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ORIGINAL ARTICLE

Long-term peridialytic blood pressure changes are related to mortality

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GRAPHICAL ABSTRACT

Long-term peridialytic blood pressure changes are related to mortality

Background

Peridialytic blood pressures decline gradually over time. Currently, it is not known whether long-term peridialytic blood pressure changes are related to mortality.

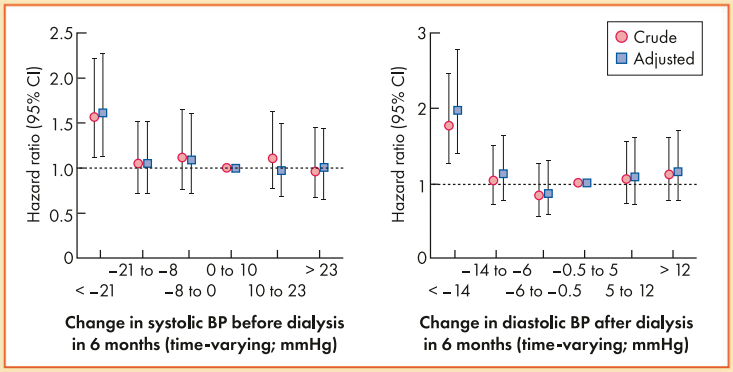
Methods

Individual participant data of 3 RCTs
- CONTRAST, 2012
- ESHOL, 2013
- FRENCHIE, 2017

HD (n=1002)
HDF (n=1009)

Relation between long-term blood pressure changes and mortality

Results



Conclusion

Long-term severe declines in pre-dialytic systolic and post-dialytic diastolic blood pressure are independently related to increased mortality, irrespective of UF-volume, BMI or dialysis modality.

NEPHROLOGY DIALYSIS TRANSPLANTATION

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KEY LEARNING POINTS

What is already known about this topic?

- Previous studies have shown a U- or J-shaped relationship between a single or a few blood pressure (BP) measurements at baseline and mortality or between a short-term change in BP and mortality.
- In chronic haemodialysis (HD) and haemodiafiltration (HDF) patients, peridialytic BP decreases gradually over time, without differences between HD and HDF.

What this study adds?

- No study before has evaluated the relationship between long-term changes in peridialytic BP and mortality or evaluated the impact of HD and HDF in this respect. We found that severe declines in pre-dialytic systolic and in post-dialytic diastolic BP in the preceding 6 months are independently associated with an increased mortality risk.
- No differences in the relationship between BP change and mortality were observed between HD and HDF.

What impact this may have on practice or policy?

- In chronic dialysis patients, peridialytic BP measurements should be interpreted in the context of their long-term changes and not just on short-term monitoring.

ABSTRACT

Background. In chronic haemodialysis (HD) patients, the relationship between long-term peridialytic blood pressure (BP) changes and mortality has not been investigated.

Methods. To evaluate whether long-term changes in peridialytic BP are related to mortality and whether treatment with HD or haemodiafiltration (HDF) differs in this respect, the combined individual participant data of three randomized controlled trials comparing HD with HDF were used. Time-varying Cox regression and joint models were applied.

Results. During a median follow-up of 2.94 years, 609 of 2011 patients died. As for pre-dialytic systolic BP (pre-SBP), a severe decline (≥21 mmHg) in the preceding 6 months was independently related to increased mortality [hazard ratio (HR) 1.61, $P = .01$] when compared with a moderate increase. Likewise, a severe decline in post-dialytic diastolic BP (DBP) was associated with increased mortality (adjusted HR 1.96, $P < .0005$). In contrast, joint models showed that every 5-mmHg increase in pre-SBP and post-DBP during total follow-up was related to reduced mortality (adjusted HR 0.97, $P = .01$ and 0.94, $P = .03$, respectively). No interaction was observed between BP changes and treatment modality.

Conclusion. Severe declines in pre-SBP and post-DBP in the preceding 6 months were independently related to mortality. Therefore peridialytic BP values should be interpreted in the context of their changes and not solely as an absolute value.

Keywords: haemodiafiltration, haemodialysis, joint models, blood pressure, long-term changes, mortality

INTRODUCTION

Worldwide, approximately 3 million patients with end-stage kidney disease (ESKD) are treated with intermittent extracorporeal dialysis techniques, including haemodialysis (HD) and haemodiafiltration (HDF) [1]. Yet, despite their lifesaving properties, both cardiovascular (CV) morbidity and mortality remain alarmingly high [2]. Besides specific renal and dialysis-related risk factors, such as the retention of uraemic toxins and bio-incompatibility of the extracorporeal circuit, traditional risk factors, including hypertension and diabetes, play an important role as well. In the general population, a log-linear, inverse relationship between blood pressure (BP) and CV survival has been well established [3]. For dialysis patients, however, this relation is less clear. Actually, in most guidelines, strict BP targets are lacking due to the absence of robust data from well-designed and sufficiently powered trials [4–6]. Previous observational studies have shown a U- or J-shaped relationship between BP values measured just before or after dialysis (peridialytic BP) and mortality, or no relationship at all [7–13]. In virtually all studies, just baseline BPs or their short-term changes were evaluated. In healthy conditions, BP is controlled by cardiac output and peripheral vascular resistance, which are both influenced by various factors, including the sympathetic nervous system and the renin–angiotensin system [8]. In HD patients, however, structural and functional derangements of the CV system, including premature vascular stiffening and left ventricular hypertrophy, may severely affect the capacity of a patient to keep BP within a normal range. Furthermore, in these patients, BP is also highly volume dependent as a result of reduced urine output [14, 15]. Due to the intermittent character of the treatment, both volume status and BP vary considerably. Generally, BP increases in the interdialytic interval due to fluid retention and declines during dialysis (intradialytic) due to obligate ultrafiltration (UF). As for the latter, both patient- and dialysis-related factors may be involved, including the pathophysiological state and reactivity of the CV system, the amount of UF needed, the UF rate and the difference between the UF rate within the dialyzer and the rate of refill from the interstitial space to the circulation.

In a large database with individual participant data (IPD) from three randomized controlled trials (RCTs) comparing HD with HDF, we recently showed that both systolic BP (SBP) and diastolic BP (DBP) decrease over time [16]. Furthermore, previously it was shown that patients treated with HDF have a superior survival when compared with HD [17]. In the current study, we evaluated whether long-term peridialytic BP changes are related to mortality and whether the relationship between long-term BP changes and mortality differs between HD and HDF.

MATERIALS AND METHODS

Study design

The present analysis was executed with the IPD of three RCTs comparing HD with online post-dilution HDF [17]. A fourth RCT, that also evaluated survival in HDF and HD patients, was omitted due to the absence of longitudinal peridialytic BP data [18]. Details of the included studies can be found elsewhere [19–21]. In short, the CONvective TRAnsport STudy (CONTRAST) included 714 ESKD patients in 27 dialysis centres in the Netherlands, Canada and Norway. The mean convection volume in HDF patients was 20.7 l/session and the median follow-up was 2.9 years. All-cause mortality was the primary endpoint. The same holds true for the Spanish Estudio de Supervivencia de Hemodiafiltración On-Line (ESHOL), which included 906 patients. In this investigation, the quarterly measured mean convection volumes in HDF patients ranged from 22.9 to 23.9 l/session and the median follow-up was 2.1 years. Lastly, the French Convective versus Hemodialysis in Elderly (FRENCHIE) study evaluated 391 patients (age ≥65 years). While intradialytic tolerance was the primary endpoint, mortality was a secondary objective. The mean reached convection volume in HDF patients ranged from 19.3 to 22.5 l/session and the median follow-up was 2.0 years. All studies randomized patients in a 1:1 ratio.

Data collection

At baseline, demographics, medical history, laboratory values and dialysis parameters were collected. Body mass index (BMI; kg/m^2) was calculated as post-dialysis weight (kg)/height (m^2). A history of CV disease (CVD) included myocardial infarction, angina pectoris, therapeutic coronary procedure, transient ischaemic attack, stroke, therapeutic carotid procedure (endarterectomy or stenting), vascular intervention (percutaneous transluminal angioplasty, revascularisation or stenting) and amputation.

BP measurements

At baseline and during follow-up, SBP and DBP were measured both before (pre) and after (post) dialysis by automatically inflated manometric cuffs using a digital monitor attached to the dialysis machine, according to standard protocols. Differences between the post- and pre-BP values (Δdialytic) were calculated by subtracting pre-BP values from post-BP values, therefore positive values represent an increase in BP during dialysis. Pulse pressure (PP) was calculated by subtracting DBP from SBP, and mean arterial pressure (MAP) by using the formula (1/3*SBP + 2/3*DBP). The average BP of three consecutive dialysis sessions was registered at baseline and every 3 (CONTRAST and ESHOL) or 6 (FRENCHIE) months thereafter. While four peridialytic BP values were measured directly [pre-dialytic SBP (pre-SBP), post-dialytic SBP (post-SBP), pre-dialytic DBP (pre-DBP) and post-dialytic DBP (post-DBP)], eight parameters were calculated: ΔSBP, ΔDBP, pre-PP, post-PP, ΔPP, pre-MAP, post-MAP and ΔMAP.

Follow-up

Several patients moved to another centre, switched to peritoneal dialysis or underwent renal transplantation, so all efforts were made to obtain complete follow-up data for all patients in this IPD analysis. Ultimately, 99.8% had complete follow-up (until death or the end of the study).

Statistical analysis

Descriptive statistics are presented as mean [standard deviation (SD)], median [interquartile range (IQR)] or number (percentage), as dictated by the data type. In all cases, model assumptions were checked and not violated. Corrected models were adjusted for age, gender, history of CVD, dialysis vintage, BMI, diabetes and, when applicable, the corresponding baseline BP (as determined by the type of BP analysed, i.e. correction for baseline pre-SBP for the analysis on the change in pre-SBP on mortality, etc.). Whenever possible, complete follow-up (i.e. intention-to-treat) was used and renal transplantation handled as a competing risk [22]. Analyses were performed with SPSS Statistics version 24 (IBM, Armonk, NY, USA) or RStudio version 1.1.456 (Posit Software, Boston, MA, USA). The R-package 'JM' was used to fit joint models [23]. To reduce chances of a type 1 statistical error due to multiple testing, the *P*-value at which a certain difference was considered statistically significant was adjusted according to the Bonferroni–Holm method [24].

Assessment of the relationship between BP and mortality using time-to-event models

To assess the comparability of the data with previous studies, we first evaluated the relationship between absolute baseline SBP and DBP and mortality using Cox proportional hazards models. Patients were divided into sextiles to account for a potential non-parametric relationship. The fourth sextile (lowest hazard for pre-SBP) was used as the reference category. Next, to evaluate the relationship between a 6-month BP change and mortality, Cox proportional hazards models with the 6-month BP change as a time-varying variable were used, allowing BP change to evolve over time. Patients without follow-up after 6 months were excluded from the analyses. Again, to account for a possible non-linear relationship between 6-month BP changes and mortality, we divided all 6-month BP changes in sextiles as determined by the change in the first 6 months (M6 − M0, positive values representing a BP increase). We then evaluated a number of potential interactions to determine whether the relationship between BP

Table 1: Baseline patient characteristics ($N = 2011$).

	Values
Demographics	
Age (years), mean (SD)	67.0 (13.7)
Sex (male), *n* (%)	1287 (64.0)
BMI (kg/m^2), mean (SD)	24.7 (4.7)
Medical history, *n* (%)	
Diabetes mellitus	540 (26.9)
Cardiovascular disease	807 (40.1)
Previous renal transplant	338 (16.8)
Dialysis characteristics	
Dialysis vintage (months), median (IQR)	28 (13–57)
Kt/V urea, mean (SD)	1.55 (0.31)
Pre-dialytic SBP (mmHg), mean (SD)	141 (25)
Post-dialytic SBP (mmHg), mean (SD)	132 (15)
Pre-dialytic DBP (mmHg), mean (SD)	72 (25)
Post-dialytic DBP (mmHg), mean (SD)	69 (14)
Laboratory values	
Haemoglobin (mg/dl), mean (SD)	11.8 (1.6)
Phosphate (mg/dl), mean (SD)	4.73 (1.55)
Parathyroid hormone (pmol/l), median (IQR)	32 (15–120)

change and mortality differed between HD and HDF patients, HD patients and HDF patients who achieved high convection volumes (>23 l/session on average; hvHDF) [17], patients with a high or low baseline BP and men and women. Next, Cox proportional hazards models were fitted with sextiles of 6-month BP changes as a time-varying variable and sextile 4 as the reference category. Using this approach, the relationship between the most recent (i.e. preceding) 6-month BP change and mortality could be assessed. Both crude and adjusted models were fitted. To determine whether the relationship between BP change and mortality was driven by changes in interdialytic weight gain, we fitted the adjusted models again and included the corresponding time-varying 6-month change in UF rate. Since correcting for the corresponding change in UF rate may be insufficient when dry weight increases, we plotted dry weight over time to evaluate a potential relative change in UF rate. Lastly, models were fitted as clustered by study to evaluate a potential study effect.

Joint models

To increase the robustness of our findings, joint models were fitted to determine the relationship between the rate of change in BP (i.e. slope) and mortality. Details concerning joint models are described extensively elsewhere [23, 25]. In short, this model combines a generalized linear mixed model (LMM) with a Cox proportional hazards model. This approach makes it possible to relate the linear long-term slope of BP to mortality. As a result, the hazard ratio (HR) per amount of BP change over time can be calculated. For the LMMs, a random intercept, slope or both were used, depending on the lowest Akaike's information criterion.

RESULTS

Baseline patient characteristics ($n = 2011$) are shown in Table 1. The mean age was 67.0 years and 64.0% were male. The mean pre-BP was 141/72 mmHg at baseline and the mean post-BP was 132/69 mmHg. Previously, baseline characteristics stratified by the original study were determined to identify potential heterogeneity between patients in the three included trials. It appeared that patients from FRENCHIE, a study specifically designed for the elderly, were older and less frequently transplanted. Furthermore, mean pre-SBP and pre-DBP were higher in CONTRAST than in the other two studies [16]. In total, 609 of 2011 patients died during a median follow-up of 2.94 years (IQR 1.93–3.00).

Potential interactions between time-varying 6-month BP change and mortality

As shown in Supplementary Table S1, all investigated interactions were not significant. Thus, the relationship between the time-varying 6-month BP change and mortality was not different between HD and HDF patients nor between patients treated with HD or hvHDF [17] nor between patients with a high or low baseline BP nor between men and women. As a result, no stratified analyses were necessary and we continued our analyses with the pooled cohort.

Baseline BP and mortality

As can be seen from Supplementary Tables S2 and S3, the overall relationship with all BP values (pre-SBP, post-SBP, ΔSBP, pre-DBP, post-DBP and ΔDBP) and mortality appeared U-shaped. No significant differences between the sextiles of absolute baseline BPs and mortality were found in the adjusted models after correcting for multiple testing for pre-SBP, post-SBP, ΔSBP, pre-DBP and post-DBP. However, in the adjusted models for ΔDBP, both sextiles 1 and 6 had a significantly higher mortality risk when compared with sextile 4.

Time-varying 6-month BP change and mortality

SBP

Both crude and adjusted HRs (aHRs) for mortality of sextiles of the time-varying 6-month changes in SBP are visualized in Fig. 1 and shown in Supplementary Table S4. Whereas patients with a moderate decline to a severe increase in pre-SBP in the preceding 6 months had a similar mortality risk, patients with a severe decline (≥21 mmHg) had a 61% increased mortality risk {aHR 1.61 [95% confidence interval (CI) 1.13–2.28]} when compared with a moderate increase. No significant differences were observed for long-term changes in post-SBP or ΔSBP.

DBP

In Fig. 2 and Supplementary Table S5, HRs of sextiles of the time-varying 6-month change in DBP are shown. A U-shaped relationship was observed between 6-month BP changes in pre-DBP, post-DBP and ΔDBP and mortality. However, when compared with a stable or moderate increase, only the mortality risks in patients with severe declines in the preceding 6 months in post-DBP and ΔDBP were statistically significant [aHR 1.96 (95% CI 1.40–2.77) and 1.69 (95% CI 1.17–2.45), respectively).

MAP and PP

In Supplementary Tables S6 and S7, the results of both crude and adjusted models are shown for the relations between

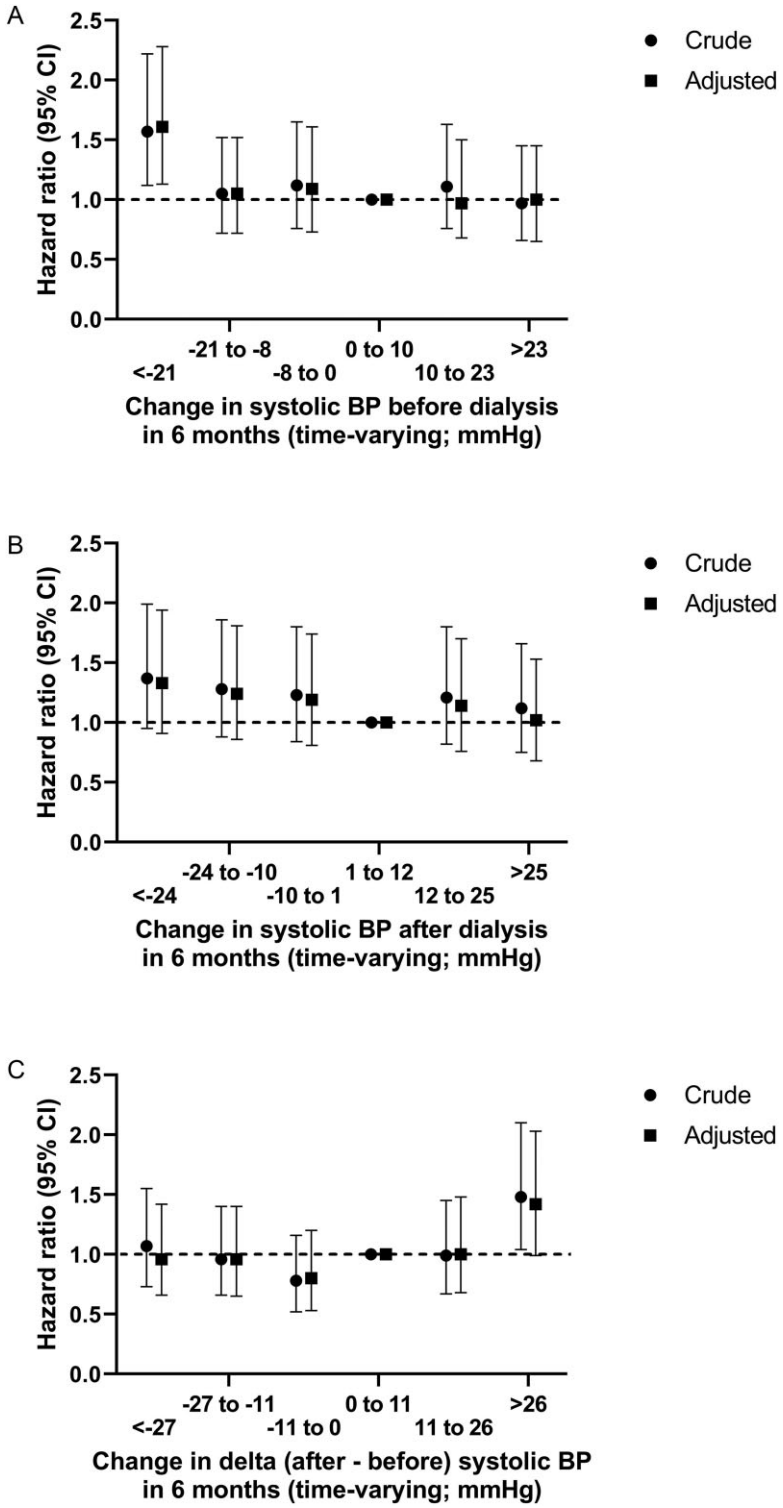

Figure 1: Relationship between the 6-month change in SBP measured **(a)** before, **(b)** after and **(c)** Δ (after − before) and mortality. Adjusted models were corrected for age, gender, history of CVD, dialysis vintage, BMI, diabetes and baseline BP (pre-dialytic SBP, post-dialytic SBP or Δdialytic SBP, respectively). Whiskers represent 95% CIs of the HR.

the 6-month changes in MAP and PP and mortality. Only a severe declining post-MAP was related to increased mortality when compared with stable or mildly increasing values [aHR 1.71 (95% CI 1.18–2.46)]. No specific shape in the relationship between a changing pre-PP or post-PP and mortality could be identified. In contrast, a severe increase in ΔPP in the preceding 6 months was related to increased mortality when compared with stable or mildly increasing values [aHR 1.89 (95% CI 1.30–2.74)].

Additional analyses

All Cox regression analyses adjusted for the 6-month change in UF rate yielded similar results. Significant

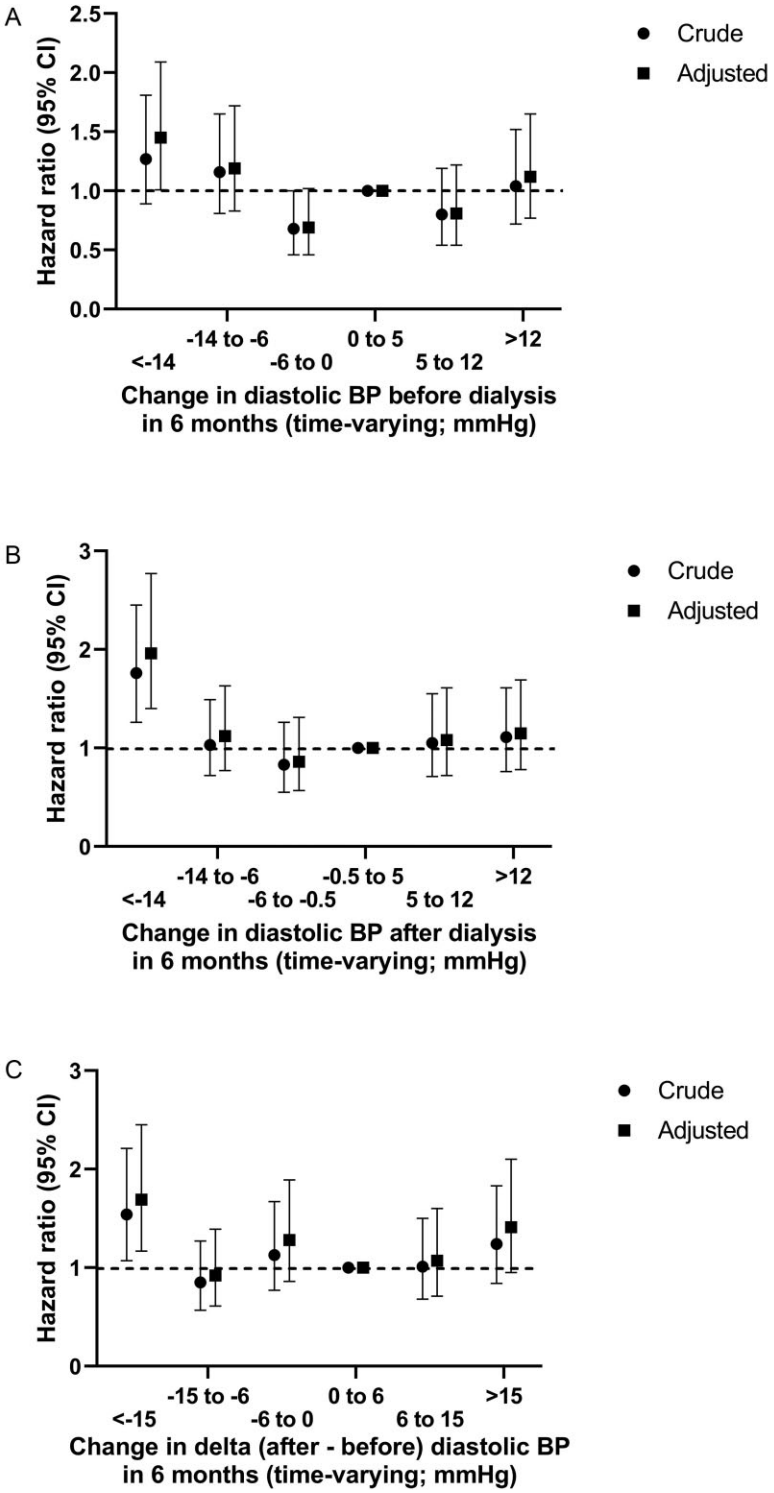

Figure 2: Relationship between the 6-month change in DBP measured **(a)** before, **(b)** after and **(c)** Δ (after − before) and mortality. Adjusted models were corrected for age, gender, history of CVD, dialysis vintage, BMI, diabetes and baseline BP (pre-dialytic DBP, post-dialytic DBP or Δdialytic DBP, respectively). Whiskers represent 95% CIs of the HR.

longitudinal changes in dry weight were not observed. Lastly, analyses clustered by study also yielded similar results (data not shown).

Joint models

In Table 2, the HRs per 5 mmHg increase in BP during follow-up are summarized.

SBP

For pre-SBP, the aHR for mortality was 0.97 (95% CI 0.94–0.99) for every 5-mmHg increase. Furthermore, a similar increase in post-SBP was related to improved survival [aHR 0.95 (95% CI 0.92–0.98)]. No relationship was found between long-term changes in ΔSBP and mortality.

Table 2: HR for mortality per 5 mmHg increase in BP during follow-up (joint models).

BP	Crude HR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
Systolic				
Pre	0.97 (0.95–1.00)	.03	0.97 (0.94–0.99)	.01
Post	0.99 (0.96–1.02)	.62	0.95 (0.92–0.98)	.002
Δ	1.03 (0.99–1.08)	.14	0.98 (0.94–1.03)	.45
Diastolic				
Pre	0.86 (0.82–0.90)	<.0005	0.98 (0.93–1.02)	.31
Post	0.82 (0.77–0.86)	<.0005	0.94 (0.88–1.00)	.03
Δ	1.02 (0.94–1.11)	.61	0.88 (0.80–0.97)	.01
MAP				
Pre	0.89 (0.86–0.93)	<.0005	0.97 (0.93–1.01)	.10
Post	0.89 (0.85–0.94)	<.0005	0.93 (0.88–0.98)	.004
Δ	1.04 (0.98–1.11)	.23	0.94 (0.88–1.01)	.09
Pulse pressure				
Pre	1.04 (1.01–1.07)	.01	0.96 (0.93–0.99)	.02
Post	1.06 (1.03–1.10)	.0002	0.96 (0.93–1.00)	.05
Δ	1.07 (0.97–1.15)	.17	1.01 (0.93–1.10)	.73

Models were adjusted for age, gender, history of CVD, dialysis vintage, BMI and diabetes.

DBP

Every 5 mmHg increase in post-DBP was related to a 6% decrease in mortality risk [aHR 0.94 (95% CI 0.88–1.00)]. Although an increase in pre-DBP was associated with a reduced mortality risk in a crude model, the difference did not reach statistical significance in the adjusted model. Interestingly, an increase in ΔDBP was also related to improved survival [aHR per 5 mmHg increase 0.88 (95% CI 0.80–0.97)].

MAP and PP

In the adjusted models, both increases in post-MAP [aHR per 5 mmHg increase 0.93 (95% CI 0.88–0.98)] and pre-PP [aHR per 5 mmHg increase 0.96 (95% CI 0.93–0.99)] were related to a reduced mortality risk.

DISCUSSION

In the present study, we analysed whether changes in peridialytic BP values in the preceding 6 months are independently related to mortality. Furthermore, multiple potential interactions, including differences in the relationship between longitudinal BP changes and mortality for patients treated with different dialysis modalities (i.e. HD versus HDF) were evaluated. As for the primary objective, it clearly appeared that severe declines in both pre-SBP and post-DBP in the preceding 6 months are related to an increased mortality risk, irrespective of age, underlying comorbidity, UF volume changes, dialysis vintage and BMI. The relationship between a declining peridialytic MAP and mortality is a reasonable consequence of these findings. In contrast, every 5 mmHg increase during follow-up in both pre-SBP and post-DBP was related to a 3% and 6% survival advantage, respectively. Decreasing BP in a population with a high prevalence of fluid overload could result from a loss of total body water due to forced UF [26]. Yet the finding that decreasing BP is associated with mortality, even in patients whose UF volume remained stable or increased, suggests that fluid underfill does not underlie these results. Second, our analyses showed that the relationship between BP changes in the preceding 6 months and mortality was similar for patients treated with HD or HDF and for patients treated with HD or hvHDF.

An important clinical consequence of our findings is that peridialytic BP values should not be interpreted in absolute values, but in the context of their longitudinal changes. In fact, most previous studies have focused on the relationship between an absolute BP value and mortality in search of specific BP targets. Results ranged from J-shaped [13] to U-shaped relations [7, 9, 10, 12], or no relationship at all [11]. Yet, virtually all studies are not only limited by their observational design, but also by the assessment of a single baseline BP measurement or the mean baseline BP of a few sessions or a short-term change, limited power and/or a limited follow-up period [27–32]. To assess whether our patient cohort is comparable to those in prior reports, we also evaluated potential associations between baseline BP parameters and mortality. The results of this exercise were highly consistent with the abovementioned studies (Supplementary Tables S2 and S3). Yet, as mentioned, our primary objective was to assess whether long-term changes in peridialytic BP values were associated with mortality. Only one study evaluated the association between ΔPP, measured as a quarterly time-varying variable, and mortality, and found a U-shaped relationship [33], suggesting that a stable PP is associated with superior survival. To the best of our knowledge, no previous study has evaluated the long-term changes in peridialytic SBP, DBP or its derivatives (MAP, PP) in relation to mortality using the current sophisticated approach.

The second objective of our study was to assess whether a relatively stable peridialytic BP profile may contribute to the superior survival of HDF versus HD [17, 34]. Apart from the removal of larger uraemic solutes [35] and less inflammation [36], it has been suggested that haemodynamic factors might play a role in this respect. Previously we showed that peridialytic BP changes are similar in both modalities [16]. Those findings, combined with the present finding that the relationship between BP changes and mortality is similar for HD and both HDF modalities, make it unlikely that the advantageous effect of HDF on survival is due to a superior long-term peridialytic BP profile.

From the joint models in the present study, it appears that an increase in pre-SBP and/or post-DBP over time is related to a lower mortality rate, independent of comorbidity or changes in UF volume and BMI. Yet, whether these findings represent the natural slope in (surviving) ESKD patients or result from interventions in fluid management and/or medication is a matter of speculation, since reliable information on these items was absent. Since dialysis patients take two to three antihypertensive drugs on average [37], and we were unable to analyse their longitudinal changes, it is premature to formulate long-term BP change targets based on the present analysis. Nonetheless, as improvements in CVD are unlikely in this population, and the relationship between BP changes and survival was independent of UF volume, increasing BP may be explained by a reduction in antihypertensive medication and/or changes in the diet (e.g. an increase in sodium intake). Since ESKD patients often suffer from compromised

microcirculation [38] and intradialytic hypotensive periods are common [39, 40], it is conceivable that a modest BP increase has a dampening effect on ischaemic injury during treatment. Thus, if anything, a reduction in antihypertensive medication may be salutary for patients with long-term decreasing peridialytic BP. Most likely, the association between a long-term peridialytic BP decrease and mortality is caused by a further deterioration of pre-existing CV derangements and/or the cumulative effect of repetitive intradialytic hypoperfusion of vital organs [41]. Future studies could evaluate the possibility to predict mortality with peridialytic BP changes.

The present study has several limitations and strengths. First, the present analysis should be considered an observational study, thus residual confounding cannot be excluded. Second, from a methodological point of view, it is important to emphasize the limitations of the relatively new joint models, which combine LMM with time-to-event analyses. An LMM generates a linear slope (i.e. a fixed difference over a fixed period of time), which is then related to mortality. As our time-varying Cox regression models indeed showed a non-linear relationship between BP changes and mortality, the currently estimated effects of the joint models may in fact be an underestimation of the true effects at the upper and lower ends of the changes. After all, if the true hazard of a decrease in BP is actually exponential above a certain threshold, the generated linear slope has a dampening effect on the estimated HR when compared with the true hazard.

Furthermore, only peridialytic BP changes were analysed. Previous research indicated that interdialytic BP measurements may have more prognostic impact than peridialytic assessments at the dialysis unit. However, measuring interdialytic BP values requires expensive equipment that is not available for all patients. Furthermore, BP self-assessment may be challenging for elderly or frail patients. In contrast, BP measurements by the dialysis machine two to three times per week are an attractive and readily available alternative. Moreover, currently it is unclear whether changes in peridialytic BP values are just as predictive for survival as absolute interdialytic BP measurements. Finally, the lack of information on fluid status and on antihypertensive drugs is an important limitation for the appraisal of long-term BP declines. Yet correction for changes in BMI or UF volume did not alter the outcome, meaning that BP declines were independent of their bidirectional changes. Important strengths of this study are the large number of patients, the meticulous prospective data collection and the long and complete follow-up until death or the end of the study for 99.8% of all patients. The various statistical approaches increase the robustness of our findings. Lastly, as the study included patients from 88 dialysis facilities in five countries, our results appear generalizable to a large proportion of the dialysis population.

In conclusion, severe declines in pre-SBP and post-DBP in the preceding 6 months are related to increased mortality, independent of dialysis modality, UF rate and BMI. Therefore, peridialytic BP values should be interpreted in the context of their long-term changes and not just on an absolute value or on short-term monitoring.

SUPPLEMENTARY DATA

Supplementary data is available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

C.L.M.d.R.v.Z. and P.A.R. were responsible for writing the manuscript and statistical analysis. M.P.C.G., M.J.N., F.J.V.I., A.D. and B.C. were responsible for critical review of the manuscript. M.L.B., S.A.E.P., R.W.M.V., M.M., F.M. and P.J.B. were responsible for data acquisition/provision. M.J.N. and M.P.C.G. were responsible for the research idea and study design. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

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