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Kidney Int. Author manuscript; available in PMC 2014 April 01.

Published in final edited form as:

Kidney Int. 2013 October ; 84(4): 795–802. doi:10.1038/ki.2013.237.

A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival

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Abstract

It is not clear to what extent changes in blood pressure (BP) during hemodialysis affect or predict survival. Studying comparative outcomes of BP changes during hemodialysis can have major clinical implications including the impact on management strategies in hemodialysis patients. Here we undertook a retrospective cohort study of 113,255 hemodialysis patients over a 5 year period to evaluate an association between change in BP during hemodialysis and mortality. The change in BP was defined as post- minus pre-hemodialysis BP and mean of BP change values during the hemodialysis session was used as a mortality predictor. The patients averaged 61 years old and consisted of 45% women, 32% African-Americans and 58% diabetics. Over a median

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DISCLOSURE

Dr. KKZ was medical director of DaVita Harbor-UCLA Long Beach during 2007-2012. Other authors have not declared any conflict of interest.

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follow-up of 2.2 years, a total of 53,461 (47.2%) all-cause and 21,548 (25.7%) cardiovascular deaths occurred. In fully adjusted Cox regression model with restricted cubic splines, there was a U-shaped association between change systolic BP and all-cause mortality. Post-dialytic drops in systolic BP between −30 to 0 mmHg were associated with greater survival, but large decreases of systolic BP (more than −30 mmHg) and any increase in systolic BP (over 0 mmHg) were related to increased mortality. Peak survival was found at a change in systolic BP of −14 mmHg. The U-shaped association was also found for cardiovascular mortality. Thus, modest declines in BP after hemodialysis are associated with the greatest survival, whereas any rise or large decline in BP is associated with worsened survival.

INTRODUCTION

Hypertension is highly prevalent in hemodialysis (HD) patients, among whom cardiovascular disease is the leading cause of death.[1] Blood pressure (BP) is typically assessed in HD patients using one of three methods which include peridialytic, intradialytic, and interdialytic measurements. BP measured at a single point in time as well as weekly averaged BP has been used.[2,3] Although peridialytic (ie, pre-HD and post-HD) BP measurements may demonstrate greater variability[4,5] and may not consistently correlate with interdialytic ambulatory BP monitoring[6], their use is supported by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines[7] and has greater applicability to clinical practice. However, a number of large epidemiologic studies using peridialytic BP measures have shown an inverse J or U-shaped association between BP and mortality in HD patients.[8–11] At this time, the optimal metric for monitoring BP in HD patients remains unclear.

Intradialytic hypotension is a frequent complication of HD that may be associated with reduced survival,[12,13] but emerging data suggests that increases in BP during or after HD may also be associated with adverse short-term outcomes.[14–16] However, the association between BP change during HD and mortality has been insufficiently evaluated in large cohorts. Furthermore, evidence from prior studies is limited by utilization of case-control designs or regression models that assume a linear relationship between BP change and mortality.[15–20] These studies may have been underpowered in detecting a U-shaped association (ie, high mortality with both increases and decreases in BP). We hypothesized that both increases and decreases in BP during HD (defined as post-HD BP *minus* pre-HD BP) are associated with increased all-cause and cardiovascular mortality independent of pre-HD BP levels. Our hypothesis was examined within a large cohort of HD patients.

RESULTS

Patients Characteristics

We studied 113,255 HD patients who were enrolled from July 1, 2001 to June 30, 2006. The end date of follow-up was June 30, 2007. These patients contributed a total of 279,000 patient-years of at-risk time, and the median (interquartile range, IQR) follow-up was 2.2 (1.2–3.6) years. During the follow-up, a total of 53,461 (47.2%) all-cause and 21,548 (25.7%) cardiovascular deaths were reported. Crude mortality rates were 191 per 1,000

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patient-years (95% confidence interval 190 – 193) and 77 per 1,000 patient-years (95% confidence interval 76 – 78), respectively. Characteristics of the patients stratified by change (Δ) in systolic BP are shown in Table 1. The overall cohort mean (standard deviation, SD) age was 61 (15) years and median (IQR) dialysis duration was 3 (1–26) months; 45% of patients were female, 32% were African-American, and 58% had diabetes. The mean (SD) Δ systolic BP and Δ diastolic BP during the follow-up were −10 (17) mmHg and −5 (10) mmHg, respectively.

Compared to patients with Δ systolic BP of −10 to <10 mmHg, patients who experienced an increase in systolic BP greater than 10 mmHg were older and had a higher prevalence of diabetes mellitus, ischemic heart disease and congestive heart failure. Using the same reference group, patients who experienced a decrease in systolic BP of at least 30 mmHg (Δ systolic BP <−30 mmHg) were younger and had a higher prevalence of diabetes mellitus but a lower prevalence of ischemic heart disease and congestive heart failure. Pre-HD systolic BP level and ultrafiltration amount per session were negatively related to Δ systolic BP level. Among the laboratory parameters, serum creatinine, albumin, phosphorus and normalized protein nitrogen appearance showed negative relationships with Δ systolic BP level.

Association of change in BP during HD with mortality

In unadjusted models, there were U-shaped associations between Δ systolic and diastolic BP and all-cause mortality (Figure 1). Large decreases (about <−45 mmHg) and increases (about > −5 mmHg) in systolic BP during HD were associated with increased mortality. In case-mix adjusted and fully adjusted (case-mix *plus* malnutrition-inflammation cachexia syndrome adjusted) models, the U-shaped associations between Δ systolic BP (Figure 2) and Δ diastolic BP (Supplementary Figure S1) with all-cause mortality were persisted. In fully adjusted models, modest declines in Δ systolic BP between −30 – 0 mmHg were associated with better survival, while both Δ systolic BP <−30 mmHg and Δ systolic BP >0 mmHg were associated with increased mortality (right panel in Figure 2). The greatest survival was observed at Δ systolic BP of −14 mmHg [adjusted hazard ratio (aHR), 0.92; 95% confidence interval (CI), 0.91 – 0.93]. Similarly, Δ diastolic BP between −15 – 5 mmHg showed better survival and the greatest survival was observed at −6 mmHg (aHR, 0.93; 95% CI, 0.91 – 0.94]. The estimates for the BP splines and other significant covariates in the final model were presented in Supplementary Table S1. When the outcome of interest was cardiovascular mortality, similar U-shaped associations with Δ systolic BP were still observed in unadjusted and fully adjusted models (Supplementary Figure S2).

Stratified analyses by pre-HD systolic BP level, ultrafiltration percentage and time-on-HD session

In fully adjusted analyses stratified according to pre-HD systolic BP, U-shaped associations between Δ systolic BP and mortality were present in categories of pre-HD systolic BP ≥120 mmHg, but not in the category of pre-HD systolic BP <120 mmHg in which only a decrease in systolic BP was associated with higher mortality (Figure 3). Although higher ultrafiltration percentage was significantly related to a greater reduction in systolic BP (r = −0.16, p <0.01), it did not modify the association between Δ systolic BP and mortality (left

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panel of Figure 4). Time-on-HD session was not significantly different according to Δ systolic BP. Associations between Δ systolic BP and mortality were same across strata of time-on-HD session (right panel in Figure 4). In addition, the model including time-on-HD session as a continuous covariate showed the same results (data not shown).

Sensitivity analyses

Variations in Δ systolic BP within patients were examined using standard deviations. Median (IQR) of standard deviation in Δ systolic BP within patients was 17.9 mmHg (11.8 – 24.8). Adjusting for the standard deviation of Δ systolic BP did not result in an appreciable change in results (Supplementary Figure S3). The association between Δ systolic BP and mortality was further evaluated across different follow-up periods: 0 to <2 years, 2 to <4 years and ≥4 years. Numbers of patients at risk were 113,255, 60,954 and 22,880, respectively. 24,903 (22%), 18,958 (31%) and 9,600 (42%) of deaths due to any cause were reported in each follow-up period. In both the 0 to <2 years and 2 to <4 years follow-up periods, the association between Δ systolic BP with mortality was U-shaped, whereas an association in the 4 to <6 years follow-up period was not observed (Supplementary Figure S4). Additional sensitivity analyses were conducted with respect to comorbidity subgroups (diabetes, ischemic heart disease and congestive heart failure), dialysis duration, residual renal function, imputation of missing values and truncation of outliers in Δ BP were described in the Online Supplementary Material. Mortality associations of pre-HD systolic BP were additionally evaluated. Overall, the main findings did not change in the sensitivity analyses.

DISCUSSION

In this cohort of 113,255 HD patients, we observed U-shaped associations between change in BP during HD treatment and mortality independent of pre-HD BP levels. These associations were significant after adjustments for differences in patients' sociodemographics, comorbidities, and laboratory covariates. Modest declines in BP during HD treatment were associated with greater survival, whereas any rise as well as large declines in BP was associated with increased mortality.

Incremental rises in systolic and diastolic BP during HD were associated with progressively greater mortality. A paradoxical increase in systolic BP frequently occurs during or immediately after HD session (~10–15% of maintenance HD patients).[21] A recent study reported that increases in systolic BP during HD were associated with increased 2-year mortality.[16] However, in stratified analysis the association was restricted to patients with pre-HD systolic BP levels <120 mmHg. This stands in contrast to our results in which the association between increases in systolic BP and mortality was observed in patients with pre-HD systolic BP ≥120 mmHg, but not in those with pre-HD systolic BP <120 mmHg. The discrepancy may exist given that the former study used a linear regression model in which the effect of a rise in BP on mortality may be obscured by the effect of BP drops. Prior data suggests that intradialytic hypertension may be a marker of volume overload rather than a causal factor for increased mortality. In patients with dilated cardiomyopathy, ultrafiltration of excess volume during HD has been associated with improvement in cardiac

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output and increases in BP presumably due to a shift towards a more optimal portion of the Frank-Starling curve.[18,19,22] In HD patients, rise in intradialytic BP was found to be a better estimate of interdialytic BP load than pre-HD BP measurement.[20,23] Findings from a study probing dry weight in HD patient also suggested that intradialytic hypertension may be a sign of excessive extracellular fluid volume.[24] It has also been suggested that increased endothelin-1-to-nitric oxide level ratios and subsequent increased peripheral vascular resistance may be a possible cause of intradialytic hypertension.[25–28] However, further studies are warranted to determine the mechanisms underlying intradialytic hypertension.

Large decreases in systolic and diastolic BP during HD (<−30 mmHg and <−15 mmHg respectively) were associated with increased mortality, whereas more moderate reductions (Δ systolic BP of −14 mmHg and a Δ diastolic BP of −6 mmHg, respectively) were associated with the greatest survival. Intradialytic hypotension is one of the most frequent complications of HD (12.5% of HD sessions observed in the HEMO study[29]), and low intradialytic systolic BP and post-HD orthostatic hypotension were associated with greater mortality.[12] In patients without coronary lesions, HD treatment has been observed to induce segmental left ventricular dysfunction that correlates with reductions in myocardial blood flow.[30] Additionally, other studies have shown that conventional HD treatment is a significant cardiovascular stressor, and that repetitive, asymptomatic HD-associated cardiac ischemia and myocardial stunning may eventually result in irreversible damage to the heart.[13,31] Intradialytic hypotension has been implicated as a key contributor of HD-induced cardiac injury.[32] Thus, it is plausible that large decreases in BP during HD directly impact mortality via cardiovascular pathways. Strategies that promote hemodynamic stability during HD such as dietary salt restriction, extended HD schedule (ie, extended-hour HD, short daily HD and nocturnal HD) and modified HD treatment prescription (ie, using a biofeedback system or cold dialysate) should be considered in order to reduce the risk of HD-induced cardiac injury. However, it should be noted that post-HD BP is likely different from the nadir BP during the HD treatment, which is likely even lower than the former. Hence, we cannot accurately examine the so-called intra-dialytic hypotension and its effect on mortality directly although we studies post-HD BP as a conservative surrogate of intradialytic hypotension that may lead to HD-associated ischemia sequence to explain our findings.

We conducted several sensitivity analyses in order to explore mechanisms, to examine potential confounders, and to evaluate for survivor bias. First, large interdialytic weight gain, ultrafiltration amount per session, and reduction in intradialytic BP have been linked.[33] However, in sensitivity analyses, ultrafiltration volume could explain only a partial proportion of systolic BP change in our analysis. Furthermore, we did not observe effect modification by ultrafiltration volume on the association between Δ BP and mortality. This suggests that ultrafiltration volume is a determinant of BP change, but is not *per se* on the causal pathway between BP change and mortality. Second, intradialytic hemodynamic instability unresponsive to interventions may result in being unable to attend HD sessions. Abbreviated time-on-HD has been related to adverse outcomes[34] and could confound the Δ systolic BP – mortality association. However, given that mean time-on-HD session was similar across Δ systolic BP groups, the main results were not biased by time-on-HD session

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in our analyses. Third, given concern that an averaged Δ systolic BP may not capture within-person BP variation over time, the standard deviation of Δ systolic BP in each patient was explored as an index of the variation. Mortality prediction with averaged Δ systolic BP was robust even after accounting for this variation. Lastly, there was a differential association between Δ systolic BP and mortality across varying follow-up periods. The association was strongest in the 0 to <2 years follow-up period, and was attenuated but remained statistically significant in the 2 to <4 years follow-up period. In the ≥4 years follow-up period, the association disappeared. This phenomenon may be due to a survival bias, suggesting that Δ systolic BP is a more important determinant of mortality in early follow-up periods compared to later periods.

The strengths of this study include its examination of the large, nationally representative and contemporary HD cohort, use of averaged BP values from numerous repeated measures over an extended follow-up period, and detailed adjustments for covariates as potential confounders of the BP change – mortality association. However, several limitations bear mention. First, in analyses examining the association between decline in BP and mortality, it is important to note that post-HD BP may not *per se* reflect the nadir BP during HD. Moreover, post-HD BP may be modified by intradialytic interventions such as change in ultrafiltration rate and saline infusion. The lack of data on what happened between the measurement of BP prior to HD and after HD is potentially a major confounder to the results reported. Although data limitations precluded our ability to examine nadir BP, further studies examining and comparing the prognostic utility of using the nadir BP and post-HD BP are needed. Second, we had no data regarding use of antihypertensive medications, which may confound and modify the association between BP change and mortality.[35,36] Additionally, data on dialysate sodium concentration, serum to dialysate sodium gradient, dialysate temperature and ultrafitration rate or profiling during HD were not available. For these reasons, we could not explore factors associated with a decline or rise in BP during HD. Third, residual renal function at the entry could not be included in the main analyses owing to large number of missing. Residual renal function is an independent predictor of mortality,[37] and may promote intradialytic BP stability by reducing interdialytic weight gains. However, residual renal function did not influence the mortality association of BP change in the subgroup with glomerular filtration rate measured at the entry. Fourth, information regarding missed HD sessions was not available, and there may have been residual confounding on this basis.[38,39] Fifth, it should be noted that information on comorbid conditions was obtained at the time of dialysis initiation prior to entry into the cohort, and was not updated during follow-up with incident comorbidities. As shown in Table 1, it is evident that those patients with a rise in BP during HD have the greatest comorbidities and are the sickest patients. It is possible that the difference in comorbidities and health status was not adequately captured in our data. Lastly, as with all observational studies causality cannot be determined, and adjustment for confounders is limited to those that are recognized and measured.

In conclusion, there is a U-shaped association between BP change during HD and mortality. Modest declines in BP are associated with greater survival, whereas any rise as well as large declines in BP is associated with decreased survival. BP change between pre- and post-HD

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could be highlighted as a therapeutic target for further improving patients' outcomes. Whether a modest BP drop by HD can lead to better survival warrants further evaluation in randomized controlled trials.

METHODS

Study Cohort

We examined data from all patients receiving dialysis treatment from July 1, 2001 to June 30, 2006 (ie, for 20 consecutive calendar quarters) in any of the 580 facilities owned by a large dialysis care provider in the United States (DaVita Inc.). As a dialysis population is a dynamic cohort with a high turnover rate, a non-concurrent cohort was formed. Prevalent patients as of July 1, 2001 were included, as were incident patients from July 1, 2001 to June 30, 2006. The first (baseline) quarter for each patient was the calendar quarter in which the patient's dialysis duration was longer than 90 days. Patients were considered to be treated on HD if they were on the therapy at the entry into cohort. During the cohort period, 164,789 patients received dialysis, among whom 116,964 patients were treated with HD and had available BP and pertinent covariate data. Patients with outlier averaged BP values ($<0.25^{th}$ and $>99.75^{th}$ percentiles; n=1,876) and missing dates of death or censoring (n=1,833) were excluded, resulting in 113,255 HD patients in the final analysis (Supplementary Figure S5). There was no significant difference in demographics between included and excluded HD patients. Follow-up time began on the date of entry into the cohort. Patients were censored at the time of death, renal transplantation, departure from DaVita facilities, or end of the study period (June 30, 2007). The study was approved by the institutional review committees of Harbor-University of California, Los Angeles (UCLA) with exemption of the requirement for a written consent form.

Demographic characteristics and comorbidities

Information for date of the first dialysis treatment, race/ethnicity, marital status, insurance and coexisting conditions were obtained from the U.S. Renal Data System (USRDS). The following coexisting comorbidities were considered: diabetes mellitus, hypertension, ischemic heart disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, malignancy, non-ambulatory state, and current smoking. Dialysis duration was defined as the duration of time between the first day of dialysis treatment and the first day that patients entered the cohort.

Blood pressure and clinical measures

Seated pre-HD and post-HD BP values were measured during every HD sessions by means of automatically inflated cuffs using a digital monitor attached to each HD machine according to standard dialysis unit protocols, and were captured electronically within the databases. All available BP values were averaged within each of the 20 calendar quarters. For instance, if a HD patient attended 39 thrice-weekly HD sessions over 13 weeks, all 39 pre-HD systolic BP values were added and divided by 39 to obtain the average pre-HD systolic BP value for that calendar quarter of the given patient. Changes (Δ) in systolic BP and diastolic BP were defined as post-HD BP *minus* pre-HD BP. It is important to note that the mean BP change, which was used in our analyses, was the average of the changes

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recorded from the serial dialysis sessions during the entire follow-up period. Pre- and post-HD body weight were collected at each dialysis session. Body mass index was calculated as: body mass index (kg/m^2) = post-HD body weight (kg) / (height [m])^2. Ultrafiltration volume per HD session (pre-HD body weight [kg] - post-HD body weight [kg]) was standardized to the post-HD body weight by calculating the percentage of ultrafiltration to post-HD body weight.

Laboratory Measures

Most of the blood samples were drawn pre-HD with the exception of post-HD serum urea nitrogen to calculate urea kinetics. Blood samples were drawn using uniform techniques in all dialysis clinics and were transported to the Central DaVita Laboratory in Deland, Florida, USA, usually within 24 hours. All laboratory values were measured via automated and standardized methods in the DaVita Laboratory. Most laboratory values, including complete blood cell counts and serum levels of urea nitrogen, albumin, creatinine, total iron binding capacity, total calcium, and phosphorus were measured monthly. Serum ferritin level was measured quarterly. Single pool Kt/V reflecting dialysis dose and normalized protein nitrogen appearance, an estimation of daily protein intake, were measured monthly.[40]

Statistical Analyses

In order to flexibly modeling the association between BP change and mortality, we employed Cox regression models using restricted cubic splines. The primary and secondary outcomes were all-cause mortality and cardiovascular mortality. The main mortality predictors were means of Δ systolic BP and Δ diastolic BP during the follow-up period. To minimize the influence of outliers, values of Δ systolic and diastolic BP beyond the 1st ~ 99th percentiles were excluded from each analysis. To compare patients' characteristics across Δ systolic BP values, patients were divided into 4 preselected categories: <−30, −30 to <−10, −10 to <10 and ≥10 mmHg.

For each analysis, 3 levels of multivariable adjustment were examined: (1) unadjusted models that included the main predictor (Δ systolic BP or Δ diastolic BP), entry calendar quarter (quarter 1 through quarter 20) and pre-HD BP levels. Models evaluating the Δ systolic BP – mortality association adjusted for pre-HD systolic BP, and the models evaluating the Δ diastolic BP –association adjusted for both pre-HD systolic BP and pre-HD diastolic BP; (2) case-mix models that included covariates in the unadjusted model as well as age, sex, diabetes mellitus, race/ethnicity (Caucasian, African-American, Hispanic, Asian and Other), comorbidities, primary insurance (Medicare, Medicaid, Private and Other), marital status (married, divorced, single, widowed), single pool Kt/V and ultrafiltration percentage; (3) models adjusted for case-mix and malnutrition–inflammation cachexia syndrome covariates, which included all of the covariates in the case-mix model as well as the 11 following surrogates of nutritional status and/or inflammation: body mass index, blood hemoglobin, serum albumin, creatinine, total iron binding capacity, total calcium, phosphorus, ferritin, peripheral white blood cell count, percentage of lymphocytes and normalized protein nitrogen appearance.[41] For body mass index, ultrafiltration percentage and laboratory covariates, averaged values during the whole follow-up were used. The assumption of proportional hazard was assessed by log-log plots and Schoenfeld residuals.

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Stratified analyses by pre-HD systolic BP level (<120, 120 – <140, 140 – <160, and ≥160 mmHg), ultrafiltration percentage (<2, 2 – <3, 3 – <4 and ≥4%) and time-on-HD session (<180, 180 – <210, 210 – <240 and ≥240 min) were conducted to evaluate for effect modification. Sensitivity analyses were conducted with consideration of within-subject standard deviations of Δ systolic BP different follow-up periods (0 – <2, 2 – <4 and ≥4 years), HD duration at the entry, glomerular filtration rate measured at the entry, and without imputation of missing data. Pre-HD systolic BP and mortality was additionally assessed. Data for age, sex, race/ethnicity, diabetes, insurance, marital status and HD duration were missing for <1%. Data for comorbidities were missing for 5%; body mass index, for 3%; laboratory covariates, for 11–13%. We handled missing values by creating a missing indicator for categorical variables and by imputing with means or medians of existing values by Δ systolic BP categories for continuous variables. All analyses were conducted with STATA, version 12.1 (Stata Corporation, College Station, TX).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The study was supported by Dr KKZ's K24-DK091419, R01-DK078106 grants from NIH/NIDDK, and a philanthropic grant from Mr. Harold Simmons. We thank DaVita Clinical Research (DCR) for providing the clinical data for this research project.

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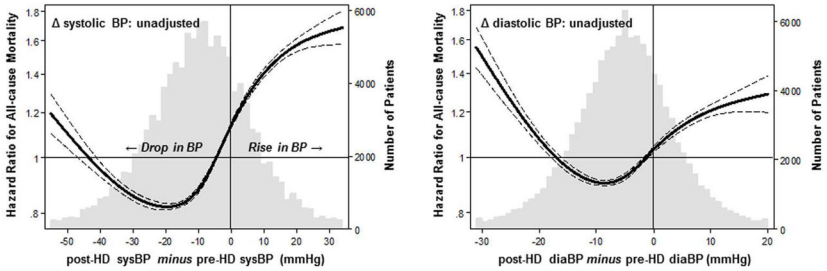

Figure 1.

Association between changes in BP during HD and all-cause mortality in 113,255 patients: *left*; systolic BP, *right*; diastolic BP

Note: The model was only adjusted for pre-HD BP value and the calendar quarter of entry. Dashed lines represent 95% confidence interval. Frequencies of observed patients are presented simultaneously. *Abbreviations*: pre-HD; pre-hemodialysis, post-HD; post-hemodialysis, sysBP; systolic blood pressure, diaBP; diastolic blood pressure.

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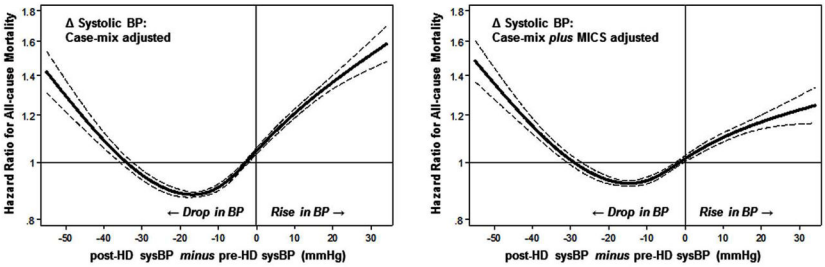

Figure 2.

Adjusted hazard ratios for all-cause mortality according to Δ systolic BP: *left*; case-mix adjusted model, r*ight*; case-mix *plus* malnutrition-inflammation cachexia syndrome adjusted model (n = 113,255)

Note: Dashed lines represent 95% confidence interval. *Abbreviations*: pre-HD; pre-hemodialysis, post-HD; post-hemodialysis, sysBP; systolic blood pressure, MICS; malnutrition-inflammation cachexia syndrome.

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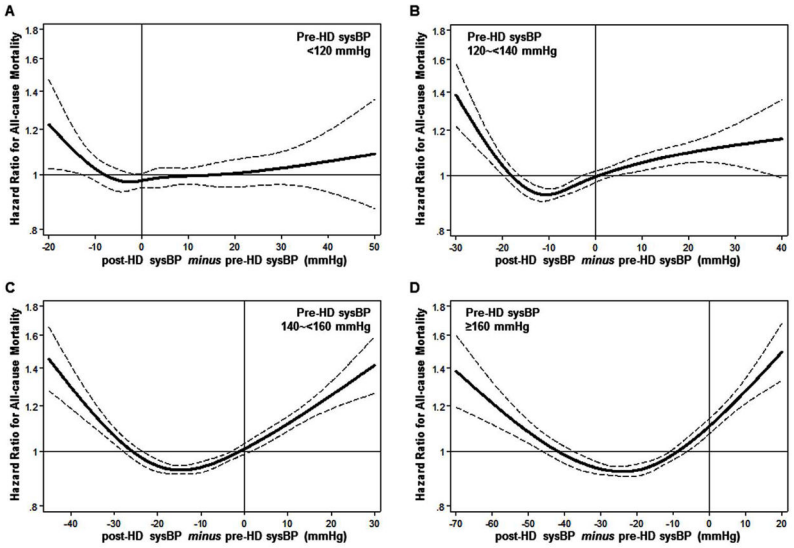

Figure 3.

Effect modification by pre-HD systolic BP level on the association between Δ systolic BP and all-cause mortality: A) pre-HD systolic BP <120 mmHg, B) 120 – <140 mmHg, C) 140 – <160 mmHg, D) ≥160 mmHg

Note: Numbers of patients were 9,053, 26,709, 42,617 and 34,876, respectively. Models were adjusted for case-mix *plus* malnutrition-inflammation cachexia syndrome covariates. Dashed lines represent 95% confidence interval. *Abbreviations*: pre-HD; pre-hemodialysis, post-HD; post-hemodialysis, sysBP; systolic blood pressure.

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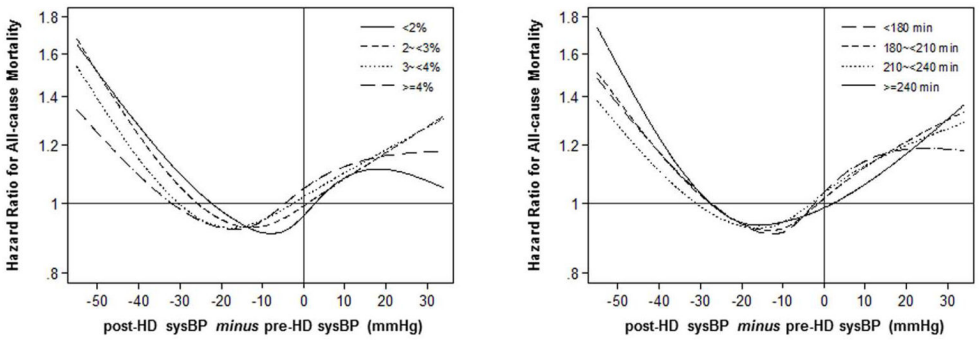

Figure 4.

Effect of ultrafiltration percentage and time-on-HD session on the association between Δ systolic BP and all-cause mortality: *left*; the model stratified by ultrafiltration percentage, *right*; the model stratified by time-on-HD session.

Note: Ultrafiltration percentage was calculated as (ultrafiltration [kg] / post-HD body weight [kg])*100, then divided into 4 categories: <2% (n = 16,330), 2 – <3% (n = 26,740), 3 – <4% (n = 34,459), and ≥4% (n = 35,726). Time-on-HD session values were divided into 4 categories: <180 min (n = 11,732), 180 – <210 min (n = 32,396), 210 – <240 min (n = 35,135) and ≥240 min (n = 20,422). The models were fully adjusted, and hazard ratios are plotted without 95% confidence interval. *Abbreviations*: pre-HD; pre-hemodialysis, post-HD; post-hemodialysis, sysBP; systolic blood pressure.

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Table 1

Characteristics of the patients stratified by Δ systolic blood pressure in 113,255 HD patients

Variables		Δ systolic BP (mmHg)				
	Total	**<−30**	**−30 ~ <−10**	**−10 ~ <10**	**≥10**	**p-value**
N (%)	113,255	11,556 (10.2)	42,166 (37.2)	47,539 (42.0)	11,994 (10.6)	
Age (years)	61 (15)	59 (14)	60 (15)	62 (16)	65 (15)	<0.001
Dialysis duration (month)†	3 (1–26)	10 (2–38)	4(2–30)	3 (1–20)	2(1–16)	<0.001
Female (%)	50,849 (44.9)	5,635 (48.8)	19,257 (45.7)	20,521 (43.2)	5,436 (45.3)	<0.001
Race/Ethnicity (%)						
Caucasian	48,715 (43.0)	4,833 (41.8)	16,933 (40.2)	21,003 (44.2)	5,946 (49.6)	<0.001
African-American	36,699 (32.4)	3,745 (32.4)	14,518 (34.4)	15,002 (31.6)	3,434 (28.6)	<0.001
Hispanic	16,368 (14.5)	1,664 (14.4)	6,314 (15.0)	6,829 (14.4)	1,561 (13.0)	<0.001
Asian	3,379 (3.0)	381 (3.3)	1,280 (3.0)	1,404 (3.0)	314 (2.6)	0.02
Co-morbidities (%)						
Diabetes	65,090 (57.5)	7,553 (65.4)	23,937 (56.8)	26,268 (55.1)	7,432 (62.0)	<0.001
Hypertension	86,131 (80.0)	8,978 (82.5)	31,837 (80.2)	35,894 (78.8)	9,422 (81.1)	<0.001
Ischemic heart disease	22,641 (21.0)	2,033 (18.7)	7,548 (19.0)	10,109 (22.2)	2,951 (25.4)	<0.001
Congestive heart failure	29,171 (27.1)	2,764 (25.4)	9,952 (25.1)	12,721 (27.9)	3,734 (32.2)	<0.001
Cerebrovascular accident	7,812 (7.3)	734 (6.8)	2,781 (7.0)	3,282 (7.2)	1,015 (8.7)	<0.001
Peripheral vascular disease	11,989 (11.1)	1,203 (11.1)	4,016 (10.1)	5,087 (11.2)	1,683 (14.5)	<0.001
Malignancy	4,894(4.5)	407 (3.7)	1,602 (4.0)	2,244 (4.9)	641 (5.5)	<0.001
Chronic obstructive pulmonary disease	6,046 (5.6)	486 (4.5)	2,055 (5.2)	2,715 (6.0)	790 (6.8)	<0.001
Inability in ambulation	3,013 (2.8)	268 (2.5)	915 (2.3)	1,369 (3.0)	461 (4.0)	<0.001
Current Smoking	5,167 (4.8)	571 (5.3)	1,957 (4.9)	2,102 (4.6)	537 (4.6)	0.02
Insurance (%)						
Medicare	72,826 (64.3)	7,579 (65.6)	26,920 (63.8)	30,332 (63.8)	7,995 (66.7)	<0.001
Medicaid	6,049 (5.3)	545 (4.7)	2,311 (5.5)	2,584 (5.4)	609 (5.1)	<0.005
Private	9,320 (8.2)	791 (6.8)	4,095 (9.7)	4,000 (8.4)	434 (3.6)	<0.001
Others	18,422 (16.3)	2,021 (17.5)	6,024 (14.3)	7,843 (16.5)	2,534 (21.1)	<0.001
Marital status (%)						
Married	45,251 (40.0)	5,081 (44.0)	16,529 (39.2)	18,463 (38.8)	5,178 (43.2)	<0.001

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Variables		Δ systolic BP (mmHg)				
	Total	<−30	−30 ~ <−10	−10 ~ <10	≥10	p-value
Divorced	7,638 (6.7)	921 (8.0)	2,853 (6.8)	3,027 (6.4)	837 (7.0)	<0.001
Single	26,495 (23.4)	2,825 (24.5)	9,952 (23.6)	11,000 (23.1)	2,718 (22.7)	0.004
Widowed	13,786 (12.2)	1,273 (11.0)	4,730 (11.2)	5,808 (12.2)	1,975 (16.5)	<0.001
BP measures (mmHg)						
Pre-HD systolic BP	149 (21)	171 (17)	155 (17)	143 (19)	136 (20)	<0.001
Post-HD systolic BP	140 (19)	130 (16)	136 (17)	141 (19)	156 (21)	<0.001
Pre-HD diastolic BP	77 (13)	86 (12)	80 (11)	75 (12)	71 (13)	<0.001
Post-HD diastolic BP	72 (11)	69 (10)	71 (10)	73 (12)	77 (13)	<0.001
Δ systolic BP	−10 (17)	−41 (11)	−18 (6)	−2 (5)	20 (10)	<0.001
Δ diastolic BP	−5 (10)	−17 (10)	−9 (7)	−2 (7)	6 (10)	<0.001
Time-on-HD session (min)	209 (35)	211 (36)	210 (34)	208 (35)	207 (36)	<0.001
Ultrafiltration (kg/session)	2.6 (1.1)	3.0 (1.2)	2.7 (1.1)	2.4 (1.1)	2.2 (1.2)	<0.001
Ultrafiltration % (%)	3.4 (1.4)	3.8 (1.4)	3.6 (1.4)	3.3 (1.4)	3.0 (1.6)	<0.001
Body mass index (kg/m^2)	26.9 (6.7)	28.3 (7.3)	27.4 (6.8)	26.4 (6.5)	26.1 (6.6)	<0.001
Laboratory measures						
Hemoglobin (g/dL)	12.0 (0.9)	12.1 (0.8)	12.1 (0.8)	12.0 (0.9)	11.8 (1.1)	<0.001
Creatinine (mg/dL)	8.1 (3.0)	8.7 (2.8)	8.6 (3.0)	7.8 (3.0)	6.8 (2.7)	<0.001
Albumin (g/dL)	3.7 (0.4)	3.8 (0.4)	3.8 (0.4)	3.7 (0.4)	3.5 (0.5)	<0.001
TIBC (mg/dL)	206 (39)	207 (37)	206 (37)	206 (40)	204 (45)	<0.001
Total calcium (mg/dL)	9.2 (0.6)	9.3 (0.6)	9.3 (0.6)	9.2 (0.6)	9.0 (0.6)	<0.001
Phosphorus (mg/dL)	5.5 (1.2)	5.8 (1.2)	5.7 (1.2)	5.4 (1.2)	5.2 (1.2)	<0.001
WBC (×10^3/mm^3)	7.41 (2.28)	7.46 (2.08)	7.34 (2.21)	7.39 (2.30)	7.72 (2.59)	<0.001
Lymphocyte (%)	20.3 (7.1)	21.0 (6.8)	21.0 (7.0)	20.0 (7.2)	18.6 (7.1)	<0.001
Ferritin (ng/mL)[†]	491 (303–707)	513 (319–723)	512 (325–718)	482 (296–701)	424 (243–658)	<0.001
Single-pool Kt/V	1.59 (0.28)	1.60 (0.26)	1.60 (0.26)	1.58 (0.29)	1.54 (0.32)	<0.001
nPNA (g/kg/day)	0.97(0.21)	1.01 (0.21)	0.99 (0.20)	0.93 (0.21)	0.90 (0.22)	<0.001

Abbreviations: BP; blood pressure, HD; hemodialysis, TIBC; total iron binding capcity, WBC; white blood cell, nPNA; normalized protein nitrogen appearance.

Note: All BP, ultrafiltration, body mass index and laboratory measures are mean values for the whole follow-up. Data are presented as percentage and mean (standard deviation).

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† Median (interquartile range) is used for dialysis duration and serum ferritin level. Dialysis duration was defined as the interval from the first dialysis to the entry into cohort. Δ BP was defined as post-HD *minus* pre-HD BP. Ultrafiltration percentage (%) was calculated as (ultrafiltration per session [kg] / post-HD body weight [kg])*100. Body mass index was calculated using post-HD body weight and height. p-values were estimated by one-way ANOVA, Kruskal-Wallis and Chi square method as appropriate. Conversion factors for units: albumin and hemoglobin in g/dL to g/L, ×10; creatinine in mg/dL to μmol/L, ×88.4; calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229. No conversion necessary for ferritin in ng/mL and μg/L, and white blood cell count in $10^3/\mu L$ and $10^9/L$.