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Original Article

Intradialytic hypotension, blood pressure changes and mortality risk in incident hemodialysis patients

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ABSTRACT

Background. Intradialytic hypotension (IDH) occurs frequently in maintenance hemodialysis (HD) patients and may be associated with higher mortality. We hypothesize that nadir intradialytic systolic blood pressure (niSBP) is inversely related to death risk while iSBP change (Δ) and IDH frequency are incrementally associated with all-cause mortality.

Methods. In a US-based cohort of 112 013 incident HD patients over a 5-year period (2007–11), using niSBP, ΔiSBP (pre-HD SBP minus niSBP) and IDH frequency (proportion of HD treatments with niSBP <90 mmHg) within the first 91 days of HD, we examined mortality-predictability at 1, 2 and 5 years using Cox models and restricted cubic splines adjusted for case-mix, comorbidities and laboratory covariates.

Results. We observed that niSBP of <90 and ≥140 mmHg had a 5-year mortality hazard ratio (HR) (95% confidence interval) of 1.57 (1.47–1.67) and 1.25 (1.18–1.33), respectively, compared with niSBP 110 to <120 mmHg. ΔiSBP of <15 and ≥50 compared with 21–30 mmHg had mortality HR of 1.31 (1.26–1.37) and 1.32 (1.24–1.39), respectively. Among patients with >40% IDH frequency, we observed a mortality HR of 1.49 (1.42–1.57) compared with 0% IDH frequency in fully adjusted models. These associations were robust at 1 and 2 years of follow-up.

Conclusion. In conclusion, we observed a U-shaped association between niSBP and ΔiSBP and mortality and a direct linear relationship between IDH frequency and mortality. Our findings lend some prognostic insight of HD blood pressure and hemodynamics, and have the potential to guide blood pressure management strategies among the HD population.

Keywords: blood pressure, hemodialysis, intradialytic hypotension, mortality, nutrition

INTRODUCTION

Intradialytic hypotension (IDH) is a well-known complication among hemodialysis (HD) patients. IDH has been associated with cardiovascular morbidity and mortality [1–3], myocardial stunning [4, 5], myocardial infarct [6], arrhythmias [6], vascular access thrombosis [7] and inadequate dialysis dose [8]. IDH has also been suggested to contribute to brain atrophy and white matter ischemia among HD patients [9–11].

In observational studies, a number of factors have been identified in association with IDH and intradialytic blood pressure (BP) variability, including ultrafiltration volume [12, 13], older age, female sex, diabetes, Hispanic ethnicity, longer dialysis vintage, increased body mass index (BMI), lower pre-HD systolic BP (SBP), increased difference in prescribed to actual post-HD weight and higher dialysate temperature [13]. However, a complete understanding of what factors may drive IDH and are involved in its mechanistic pathways has not been fully elucidated.

A consensus on definition of IDH and recommendations to guide clinicians on its management is also lacking. The

National Kidney Foundation Disease Outcomes Quality Initiative (KDOQI) defines IDH as a drop in SBP of ≥20 mmHg or mean arterial pressure of ≥10 mmHg, presence of end-organ ischemia and requirement for intervention to increase BP or improve symptoms [14]. But in a recent publication [15], the definition of IDH has come into question and was looked at more closely. Nadir-based definitions of IDH were more strongly associated with mortality rather than the change in intradialytic SBP (ΔiSBP), whereas previous studies [6, 16, 17] showed mixed associations with ΔiSBP and frequency of IDH with mortality. Intradialytic BP characteristics and changes are deserving of further research and emphasis given their importance in prognostication and implications on HD management.

In this study, we sought to evaluate a comprehensive set of dialysis-related BP variables including nadir intradialytic SBP (niSBP), ΔiSBP and frequency of IDH and their relationship to short-term and long-term mortality in a large national cohort of incident HD patients during the first patient quarter of initiating dialysis.

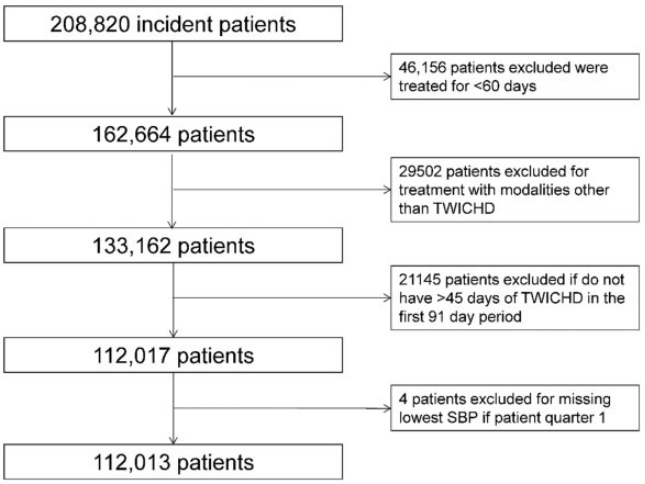

FIGURE 1: Algorithm of patient selection for cohort construction. TWICHD, thrice-weekly in-center HD.

MATERIALS AND METHODS

Study cohort

We conducted an observational study using data from a US-based large dialysis organization (LDO) with detailed pre-, post- and niSBP and nadir intradialytic diastolic BPs, pre- and post-dialysis weights; comorbidities; laboratory tests; dialysis treatment characteristics; and vital status. The original source population contained a cohort of 208 820 incident adult dialysis patients receiving care within one of the LDO's dialysis treatment facilities during a 5-year period (1 January 2007–31 December 2011). Patients were included in the study cohort if pre-, post-, niSBP and nadir intradialytic diastolic BPs were available during the first 91 days of dialysis treatment (baseline patient quarter), had at least 60 days dialysis vintage ('60-day rule' as used by the US Renal Data System) and underwent thrice-weekly in-center HD. The final study population consisted of 112 013 HD patients (Figure 1) with only four patients excluded for not having intradialytic BPs. The study was approved by the institutional review committees of the University of California Irvine and the University of Washington. Given the large sample size, anonymity of the patients studied and nonintrusive nature of the research, the requirement for written consent was waived.

Demographic characteristics and comorbidities

Information on race/ethnicity, primary insurance, dialysis access type and comorbidities were obtained from the LDO's electronic records database. In this database, race/ethnicity is self-categorized in that dialysis patients select the race and/or ethnicity with which they most closely identified according to definitions by the US Census Bureau [18]. Furthermore, presence or absence of the following preexisting comorbid conditions were obtained from International Classification of Diseases, Ninth Revision codes from the LDO's electronic records database: (i) diabetes mellitus, (ii) hypertension, (iii) congestive heart failure, (iv) atherosclerotic heart disease, (v) cerebrovascular disease, (vi) other cardiovascular disease, (vii) chronic obstructive pulmonary disease, (viii) history of cancer, (ix) HIV, (x) alcohol abuse and (xi) substance abuse.

BP and clinical measures

Seated pre-, post- and niSBP and nadir intradialytic diastolic BPs (mmHg) were measured for all patients during every dialysis session per standard dialysis unit protocols via 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 the baseline patient quarter; patients had a mean ± standard deviation (SD) and median of 31 ± 8 and 34 number of treatments during the quarter, respectively (Supplementary data, Table S1). Intradialytic changes (Δ) in SBP and diastolic BP were defined as pre-HD BP minus lowest intradialytic BP. Pre- and post-HD body weight were collected at each dialysis session. BMI was calculated as: BMI (kg/m^2) = post-HD body weight (kg)/[height (m)]^2. Ultrafiltration volume per HD session was calculated as pre-HD body weight (kg) − post-HD body weight (kg). To minimize measurement variability, all repeated laboratory and clinical measurements for each patient during the baseline patient quarter (period of first 91 days from dialysis start) were averaged.

Laboratory measures

Blood samples were drawn using uniform techniques in all dialysis clinics and were transported to the LDO's central laboratory in Deland, FL, USA, usually within 24 h. All laboratory values were measured via automated and standardized methods in the LDO's central laboratory. Most laboratory parameters were measured monthly, including urea nitrogen, albumin, creatinine, total iron binding capacity, bicarbonate, phosphorus and calcium. Serum ferritin was measured at least quarterly. Hemoglobin was measured at least monthly in all patients and weekly to biweekly in most patients. *Kt/V* was used to estimate dialysis dosage, and normalized protein catabolic rate (nPCR)

was measured monthly as an indicator of daily protein intake. Most blood samples were collected before dialysis, except for post-dialysis serum urea nitrogen to calculate urea kinetics.

Exposure and outcome definition

Initial quartile mean niSBP, mean ΔiSBP and frequency of IDH were the primary exposures of interest. niSBP was divided into seven exposure categories <90, 90 to <100, 100 to <110, 110 to <120 (reference), 120 to <130, 130 to <140 and ≥140 mmHg. We defined ΔiSBP as pre-HD SBP minus niSBP. ΔiSBP was divided into six categories: ≤15, 16–20, 21–30 (reference), 31–40, 41–50 and ≥51 mmHg. The relative frequency of IDH was defined as the proportion of HD treatments where the patient's niSBP was <90 mmHg. Proportion of IDH was divided into six categories for analysis: 0 (reference), >0–5%, >5–10%, >10–20%, >20–40% and >40%. All categories were chosen based on clinically relevant cut-offs with at least 5% of cohort population. Referent groups were also chosen with clinically relevant cut-off BPs.

Associations of iSBP exposure measurements with all-cause mortality within 1, 2 and 5 years of dialysis initiation were examined. Patients were followed from the date of dialysis initiation until death, renal transplantation, departure from the LDO's facilities or at the end of the study period (31 December 2011), whichever occurred first.

Statistical analyses

To compare patients' characteristics across ΔiSBP values, descriptive data were summarized using proportions, mean (±SD) and medians (IQR) as appropriate, and were compared using parametric and non-parametric tests for trend. In order to flexibly model associations of intradialytic BP indices with mortality outcomes, we employed Cox regression models using restricted cubic splines with four knots (5th, 35th, 65th and 95th percentiles) and reference at median exposure value. Cox proportional hazards regression models using categorical exposures were additionally estimated.

For each exposure, we conducted three levels of hierarchical multivariable adjustment: (i) unadjusted that included the main predictor; (ii) case-mix adjusted that additionally adjusted for age, sex, diabetes, race/ethnicity (Caucasian, African-American, Hispanic, Asian and Other), primary insurance (Medicare, Medicaid and Other), vascular access [catheter, arteriovenous (AV) graft, AV fistula, AV other, unknown], dialysis adequacy (spKt/V), dialysis run-time, BMI, ultrafiltration volume per dialysis session, mean pre-HD diastolic BP and mean pre-HD SBP, and the following 12 comorbidities: hypertension, atherosclerotic heart disease, congestive heart failure, cerebrovascular disease, other cardiovascular disease, dyslipidemia, chronic obstructive pulmonary disease, liver disease, history of cancer, HIV, substance and alcohol abuse; and (iii) case-mix and malnutrition and inflammatory complex syndrome (MICS) that additionally adjusted for serum albumin, creatinine, bicarbonate, hemoglobin, white blood cell (WBC) count, calcium, phosphorus, ferritin, total iron binding capacity, nPCR, alkaline phosphatase, percent iron saturation and mean pre-dialysis weight.

In order to assess for potential effect modification, associations of each exposure with 5-year mortality outcomes in fully adjusted models were examined across *a priori* selected subgroups. Missing covariate data were <2% for laboratory and demographic variables, and complete case analyses methods were used for all analyses. In sensitivity analysis, associations were examined using imputation by means or medians or creation of a missing category for missing data. The assumption of proportional hazards was assessed by log–log plots and Schoenfeld residuals. Analysis and figure construction were performed with Stata version 13.1 (Stata Corporation, College Station, TX, USA).

RESULTS

Study population description

Our analytical cohort included 112 013 incident HD patients who initiated dialysis from 1 January 2007 to 31 December 2011; where 112 003 patients met definition criteria for ΔiSBP and proportion of IDH. Patients' mean ± SD age was 63 ± 15 years old with 43% female, 31% African-Americans and 58% diabetics. Patients had a median (IQR) follow-up time of 493 (231,921) days. Baseline patient characteristics stratified by ΔiSBP values are shown in Table 1. There were a total of 29 245 deaths (26%) over the observation period (154 deaths per 1000 patient-years).

Patients with larger ΔiSBP values tended to be younger, female, diabetic, Hispanic and had a lower prevalence of atherosclerotic disease, other cardiovascular disease and hypertension, but a higher prevalence of congestive heart failure. These patients additionally had larger accompanying changes in intradialytic diastolic BPs, pre- and post-SBP and diastolic BPs, pre- and post-weight, BMI and larger ultrafiltration volumes per session. Additionally, patients in groups with larger mean ΔiSBP had lower mean niSBP. Among the laboratory parameters, patients with larger ΔiSBP values had higher levels of serum phosphorus, parathyroid hormone, hemoglobin, nPCR, percent iron saturation and lower bicarbonate levels.

Baseline patient characteristics stratified by niSBP and proportion of IDH event categories are provided in Supplementary data, Table S1 and S2. Patients with a lower niSBP or a higher proportion of IDH events similarly were more likely to be older, male, non-Hispanic white, non-diabetic patients with a higher dialysis dose, lower pre- and post-HD body weight and lower pre- and post-HD BPs. Notably, patients in groups with lower niSBP have lower mean pre-HD and post-HD SBPs.

Association of nadir intradialytic BP with mortality

In unadjusted models, compared with patients with niSBP of 110 to <120 mmHg, patients with a baseline mean niSBP <90 mmHg had 5-year mortality hazard ratio (HR) [95% confidence interval (CI)] of 3.14 (2.98–3.31), while patients with a mean niSBP >120 mmHg demonstrated a survival benefit (Figure 2 and Supplementary data, Table S3). However, after adjustment for case-mix covariates, niSBP exhibited a U-shaped association with 5-year all-cause mortality where patients with both higher (>140 mmHg) and lower (<90 mmHg) niSBP had mortality HRs of 1.43 (1.35–1.52) and 1.73 (1.63–1.84), respectively, compared with the reference. This U-shaped association

Table 1. Characteristics of the patients stratified by ΔiSBP in 112 003 HD patients

	ΔiSBP (mmHg)							
	Total	≤15	16–20	21–30	31–40	41–50	≥51	P-value
n (%)	112 003	9803 (9)	14 792 (13)	37 668 (34)	28 063 (25)	14 428 (13)	7249 (6)	
Age (years)	63 ± 15	63 ± 16	62 ± 16	63 ± 16	63 ± 14	63 ± 14	61 ± 13	<0.001
Female (%)	43	33	36	41	47	51	56	<0.001
Diabetes (%)	58	53	51	54	61	67	71	<0.001
Race (%)								
Caucasian	47	48	48	48	47	44	42	<0.001
African-American	31	30	31	32	32	31	27	0.009
Hispanics	15	15	14	13	14	17	22	<0.001
Asians	3	3	3	3	3	4	4	<0.001
Others	4	3	3	3	4	4	5	<0.001
Insurance (%)								
Medicare	54	53	52	53	54	54	54	<0.001
Medicaid	7	8	7	7	7	7	7	0.285
Others	40	39	41	40	39	39	39	0.001
Access type (%)								
CVC ΔiSBP	74	75	75	74	74	74	73	<0.001
AV fistula	15	13	14	16	16	15	13	0.104
AV graft	4	3	4	4	4	4	4	<0.001
AV other	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.223
Unknown	7	9	7	6	6	7	9	0.067
sp*Kt*/*V*	1.47 ± 0.33	1.41 ± 0.32	1.44 ± 0.32	1.46 ± 0.33	1.48 ± 0.32	1.49 ± 0.32	1.51 ± 0.32	<0.001
URR	68 ± 7	68 ± 7	68 ± 7	68 ± 7	69 ± 7	69 ± 7	69 ± 7	<0.001
KRU	3.3 (1.7, 5.5)	2.9 (1.4, 5.1)	3.2 (1.6, 5.4)	3.3 (1.7, 5.5)	3.4 (1.7, 5.6)	3.4 (1.8, 5.6)	3.2 (1.7, 5.2)	<0.001
Comorbidities (%)								
Atherosclerotic heart disease	14	15	15	14	14	14	13	<0.001
Congestive heart failure	36	37	36	36	37	38	38	0.006
Other cardiovascular disease	15	16	16	15	15	15	14	<0.001
Cerebrovascular accident	2	2	2	2	2	2	2	0.001
Hypertension	51	48	52	52	52	49	47	<0.001
Chronic obstructive pulmonary disease	5	5	5	5	5	5	5	<0.001
Cancer	2	2	3	3	2	2	2	<0.001
HIV	0.5	0.7	0.6	0.6	0.4	0.3	0.2	<0.001
Dyslipidemia	25	23	24	25	25	26	25	0.801
Liver disease	1	2	2	2	1	1	1	<0.001
Alcohol	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.028
Substance abuse	0.2	0.3	0.2	0.3	0.2	0.2	0.2	0.004
Mean pre-weight (kg)	82 ± 23	78 ± 19	80 ± 21	82 ± 22	84 ± 24	84 ± 24	82 ± 24	<0.001
Mean post-weight (kg)	80 ± 22	76 ± 19	78 ± 20	80 ± 22	82 ± 24	82 ± 24	80 ± 23	<0.001
Ultrafiltration (kg/session)	2.0 ± 0.9	2.0 ± 0.9	2.0 ± 0.9	2.0 ± 0.9	2.0 ± 0.9	2.1 ± 0.9	2.2 ± 0.9	<0.001
Body mass index (kg/m^2)	28 ± 7	26 ± 6	27 ± 7	28 ± 7	29 ± 8	29 ± 8	29 ± 8	<0.001

BP measures (mmHg)								
Systolic								
Pre-HD SBP	147 ± 19	129 ± 18	135 ± 17	143 ± 16	152 ± 15	161 ± 15	171 ± 15	<0.001
niSBP	116 ± 16	117 ± 18	117 ± 17	118 ± 16	117 ± 15	115 ± 14	110 ± 13	<0.001
ΔiSBP	30 ± 12	12 ± 3	18 ± 1	25 ± 3	35 ± 3	44 ± 3	57 ± 6	<0.001
IDH events	1 (0, 4)	0 (0, 2)	1 (0, 3)	1 (0, 3)	2 (0, 4)	2 (1, 5)	3 (1, 7)	<0.001
Proportion of IDH (%)	4 (0, 13)	0 (0, 3)	3 (0, 9)	3 (0, 10)	5 (0, 13)	8 (3, 17)	11 (3, 25)	<0.001
Post-HD SBP	144 ± 18	140 ± 22	141 ± 20	143 ± 18	146 ± 17	147 ± 16	147 ± 16	<0.001
Diastolic								
Pre-HD diastolic BP	77 ± 12	71 ± 12	73 ± 12	76 ± 12	79 ± 11	82 ± 11	86 ± 12	<0.001
Nadir intradialytic diastolic BP	66 ± 11	66 ± 12	67 ± 11	67 ± 11	66 ± 10	64 ± 10	62 ± 9	<0.001
Intradialytic Δ diastolic BP	11 ± 7	5 ± 3	7 ± 3	9 ± 4	13 ± 5	17 ± 6	24 ± 8	<0.001
Post-HD diastolic BP	76 ± 11	75 ± 13	75 ± 12	76 ± 11	76 ± 11	76 ± 10	76 ± 10	<0.001
Time-on-HD session (min)	211 ± 24	210 ± 24	211 ± 23	211 ± 23	212 ± 24	212 ± 24	211 ± 24	<0.001
Serum laboratory values								
Albumin (g/dL)	3.5 ± 0.5	3.4 ± 0.5	3.5 ± 0.5	3.5 ± 0.5	3.5 ± 0.5	3.5 ± 0.5	3.5 ± 0.5	<0.001
Calcium (mg/dL)	9.0 ± 0.6	9.0 ± 0.6	9.1 ± 0.6	9.1 ± 0.6	9.1 ± 0.6	9.1 ± 0.6	9.1 ± 0.6	<0.001
Phosphorus (mg/dL)	5.0 ± 1.2	4.7 ± 1.1	4.8 ± 1.2	4.9 ± 1.1	5.0 ± 1.1	5.1 ± 1.2	5.2 ± 1.2	<0.001
Ferritin (ng/mL)	283 (164, 486)	282 (163, 504)	286 (161, 505)	287 (166, 495)	279 (163, 473)	281 (166, 469)	281 (164, 474)	<0.001
iPTH (pg/mL)	313 (197, 486)	273 (169, 429)	291 (180, 455)	309 (193, 482)	325 (206, 501)	337 (218, 515)	342 (220, 517)	<0.001
Hemoglobin (g/dL)	11.1 ± 1.2	10.8 ± 1.2	11.0 ± 1.2	11.1 ± 1.2	11.2 ± 1.2	11.3 ± 1.1	11.4 ± 1.1	<0.001
WBC ($\times 10^3/mm^3$)	7.8 ± 2.7	7.5 ± 2.8	7.7 ± 2.9	7.8 ± 2.8	7.9 ± 2.6	8.0 ± 2.4	8.0 ± 2.3	<0.001
Alkaline phosphatase (IU/L)	87 (69, 115)	95 (72, 136)	87 (68, 119)	85 (67, 112)	86 (69, 111)	88 (71, 114)	92 (73, 118)	<0.001
Bicarbonate (meq/L)	24 ± 3	24 ± 3	24 ± 3	24 ± 3	24 ± 3	23 ± 3	23 ± 3	<0.001
Creatinine (g/dL)	5.9 ± 2.4	5.5 ± 2.5	5.9 ± 2.5	6.0 ± 2.4	5.9 ± 2.3	5.8 ± 2.2	5.8 ± 2.0	<0.001
TIBC (mg/dL)	225 ± 49	221 ± 54	223 ± 52	224 ± 50	227 ± 47	226 ± 46	227 ± 45	<0.001
Iron saturation (%)	23 ± 9	22 ± 10	23 ± 10	23 ± 9	23 ± 9	23 ± 8	24 ± 8	<0.001
nPCR (g/kg/day)	0.77 (0.64, 0.92)	0.72 (0.59, 0.87)	0.75 (0.62, 0.90)	0.76 (0.63, 0.91)	0.78 (0.65, 0.93)	0.79 (0.67, 0.94)	0.80 (0.67, 0.95)	0.890

CVC, central venous catheter; spKTV, single pool KTV; URR, urea reduction ratio; KRU, residual renal function; iPTH, intact parathyroid hormone; TIBC, total iron binding capacity. Δ BP was defined as nadir intradialytic BP minus pre-HD BP. Body mass index was calculated using post-HD body weight and height. P-values were estimated by parametric and non-parametric tests for trend as appropriate. Data presented as proportions, mean ±SD, or median (IQR) where applicable.

persisted after further adjustment for markers of malnutrition and inflammation, as well as in fully adjusted models for 1-year and 2-year mortality outcomes (Figure 2C). Similar results were seen in models using restricted cubic splines (Figure 2A) as well as across subgroup strata (Figure 3), including substrata of cardiovascular comorbidities (Supplementary data, Figure S1). Older patients (≥65 years) with a niSBP <90 mmHg had a mortality HR of 1.94 (1.72–2.18) while younger patients (<65 years) had an HR of 1.42 (1.31–1.54) (P-for-interaction <0.001). In addition, associations of niSBP <90 mmHg with 5-year mortality compared with the referent were incrementally stronger across strata of dialysis treatment time.

Association of change in intradialytic BP with mortality

In the total cohort, patients on average had a baseline mean drop or change in SBP of 30 ± 12 mmHg from their pre-HD SBP measurement to their nadir or lower iSBP. Using a reference group of ΔiSBP 20 to ≤30 mmHg, in unadjusted models patients with <15 mmHg iSBP drop had 5-year all-cause mortality HR of 1.60 (1.54–1.66) (Figure 4 and Supplementary data, Table S4). However, after adjustment with case-mix covariates, including pre-dialysis BPs, associations of ΔiSBP with 5-year all-cause mortality were U-shaped. Compared with the referent, patients with <15 mmHg drop had an HR of 1.31 (1.26–1.37) and patients with ≥50 mmHg drop had an HR of 1.32 (1.24–1.39). With additional adjustment for MICS covariates, associations were only slightly attenuated. Similar results were seen in models using restricted cubic splines (Figure 4A), 1-year and 2-year mortality outcomes (Figure 4C) and across most subgroup strata (Figure 5). However, there was significant effect modification by pre-HD SBP (P-for-interaction = 0.0012), whereas patients with pre-HD SBP >160 mmHg exhibited no difference in mortality risk according to ΔiSBP.

Association of proportion of intradialytic hypotensive events with mortality

In our cohort 65% ($n = 72\,983$) of HD patients had at least one hypotensive event during their first 91 days of HD. The median (IQR) number of hypotensive events during the baseline patient quarter was 1 (0, 4), while the median (IQR) proportion of IDH events (frequency of events divided by the total number of dialysis treatments per baseline patient quarter) was 4% (0–13%). Using patients with no IDH event in the baseline quarter (0%) as reference, there was an incremental association between a higher proportion of IDH with mortality outcomes (Figure 6 and Supplementary data, Table S5). In unadjusted models, patients who had a hypotensive event in >40% of dialysis treatments during the baseline quarter had a 5-year mortality HR of

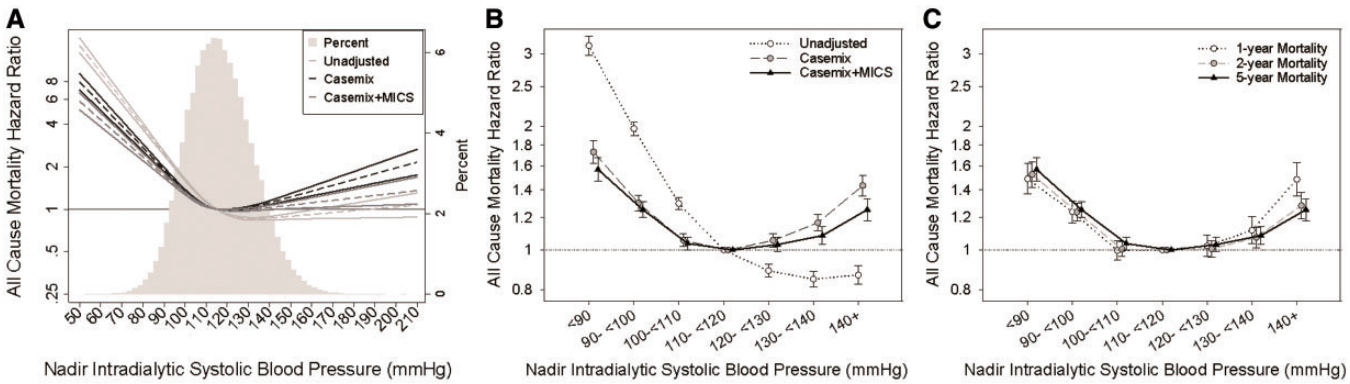

FIGURE 2: Association of niSBP with all-cause mortality. (**A**) Restricted cubic splines showing 5-year mortality for unadjusted, case-mix and case-mix + MICS adjustments. (**B**) Five-year mortality for unadjusted, case-mix and case-mix + MICS. (**C**) One-, 2- and 5-year mortality for case-mix + MICS. In splines, dashed lines represent HR and solid lines and error bars represent 95% CI.

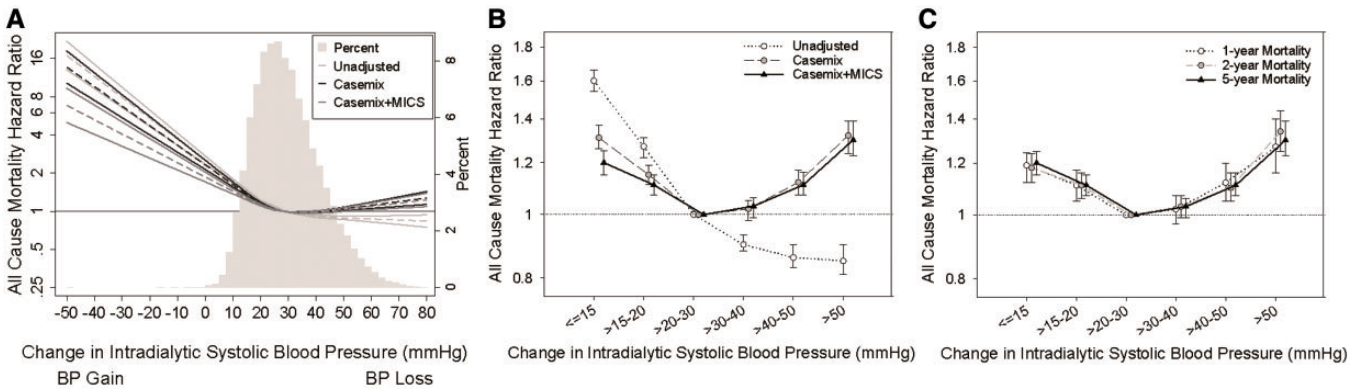

FIGURE 3: Association of ΔiSBP with all-cause mortality. (A) Restricted cubic splines showing 5-year mortality for unadjusted, case-mix, and case-mix+MICS adjustments. (B) Five-year mortality for unadjusted, case-mix and case-mix+MICS. (C) One-, 2- and 5-year mortality for case-mix+MICS. In splines, dashed lines represent HR and solid lines and error bars represent 95% CI.

3.11(2.98–3.25). After adjustment for case-mix covariates including pre-dialysis BPs, associations were modestly attenuated, but maintained the incremental shape, as observed in both categorical analysis and restricted cubic spline models. In case-mix adjusted models, compared with the referent, patients with >40% proportion of IDH had an HR of 1.65 (1.57–1.73) higher mortality risk. After further adjustment with MICS covariates in the fully adjusted model, this association was slightly attenuated with an HR of 1.49 (1.42–1.57). Patients with 20 to <40% and 10 to <20% proportion of IDH had an HR of 1.14 (1.09–1.19) and 1.05 (1.01–1.10), respectively. Proportion of IDH associations with 1- and 2-year mortality (Figure 6C) and across subgroup strata for 5-year outcomes showed similar results (Figure 7). Older patients with a proportion of IDH >40% had an HR of 1.80 (1.64–1.98) compared with referent, while younger patients had an HR of 1.38 (1.29–1.47) (P-for-interaction <0.001).

For all exposure associations, multivariable adjusted models using imputed covariate data compared with complete case methods provided similar results (Supplementary data, Table S6).

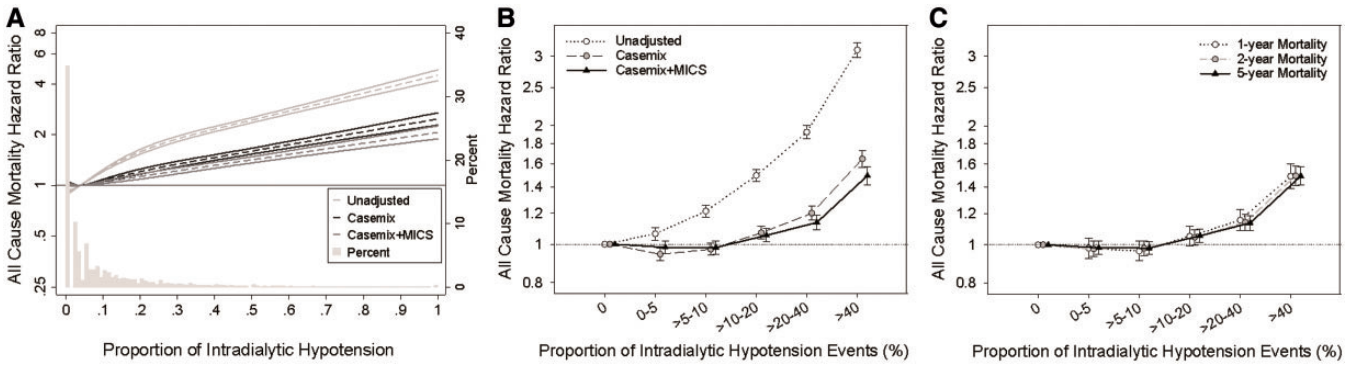

FIGURE 4: Association of proportion of intradialytic hypotension with all-cause mortality. (**A**) Restricted cubic splines showing 5-year mortality for unadjusted, case-mix and case-mix + MICS adjustments. (**B**) Five-year mortality for unadjusted, case-mix and case-mix + MICS. (**C**) One-, 2- and 5-year mortality for case-mix + MICS. In splines, dashed lines represent HR and solid lines and error bars represent 95% CI.

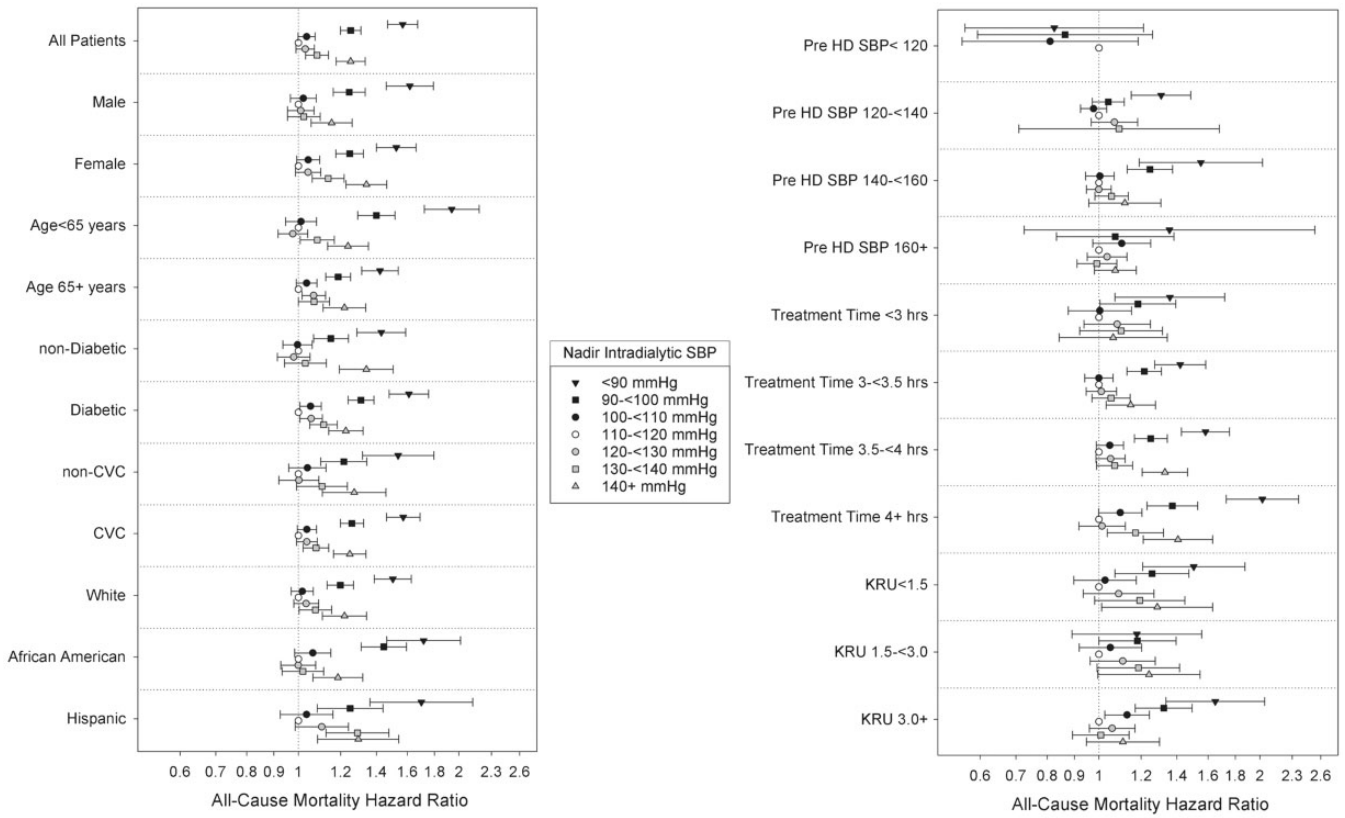

FIGURE 5: Association of nadir intradialytic systolic blood pressure and 5-year all-cause mortality indicated by HR with 95% CI for various stratifications and adjusted for case-mix + MICs covariates. Abbreviations: CVC, central venous catheter; HD, hemodialysis; SBP, systolic blood pressure; KRU, residual urea clearance (mL/min).

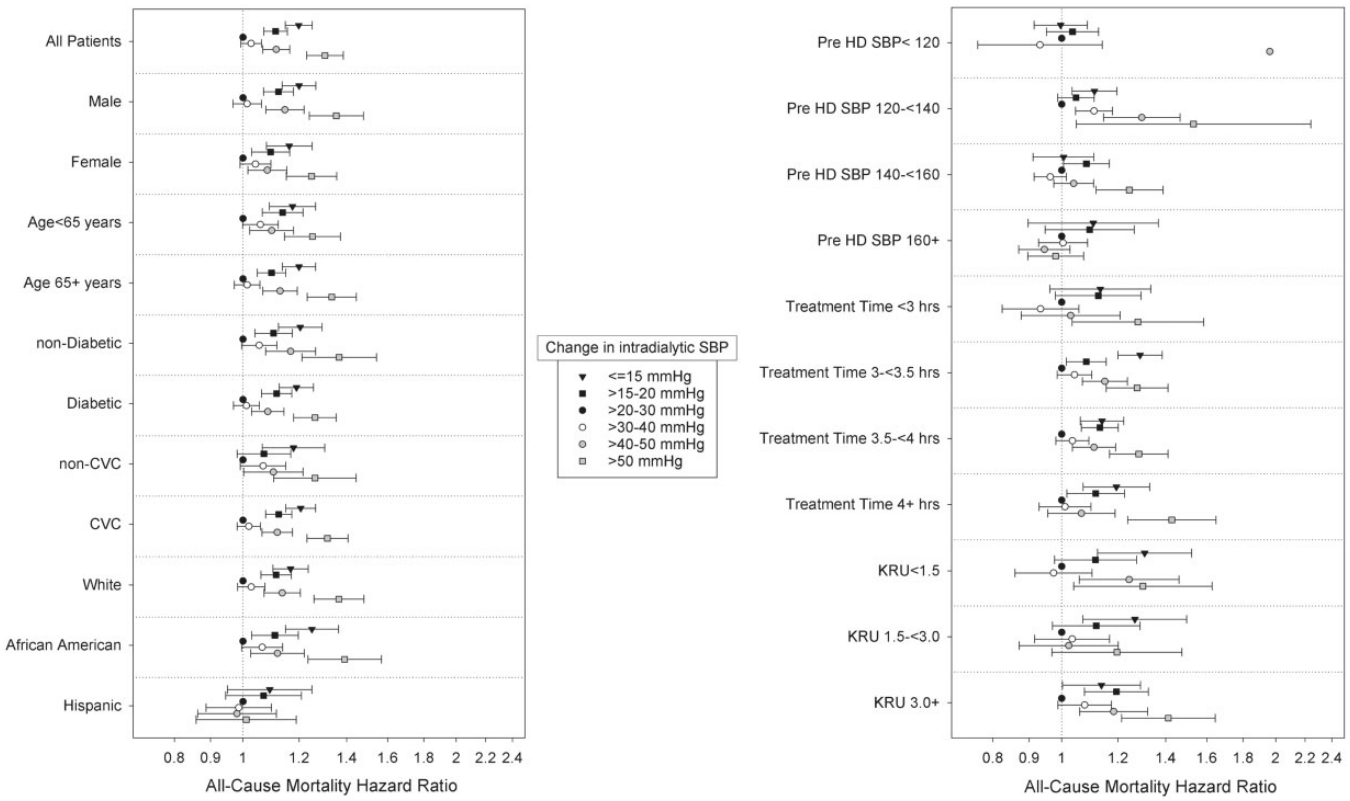

FIGURE 6: Association of ΔiSBP and 5-year all-cause mortality indicated by HR with 95% CI for various stratifications and adjusted for case-mix+MICs covariates. Abbreviations: CVC,central venous catheter, HD, hemodialysis, SBP, systolic blood pressure, KRU, residual urea clearance (mL/min).

DISCUSSION

IDH is a frequent complication of HD that results from patients' inability to tolerate ultrafiltration with dialysis treatments typically from an imbalance of intravascular volume removal and the inadequacy of hemodynamic compensatory mechanisms such as vascular shunting to the central circulation, increased vascular resistance in the splanchnic and cutaneous beds, increasing arterial tone and increasing cardiac output [19, 20].

Variable IDH definitions used for prognostication have led to some discrepancies in outcome associations [15]. In our study, we used a comprehensive set of dialysis-related BP variables that included niSBP, ΔiSBP and nadir-based definition of IDH frequency to evaluate their associations with all-cause mortality. In our analysis of 112 013 incident HD patients, we observed niSBP and ΔiSBP to have a U-shaped associations with short- and long-term mortality, whereas the frequency of IDH had a direct linear association. Additionally, patients with lower niSBP tended to have lower pre- and post-HD SBPs, while patients with larger ΔiSBPs tended to have lower niSBP during dialysis.

niSBP <90 mmHg has shown to hold the most consistent association with mortality and now niSBP <100 mmHg seems to show increasing mortality risk in our own study and another recent study [15]. These two niSBP 'cut-offs' may prove useful for defining IDH and providing clinicians with an intervention point for preventing adverse outcomes. Given that niSBP <90 mmHg carries the greatest risk, it may be most prudent for clinicians to target interventions prior to this occurrence. In our study of incident HD patients, we found niSBP of 90 to <100 mmHg had a 25% higher mortality risk at 5-year outcomes when fully adjusted. In Flythe *et al.*'s study of a prevalent LDO cohort of 10 392 patients, niSBP <100 mmHg similarly showed 13% increase in adjusted risk with the authors noting their associations were most robust when pre-HD SBP was ≥160 mmHg [15]. Given these recent associations in large population cohorts, an niSBP of <100 mmHg may be an intervention point for clinicians to consider in the future for asymptomatic HD patients.

Another sign heralding need for intervention may be drops in ΔiSBP. In our study, large drops in ΔiSBP such as ≥50 mmHg were associated with a 30% higher mortality risk where the mortality risk starts to rise at ≥40 mmHg. In previous studies, drops in ΔiSBP associations with mortality do vary. Flythe *et al.* showed larger drops of ≥30 mmHg were only found to be associated with mortality in combination with niSBP <90 mmHg in both the Hemodialysis (HEMO) Study cohort and their LDO cohorts [15], whereas Shoji *et al.* found ΔiSBP drops of ≥40 mmHg were associated with higher mortality risk [16]. Although there is not a definitive cut-off for

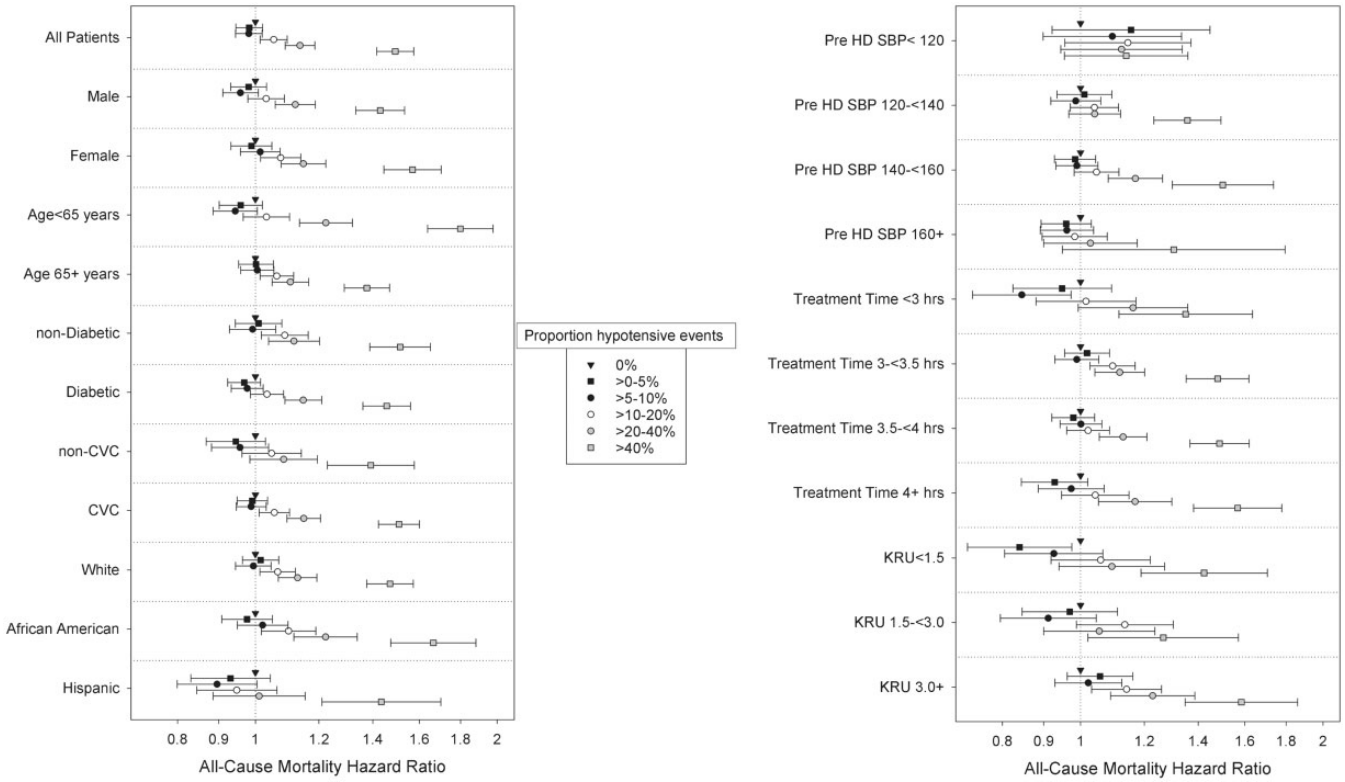

FIGURE 7: Association of proportion of IDH and 5-year all-cause mortality indicated by HR with 95% CI for various stratifications and adjusted for case-mix + MICs covariates. Abbreviations: CVC,central venous catheter; HD, hemodialysis; SBP, systolic blood pressure; KRU, residual urea clearance (mL/min).

ΔiSBP drops, in our study, ΔiSBP drops of ≥40–50 mmHg may be potential points of intervention to consider.

These potential cut-off BPs for IDH would not only allow us to better define IDH and when interventions are most prudent, but they will also allow us to study our armament of interventions. Currently our interventions to IDH are reactive, relying upon rapid nursing assessment and intervention. Typical reactive interventions include: repositioning patient to optimize hemoperfusion of vital organs (supine or Trendelenburg position); cessation of ultrafiltration; fluid resuscitation via isotonic saline, hypertonic saline or glucose; and in some centers albumin and cessation of dialysis [13, 21]. Although these interventions are necessary and beneficial, they may not prevent the adverse consequences of IDH events.

As such, preventative strategies for at-risk patients have been developed. One example includes the KDOQI guidelines for factors related to IDH treatment divided into patient and dialysis-related factors. Patient-related factors include maintenance of accurate dry weights, minimizing interdialytic weight gain, discontinuation of pre-HD antihypertensive medications, avoiding long-acting vasodilators, avoidance of eating before or during dialysis treatments and secondary work-up for cardiac etiologies of hypotension. The dialysis-related factors include avoidance of aggressive ultrafiltration and/or ultrafiltration rate with the possible use of isolated ultrafiltration prior to ultrafiltration with dialysis, ultrafiltration modeling and sodium modeling to achieve patient dry weights [22].

But evidence-based dialysis preventative interventions are somewhat limited. Increasing dialysis time or frequency can be employed for decreasing ultrafiltration rate with more gradual ultrafiltration but relies on patient compliance with treatments [23]. Dialysate temperature cooling has the best supportive evidence for decreasing the frequency and intensity of IDH [24–27] but is reliant upon patient tolerance. Other dialysis-related strategies include isothermic dialysis, dialysate calcium modeling and dialysate sodium modeling [28–30]. Pharmacological interventions are also few, including midodrine [31], L-carnitine [32–34] and sertraline [35], and are often limited by side-effect profiles. Biofeedback blood volume monitoring has also had a favorable impact on IDH prevention [36]. However, despite having these prevention strategies, we possess few randomized clinical studies and robust objective assessments of intravascular volume and IDH with long-term clinical outcomes, including which interventions are most beneficial and cost-effective.

The current preventative and reactive interventions are helpful but patients are still incurring the associated risk of having the IDH event. In our study, the proportion or frequency of IDH was incrementally associated with higher mortality with as little as 20% frequency and with the strongest effect for patients with >40% frequency of IDH. Similarly, in other recent studies, Flythe *et al.*'s analysis of the HEMO cohort ($n = 1409$) and Tisler *et al.*'s Hungarian cohort ($n = 263$) showed greater mortality in patients with higher IDH frequency [15, 17]. As such, reversing IDH events may in itself not be enough to reduce the

associated mortality risk, and improved prevention may likely be the driving factor to improving outcomes. In future IDH studies, we will need to discover the association of various possible mechanistic factors with IDH and its adverse outcomes as this may lead to further possible avenues of IDH prevention and understanding the hemodynamic mechanism of intradialytic BP and volume variability.

New areas of niSBP to further explore include patients with small drops in ΔiSBP or high niSBP. In our study, these patient groups did have higher mortality where ΔiSBP drops $\leq$15 and niSBP $\geq$140 mmHg had 20% and 25% higher 5-year mortality risk, respectively, when fully adjusted. Associations were also similar for short-term outcomes of 1 and 2 years. No previous studies to our knowledge have demonstrated these finding with intradialytic BPs. This may represent the subset of HD patients who are unable to mount a BP response to ultrafiltration, but the etiology of these observations are unclear and need further study.

In our study, we also aimed to investigate which iSBP characteristics may be most beneficial for HD patients. In our cohort, the ideal niSBP seemed to range from 100 to $<$130 mmHg and ΔiSBP drop was from 20 to $<$40 mmHg where these iSBP groups demonstrated minimal associated short-term and/or long-term increased mortality risk. Stratification by dialysis treatment time did not alter the ideal niSBP and drop in ΔiSBP groups. Pre-HD SBP stratification and urine urea clearance as surrogates for residual kidney function both showed similar associations as well, with the exception of patients with pre-HD SBP of $>$160 mmHg who exhibited no difference in risk association according to ΔiSBP. Although the concept of ideal niSBP and ΔiSBP drop needs further investigation, this may allude to using niSBP and drops in iSBP parameters themselves to guide dialysis treatment regimens.

The strengths of this study include: the use of a large, nationally representative and contemporary HD cohort; extended follow-up period of up to 5 years; robust serial measurements of intradialytic BP; and detailed capturing of comorbidity and laboratory data. Important limitations include lack of data related to any intervention, symptoms and BP-altering medications that may confound and modify our associations. Additionally, data on dialysis treatment regimens (dialysate Na/K bath or temperature) were not available. Although we rigorously adjusted for clinically relevant covariates including several established risk factors such as pre-HD BP, we cannot deny the possibility of residual confounding and/or the presence of unmeasured confounders.

In conclusion, the niSBP and ΔiSBP exhibit a U-shaped relationship with mortality, and frequency of IDH has a positive incremental association with mortality. Seeking to identify the optimal intradialytic BPs, niSBP and ΔiSBP are important in driving targeted interventions that clinicians may be able to implement to improve IDH outcomes. Further studies will be necessary to identify any modifiable risk factors for IDH and its associated outcomes and to further understand the role of intradialytic BP non-responsive to dialysis and ultrafiltration.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

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