality in hypertensive hemodialysis patients [27] [28]. On the other hand, intradialytic hypotension is also associated with a worse outcome [29, 30]. In a Japanese study of 545 patients with a total of 3261 hemodialysis sessions, intradialytic hypotension occurred in 14.4% of sessions [31]. Overall, the effects of intradialytic hypertension and hypotension could not be accounted for in our mortality analysis.
2. The 4 D study was not planned to study the effect of blood pressure on outcome, but focused on the effect of a statin on patient outcome. From a methodological point of view, a post-hoc analysis is a different approach than, for example, a randomized, double-blind study. A study explicitly designed for this purpose would be desirable in order to provide better scientific evidence of the predictive value of the various blood pressure parameters.
3. Most importantly, the 4D study included a very high-risk patient population. These were exclusively patients with end-stage renal disease and diabetes mellitus with a mean duration of 18.1 years, non-diabetics (with a lower mortality risk) therefore were excluded. The combined effects of long-term diabetes mellitus in patients with a mean age as high as 66 years in combination with end-stage renal disease, preexisting cardiovascular disease (heart failure, CAD) in the majority and smoking in 40 % on cardiovascular and all-cause mortality is considered to be extraordinarily high. Therefore, in patients with end-stage renal disease and long-lasting diabetes mellitus from the 4D study, blood pressure parameters may no longer be predictive for cardiovascular and all-cause mortality, presumably because there is a very high rate of competing mortality risk factors and competing all-cause and cardiovascular mortality in this patient cohort. This assumption is also supported by findings of both the 4D study and the AURORA trial [18, 32], which showed that the very effective reduction of cardiovascular mortality in other high-risk cohorts with statin therapy, could not be reproduced in these cohorts of dialysis patients. Furthermore, in a study with 1243 chronic dialysis patients PP was even more potent than SBP or DBP as an independent predictor of all-cause mortality for non-diabetics, but not for diabetics in the same study [23].
In conclusion, in patients with end-stage renal disease and longstanding diabetes mellitus in the 4D study, there are, besides methodological issues of blood pressure measurements and timing of measurements, probably too many competing risk factors for all-cause and CV mortality, so that blood pressure parameters are no longer able to predict mortality.

Statements

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The data reported in the present manuscript are part of the medical doctoral thesis of Aruscha Asgari.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the Medical Faculty of the University of Würzburg on October 13, 1997 (approval number: 104/97). Independent Ethics Committees or Institutional Review Boards of the participating centers approved the protocol and all its amendments. The study was conducted

according to the Declaration of Helsinki with all its amendments as well as in accordance with GCP (Good Clinical Practice) and ICH (International Conference on Harmonization of Technical Requirements) regulations. Written informed consent was obtained from all patients.

Data Availability Statement

All relevant data generated or analysed during this study are included in this article. According to the German Data Protection Act and the consent given by the study participants, data cannot be released to the public domain. Data may be made available to researchers upon reasonable request. Further enquiries can be directed to the Principal Investigator of the 4D study Prof. Christoph Wanner.

Conflict of Interest Statement

- Prof. Dr. med. B. K. Krämer reports lecture fees and/or advisory board memberships and/or study participation from Astellas, Bayer, Boehringer Ingelheim, Chiesi, Riepharm, Pfizer, Sanofi, Servier, and Vifor Pharma, all outside the submitted work. He is the past president of the German Hypertension Society DHL.
- Dr. rer. nat. Marcus E. Kleber is employed by Synlab Holding Deutschland GmbH.
- Prof. Dr. med. W. März reports grants and personal fees from: Aegerion Pharmaceuticals, AMGEN, Sanofi, Alexion Pharmaceuticals, BASF, Abbott Diagnostics, Numares AG, Berlin-Chemie, Akzea Therapeutics; grants from: Siemens Healthineers, Astrazeneca, Bayer Vital GmbH, bestbion dx GmbH, Boehringer Ingelheim Pharma GmbH Co KG, Immundiagnostik GmbH, Merck Chemicals GmbH, MSD Sharp and Dohme GmbH, Novartis Pharma GmbH, Olink Proteomics, other from Synlab Holding Deutschland GmbH, all outside the submitted work.
- The remaining authors have no conflicts of interest to declare.

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Author Contributions

Babak Yazdani and Bernhard K. Krämer designed the research, wrote the first draft of the manuscript, did the literature research and interpreted the results. Marcus Kleber and Graciela Delgado made statistical analyses. Gökhan Yücel, Aruscha Asgari, Niklas Ayasse, Clara Daschner and Winfried März helped to discuss the results and thereby made essential contributions to the manuscript. Andreas L.H. Gerken proofread the manuscript and made important intellectual contributions. Christoph Wanner is principal investigator of the 4D study and was instrumental in performing of the study and providing the data for analysis.

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Figure Legends

Figure 1. Forest plot for PP, MAP, SBP and DBP, considered as continuous variables, regarding cardiovascular mortality (A) and all-cause mortality (B), adjusted for age and sex

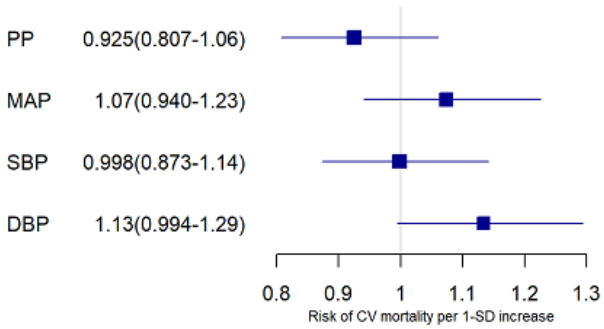
Figure 2. Forest plot for different PP, MAP, SBP and DBP tertiles regarding cardiovascular mortality **(A)** and all-cause mortality **(B),** adjusted for age and sex. SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, MAP: mean arterial pressure.

Figure 3. HR-plot for PP (pulse pressure) regarding cardiovascular mortality **(A)** and all-cause mortality **(B)**, adjusted for age and sex.

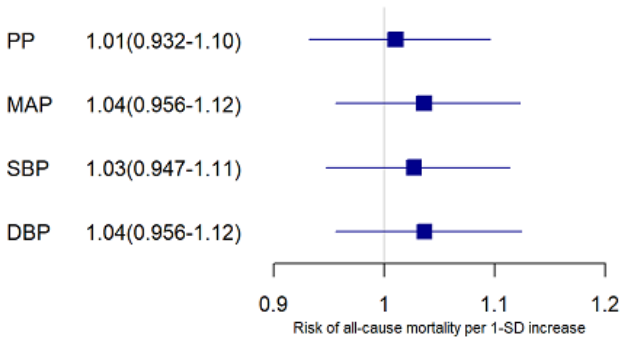
Figure 4. HR-plot for SBP (systolic blood pressure) regarding cardiovascular mortality **(A)** and all-cause mortality **(B)**, adjusted for age and sex.

Figure 5. HR-plot for DBP (diastolic blood pressure) regarding cardiovascular mortality **(A)** and all-cause mortality **(B)**, adjusted for age and sex.

Figure 6. HR-plot for MAP (mean arterial pressure) regarding cardiovascular mortality **(A)** and all-cause mortality **(B)**, adjusted for age and sex.



A)



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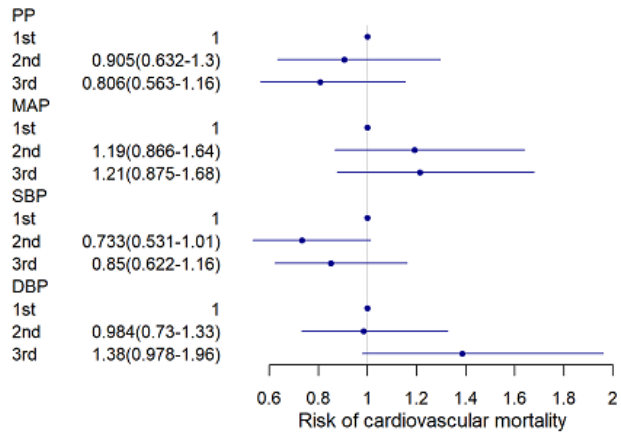
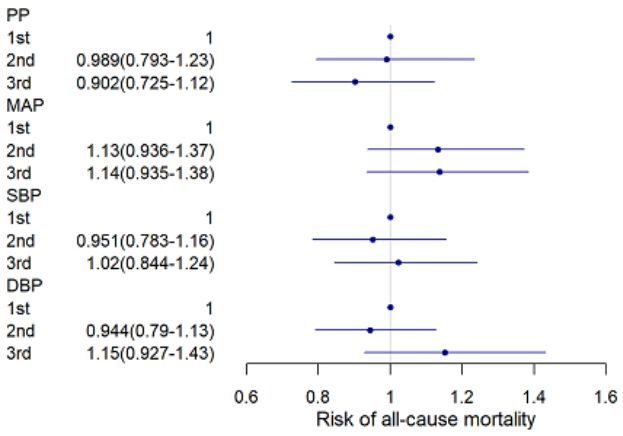


A)



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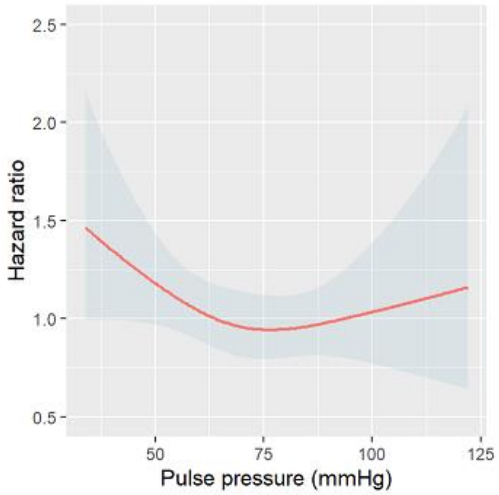

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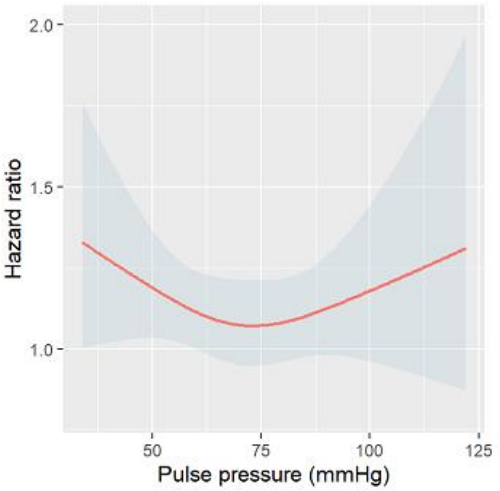

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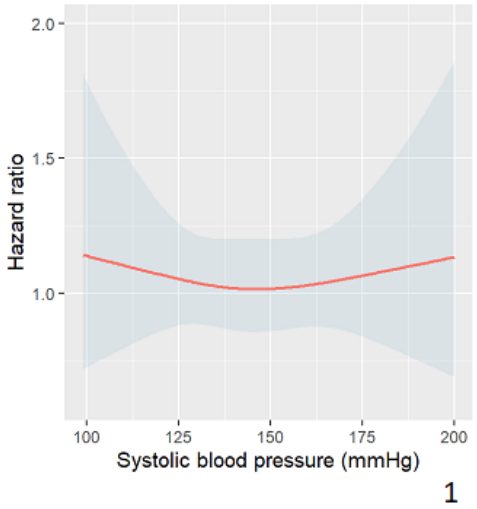

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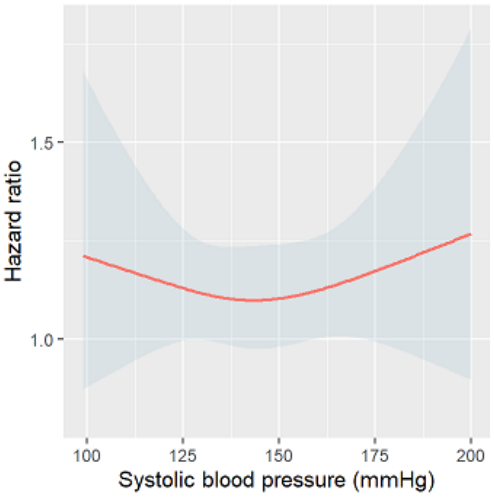

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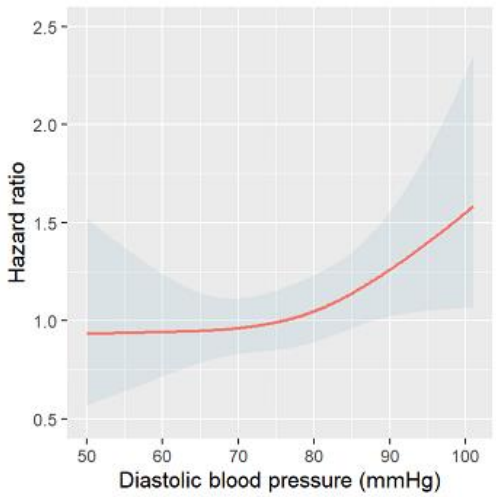

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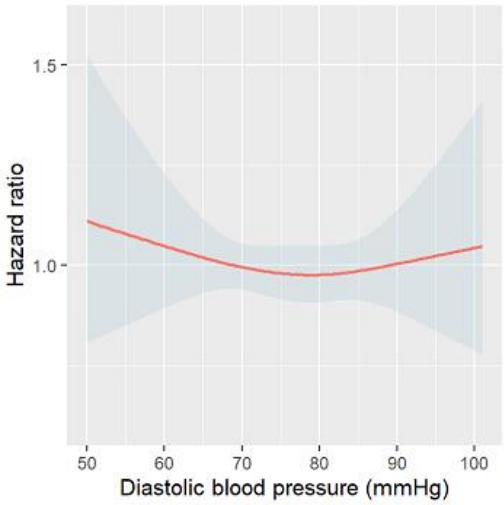

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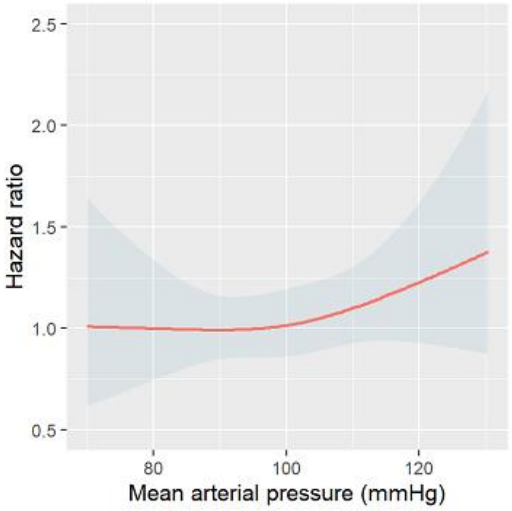

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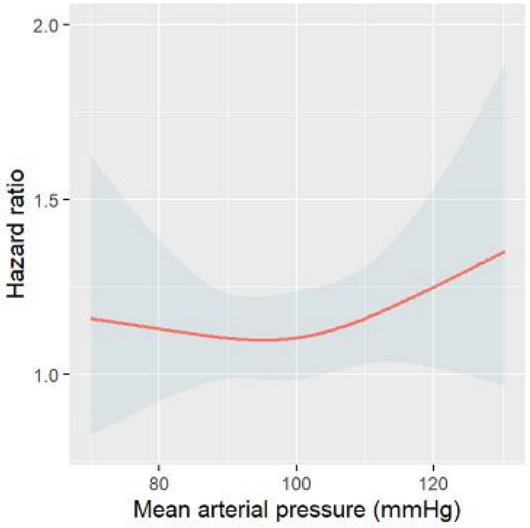

B)

Table 1. Baseline parameters in patients receiving maintenance dialysis for different PP tertiles

	All patients	1.Tertile	2.Tertile	3.Tertile	
PP (mmHg)	70.2	≤ 61 (N=496)	61-81 (N=489)	≥81 (N=270)	P*
Age (years)	66.3 (8.24)	66.4(8.3)	66.0(8.3)	66.7(8)	0.514
Male sex (%)	53.9	54.0	55.0	51.9	0.704
BMI (kg/m2)	27.5 (4.80)	27.9(4.73)	27.4(4.62)	27.2(5.21)	0.704
LDL-C (mg/dl)	126 (29.9)	125.0(29.7)	125.0(29.7)	128.0(30.5)	0.448
HDL-C (mg/dl)	36.2 (13.2)	36.0(12.8)	36.2(12.9)	36.5(14.4)	0.897
TG (mg/dl)	223 (149-326)	226.0(155-340)	223.0(147-322)	212.0(148-316)	0.413
SBP (mmHg)	146 (22.0)	127.2(13.7)	149.6(12.1)	172.1(17)	<0.001
DBP (mmHg)	75.8 (11.0)	75.2(10.3)	76.4(10.9)	75.7(12.4)	0.207
Fasting glucose (mg/dl)	152 (119-169)	152.0(117-170)	152.0(120-169)	152.0(120-171)	0.891
hsCRP (mg/l)	6.40 (2.70-11.13)	6.8(2.8-11.83)	6.7(2.7-11.13)	5.3(2.6-11.13)	0.239
CAD (%)	21.1	24.0	20.2	17.4	0.086
Heart failure (%)	35.4	36.5	32.9	37.8	0.327
Smoker (current or ex, %)	40.4	40.9	40.3	39.6	0.939
Diabetes duration (years)	18.1 (11.8-23.3)	18.1(11.67-23.25)	18.1(11.83-23.17)	18.1(12.69-23.98)	0.407
Dialysis duration (months)	5.95(3.09-11.5)	6.09(2.99-11.55)	5.91(3.42-12.12)	5.39(2.7-11.05)	0.134
Atorvastatin (%)	49.3	48.0	50.7	49.3	0.692
ACE inhibitor (%)	46.5	45.0	45.8	50.7	0.284
AT2 antagonist (%)	11.9	9.9	11.9	15.6	0.068
Betablocker (%)	36.7	40.5	35.0	33.0	0.068
Calcium antagonist (%)	40.8	31.9	42.3	54.4	<0.001
Diuretic (%)	80.2	80.0	79.8	81.5	0.840
Antiplatelet drug (%)	51.6	48.4	54.6	52.2	0.145
Anticoagulant drug (%)	14.7	18.3	13.9	9.6	0.004

* ANOVA (non-normally distributed variables were log transformed before entering analyses) or $\chi 2$ test; SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, ACE: angiotensin Converting Enzyme, CAD: Coronary artery disease.

Data given as mean (SD) or median (25^{th} to 75^{th} percentile) for continuous values or percentage for categorical variables