Association of Mortality Risk with Various Definitions of Intradialytic Hypotension

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ABSTRACT

Intradialytic hypotension is a serious and frequent complication of hemodialysis; however, there is no evidence-based consensus definition of intradialytic hypotension. As a result, coherent evaluation of the effects of intradialytic hypotension is difficult. We analyzed data from 1409 patients in the HEMO Study and 10,392 patients from a single large dialysis organization to investigate the associations of commonly used intradialytic hypotension definitions and mortality. Intradialytic hypotension definitions were selected *a priori* on the basis of literature review. For each definition, patients were characterized as having intradialytic hypotension if they met the corresponding definition in at least 30% of baseline exposure period treatments or characterized as control otherwise. Overall and within subgroups of patients with predialysis systolic BP<120 or 120–159 mmHg, an absolute nadir systolic BP<90 mmHg was most potently associated with mortality. Within the subgroup of patients with predialysis BP≥160 mmHg, nadir BP<100 mmHg was most potently associated with mortality. Intradialytic hypotension definitions that considered symptoms, interventions, and decreases in BP during dialysis were not associated with outcome, and when added to nadir BP, symptom and intervention criteria did not accentuate associations with mortality. Our results suggest that nadir-based definitions best capture the association between intradialytic hypotension and mortality.

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Intradialytic hypotension (IDH) is a serious complication of hemodialysis (HD). IDH has been associated with subsequent vascular access thrombosis,[1] inadequate dialysis dose,[2] and mortality.[3,4] Additionally, IDH-precipitated fluid administration and early HD termination can leave patients volume-expanded and at risk for associated cardiovascular morbidity.[5]

IDH prevalence reports range from 15% to 50% of ambulatory HD sessions.[6] This wide range is explained, in part, by differing criteria used to define IDH. There is no consensus definition. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines define IDH as a decrease in either systolic BP (SBP)≥20 mmHg or mean arterial pressure≥10 mmHg as well as associated symptoms.[7] Others define IDH on the basis of a requisite SBP fall during treatment accompanied by interventions, such as saline bolus administration, ultrafiltration (UF) reduction, or blood flow reduction.[8] Because symptom and intervention data are often unavailable in large databases, some IDH definitions are based exclusively on SBP measurements, such as SBP reduction by some requisite amount during treatment (20, 30, and 40 mmHg) or nadir intradialytic SBP below a threshold value (90, 95, and 100 mmHg).[9–13]

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Compound definitions are also common; examples include ≥30-mmHg SBP fall+nadir SBP<110 mmHg and ≥20-mmHg SBP fall+fluid bolus±symptoms.[14,15]

Discrepancies in IDH definitions limit synthesis of the existing data regarding putative IDH sequelae and potential strategies for IDH prophylaxis and treatment. Despite the large body of data surrounding IDH, there is surprisingly little evidence linking IDH to mortality. Shoji *et al.*[3] showed that ≥40-mmHg SBP fall and nadir SBP (separately) predict 2-year mortality. Contrastingly, Tisler *et al.*[4] reported no association between mortality and frequent IDH (defined as ≥10 treatments during a 10-month run-in period in which nadir SBP<90 mmHg or 30-mmHg SBP fall+associated symptoms and intervention). To assemble a coherent evidence base that can guide clinical decisions, it is imperative that we develop a consistent, evidence-based IDH definition.

We undertook this study to examine the association of commonly used IDH definitions and mortality. IDH definitions (Table 1) were selected *a priori* by literature review. We conducted a secondary analysis of the Hemodialysis (HEMO) Study to test mortality associations across a range of IDH definitions, taking advantage of HEMO-reported intradialytic SBP, symptom, and intervention data. We then performed a replication study to confirm results and explore IDH–mortality associations across categories of pre-HD SBP using data from a nationally representative cohort of patients on prevalent, three times per week, in-center HD from a single large dialysis organization (LDO).

RESULTS

Baseline Characteristics of Cohorts

Characteristics of the HEMO and LDO cohorts are presented in Table 2. Compared with patients without Nadir90-defined IDH, patients with Nadir90-defined IDH in both cohorts were more likely to be women, be of longer dialytic vintage, be dialyzed by catheter, and have lower pre-HD SBP and albumin; they were less likely to be prescribed calcium channel blockers, α-blockers, and other antihypertensive agents.

Table 1. *A priori* IDH definitions

Term	Definition
Nadir90	Minimum intradialytic SBP<90 mmHg
Nadir100	Minimum intradialytic SBP<100 mmHg
Fall20	(Pre-HD SBP−minimum intradialytic SBP) ≥20 mmHg
Fall30	(Pre-HD SBP−minimum intradialytic SBP) ≥30 mmHg
Fall20Nadir90	(Pre-HD SBP−minimum intradialytic SBP) ≥20 mmHg and minimum intradialytic SBP<90 mmHg
Fall30Nadir90	(Pre-HD SBP−minimum intradialytic SBP) ≥30 mmHg and minimum intradialytic SBP<90 mmHg
KDOQI	(Pre-HD SBP−minimum intradialytic SBP) ≥20 mmHg and symptoms of cramping, headache, lightheadedness, vomiting, or chest pain during HD
HEMO	Fall in SBP resulting in intervention of UF reduction, blood flow reduction, or saline administration

Primary Analyses

In 1409 patients in the HEMO cohort, patients underwent 12,561 treatments during the baseline exposure period of approximately 6 months (mean=8.9±1.6 sessions/patient) (Supplemental Figure 1A displays the study timeline). Figure 1 displays the IDH frequency by definition: 19.1% of sessions had HEMO-defined IDH, and 11.3% of sessions had Nadir90-defined IDH. Overall, 25.0% of patients experienced HEMO-defined IDH in at least 30% of the baseline treatments, and 11.9% of patients experienced Nadir90-defined IDH in at least 30% of the baseline treatments. During the subsequent 2-year at-risk period, 432 (30.7%) patients died.

In unadjusted analyses, meeting the Nadir90, Fall20Nadir90, Fall30Nadir90, and HEMO IDH definitions in at least 30% of baseline sessions (versus not) was each associated with higher 2-year mortality. After adjustment for potential confounders, only Nadir90 (versus not) remained associated with higher 2-year mortality: adjusted odds ratio (OR), 1.56; 95% confidence interval (95% CI), 1.05 to 2.31 (Figure 2, Table 3).

In 10,392 patients in the LDO cohort, patients underwent 136,754 treatments during the baseline period of 30 days (mean=13.3±1.3 sessions/patient) (Supplemental Figure 1B displays the study timeline). The frequencies of IDH by different definitions were similar to those in the HEMO cohort (Figure 1): 9.7% of sessions had Nadir90-defined IDH. Overall, 10.1% of patients experienced Nadir90-defined IDH in at least 30% of the baseline treatments. During the subsequent 1-year at-risk period, 1253 (12.1%) patients died.

In unadjusted analyses, IDH (by each definition) in at least 30% of sessions (versus not) was associated with 1-year mortality; Nadir90 had the most potent association with higher mortality: unadjusted OR, 2.10; 95% CI, 1.78 to 2.47. After multivariable adjustment, only Nadir90 (versus not) remained associated with higher 1-year mortality: adjusted OR, 1.30; 95% CI, 1.07 to 1.57 (Figure 2, Tables 3).

Secondary Analyses

Corroborative time-to-death analyses with Nadir90 were conducted in the full HEMO cohort (n=1753). There were 809 deaths, and the median at-risk time was 2.3 years. Nadir90 in at least 30% of sessions (versus not) was associated with higher mortality risk: adjusted hazard ratio (HR), 1.38; 95% CI, 1.11 to 1.71. Associations between other IDH definitions and mortality did not reach statistical significance. Analogous analyses were performed in the LDO cohort. Both Nadir90 and Fall20-Nadir90 in at least 30% of sessions (versus not) were associated with higher mortality risk, and the magnitude of association was greater for Nadir90: adjusted HR, 1.22; 95% CI, 1.10 to

Table 2. Baseline characteristics of the HEMO (*n*=1409) and LDO (*n*=10,392) cohorts across binary Nadir90-defined IDH

Characteristic	HEMO Cohort		LDO Cohort	
	(+) Nadir90 (*n*=167)	(−) Nadir90 (*n*=1242)	(+) Nadir90 (*n*=1055)	(−) Nadir90 (*n*=9337)
Age (per 10 yr)	60.5±12.8	58.2±13.9	64.2±13.8	61.2±14.9
Women	108 (64.7%)	676 (54.4%)	548 (51.9%)	4220 (45.2%)
Black	97 (58.1%)	808 (65.1%)	330 (31.3%)	3860 (41.3%)
ICED[a]			[a]	[a]
≤1	30 (18.0%)	448 (36.1%)		
2	54 (32.3%)	404 (32.5%)		
3	83 (49.7%)	390 (31.4%)		
Diabetes	88 (52.7%)	543 (43.7%)	644 (61.0%)	5593 (59.9%)
Heart failure	71 (42.5%)	505 (40.7%)	479 (45.4%)	4167 (44.6%)
Peripheral vascular disease	62 (37.1%)	313 (25.2%)	424 (40.2%)	4325 (46.3%)
Cerebrovascular disease	36 (21.6%)	248 (20.0%)	40 (3.8%)	283 (3.0%)
Coronary artery disease	79 (47.3%)	484 (39.0%)	163 (15.5%)	1278 (13.7%)
Vintage (yr)				
≤1.0	37 (22.2%)	326 (26.2%)	233 (22.1%)	2667 (28.6%)
1.1–1.9	33 (19.8%)	248 (20.0%)	137 (13.0%)	1467 (15.7%)
2.0–3.9	30 (17.9%)	291 (23.4%)	243 (23.0%)	2326 (24.9%)
≥4.0	67 (40.1%)	377 (30.4%)	440 (41.7%)	2860 (30.6%)
Missing	0	0	2 (0.2%)	17 (0.2%)
Access				
Graft	101 (60.5%)	752 (60.6%)	328 (31.3%)	2876 (31.0%)
Fistula	46 (27.5%)	410 (33.0%)	338 (32.3%	3486 (37.6%)
Catheter	20 (12.0%)	90 (6.4%)	382 (36.4%)	2909 (31.4%)
Post-HD weight (kg)[b]				
Quartile 1	40 (24.0%)	313 (25.2%)	292 (27.7%)	2309 (24.7%)
Quartile 2	39 (23.4%)	313 (25.2%)	267 (25.3%)	2330 (25.0%)
Quartile 3	36 (21.5%)	316 (25.4%)	248 (23.5%)	2348 (15.1%)
Quartile 4	52 (31.1%)	300 (24.2%)	248 (23.5%)	2350 (25.2%)
Treatment time delivered (min)	213.5±23.0	211.1±23.0	216.5±28.8	215.0±28.5
UF volume (L)	2.9±0.9	2.9±0.9	2.8±1.2	2.7±1.2
Pre-HD SBP (mmHg)				
≤129	67 (40.1%)	114 (9.2%)	488 (46.2%)	911 (9.8%)
130–159	73 (43.7%)	665 (53.5%)	429 (40.7%)	4940 (52.9%)
≥160	27 (16.2%)	463 (37.3%)	138 (13.1%)	3486 (37.3%)
Nonoliguric (>200 ml/d)[a]	10 (6.0%)	140 (11.3%)	[a]	[a]
Albumin (g/dl)				
≤2.9	7 (4.2%)	45 (3.6%)	97 (9.2%)	425 (4.6%)
3–3.9	150 (89.8%)	1026 (82.6%)	595 (56.4%)	5048 (54.1%)
≥4	10 (6.0%)	171 (13.8%)	359 (34.0%)	3795 (40.6%)
Missing	0	0	4 (0.4%)	69 (0.7%)
Hematocrit[a] (%)	33.8±4.5	33.1±4.2	[a]	[a]
Hemoglobin[a] (g/dl)	[a]	[a]	12.1±1.4	12.2±1.4
Hospitalized during exposure period[c]	61 (36.5%)	376 (30.3%)	332 (31.5%)	2811 (30.1%)
β-Blocker use	30 (18.0%)	362 (29.2%)	89 (8.5%)	839 (9.0%)
Calcium channel blocker	49 (29.3%)	643 (51.8%)	84 (8.0%)	964 (10.3%)
Renin-angiotensin system blocker use	27 (16.2%)	314 (25.3%)	98 (9.3%)	910 (9.8%)
Nitrate use	33 (19.8%)	221 (17.8%)	33 (3.1%)	275 (3.0%)
α-Blocker use	3 (1.8%)	76 (6.1%)	1 (0.1%)	120 (1.3%)
Other antihypertensive use	14 (8.4%)	306 (24.6%)	80 (7.6%)	940 (10.1%)
High Kt/V group[a]	86 (51.5%)	623 (50.2%)	[a]	[a]

Table 2. Continued

Characteristic	HEMO Cohort		LDO Cohort	
	(+) Nadir90 (*n*=167)	(−) Nadir90 (*n*=1242)	(+) Nadir90 (*n*=1055)	(−) Nadir90 (*n*=9337)
equilibrated Kt/V[a]	[a]	[a]		
<1.2			209 (19.8%)	2152 (23.0%)
≥1.2			812 (77.0%)	6850 (73.4%)
Missing			34 (3.2%)	335 (3.6%)
High-flux group[a]	91 (54.5%)	613 (49.4%)	[a]	[a]

Positive (+) IDH defined as meeting the Nadir90 defined IDH definition (minimum intradialytic SBP<90 mmHg) in ≥30% of exposure period dialysis sessions. Values are presented as mean (SD) or *n* (%).

[a]Not available in both cohorts.

[b]HEMO cohort (quantile 1: ≤62.7, quantile 2: 62.8–74.1, quantile 3: 74.2–89.1, quantile 4: ≥89.2 kg); LDO cohort (quantile 1: ≤58.7, quantile 2: 58.8–67.7, quantile 3: 67.8–78.1, quantile 4: ≥78.2).

[c]Missed HD sessions used as a surrogate for hospitalizations in LDO cohort.

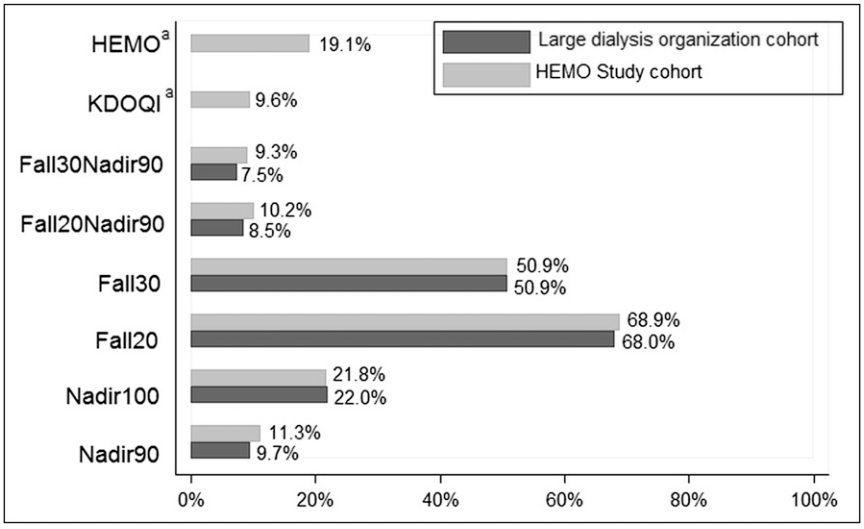

Figure 1. Frequency of IDH was similar across both cohorts. Frequency of IDH was defined by the number of dialysis sessions with events meeting the specified IDH definition divided by the total number of dialysis treatments in the baseline period. Fall20, (pre-HD SBP−minimum intradialytic SBP) ≥20 mmHg; Fall20Nadir90: (pre-HD SBP−minimum intradialytic SBP) ≥20 mmHg and minimum intradialytic SBP<90 mmHg; Fall30, (pre-HD SBP−minimum intradialytic SBP) ≥30 mmHg; Fall30Nadir90, (pre-HD SBP−minimum intradialytic SBP) ≥30 mmHg and minimum intradialytic SBP<90 mmHg; HEMO, fall in SBP resulting in intervention of UF reduction, blood flow reduction, or saline administration; KDOQI, (pre-HD SBP − minimum intradialytic SBP) ≥20 mmHg and symptoms of cramping, headache, lightheadedness, vomiting, or chest pain during HD; Nadir90, minimum intradialytic SBP<90 mmHg; Nadir100, minimum intradialytic SBP<100 mmHg. [a]HEMO and KDOQI definitions of IDH could not be assessed in the LDO cohort because of the lack of symptom and intervention data in this cohort.

Additionally, we investigated whether adding criteria for intradialytic symptoms (cramping, headache, lightheadedness, vomiting, or chest pain) or intervention (fluid bolus administration, UF reduction, or blood flow reduction) to Nadir90 altered the association with mortality. No associations between Nadir90+symptoms or Nadir90+intervention and outcome were observed in adjusted analyses (Table 3).

Finally, we examined IDH definition–mortality associations across pre-HD SBP strata of ≤129, 130–159, and ≥160 mmHg in the LDO cohort. Restriction subgroup analyses showed differences in Nadir90–mortality associations across strata (*P* interaction=0.02). In stratified analyses, Nadir90 in at least 30% of sessions (versus not) was most potently associated with 1-year mortality in the ≤129- and 130–159-mmHg SBP strata. In the ≥160-mmHg pre-HD SBP strata, Nadir100 (versus not) was most potently associated with mortality (Table 4). To investigate the association of greater SBP falls during dialysis, we examined the association of 1-year mortality and 10-mmHg incremental increases in SBP fall across pre-HD SBP strata; no associations between greater SBP falls and outcome were observed (Table 4).

1.35 for Nadir90 and HR, 1.14; 95% CI, 1.02 to 1.27 for Fall20-Nadir90.

To examine dose response, we categorized patients as having <5%, 6%–29%, 30%–49%, and ≥50% of baseline treatments with Nadir90-defined IDH. Compared with <5% treatments, higher frequency of Nadir90-defined IDH was incrementally associated with greater 2-year mortality (*P* trend=0.02) (Figure 3).

DISCUSSION

There is no consensus evidence-based definition of IDH. As a result, the existing evidence base is fraught with many definitions, rendering data synthesis impossible. Our analysis shows that an absolute intradialytic nadir SBP<90 mmHg is most potently associated with mortality; this association was consistent across pre-HD SBP strata of ≤129 and 130–159

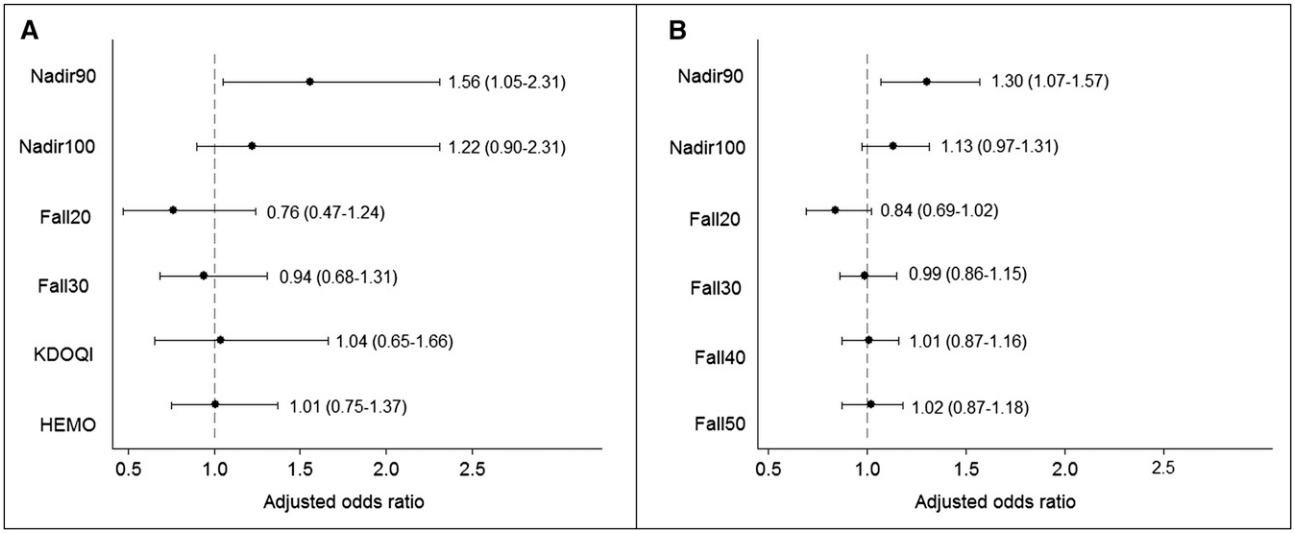

Figure 2. Adjusted associations between IDH definitions and mortality in (A) the HEMO cohort and (B) the LDO cohort. Outcome for the HEMO cohort is 2-year mortality, and outcome for the LDO cohort is 1-year mortality. IDH was defined as ≥30% of the exposure period HD sessions meeting the specified definition. Multivariate logistic models for the HEMO cohort were adjusted for age (per 10 years), sex, race (black or nonblack), ICED (≤1, 2, or 3), smoking status (current smoker or nonsmoker), diabetes, heart failure, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, vintage (≤0.9, 1–1.9, 2–3.9, or ≥4 years or missing), access (graft, fistula, or catheter), postdialysis weight (quartiles; kilograms), delivered treatment time (minutes), albumin (≤2.9, 3–3.9, or ≥4 g/dl or missing), hematocrit (percentage), UF volume (liters), predialysis SBP (≤129, 130–159, or ≥160 mmHg), residual renal function (≤200 or >200 ml/d), hospitalization during exposure period (yes or no), Kt/V group (high or low), flux group (high or low), center, and use of α-adrenergic blocker, renin-angiotensin system blocker, β-blocker, calcium channel blocker, nitrates, or other antihypertensives. Multivariate logistic models for the LDO cohort were adjusted for age (per 10 years), sex, race (black, nonblack, or missing), diabetes, heart failure, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, vintage (≤0.9, 1–1.9, 2–3.9, or ≥4 years or missing), access (graft, fistula, or catheter), postdialysis weight (quartiles; kilograms), delivered treatment time (minutes), albumin (≤2.9, 3–3.9, or ≥4 g/dl or missing), hemoglobin (grams per deciliter), UF volume (liters), predialysis SBP (≤129, 130–159, or ≥160 mmHg), equilibrated Kt/V (<1.2, ≥1.2, or missing), missed sessions during exposure period (0, 1, 2, or ≥3), and use of α-adrenergic blocker, renin-angiotensin system blocker, β-blocker, calcium channel blocker, nitrates, or other antihypertensives.

mmHg. Intradialytic nadir SBP<100 mmHg was most strongly associated with mortality in the pre-HD SBP strata of ≥160 mmHg. The data suggest a dose–response relationship between Nadir90 and mortality: greater frequency of Nadir90-defined IDH is associated with incrementally greater mortality risk. In our analysis, IDH definitions on the basis of intradialytic SBP fall, symptoms, and interventions without consideration of the absolute nadir SBP were not significantly associated with outcome. Finally, adding symptom and intervention criteria to nadir SBP definitions did not augment their strengths of association with mortality.

Prior observational studies have shown inconsistent associations between IDH and mortality. Shoji *et al.*[3] examined the effect of IDH on mortality in 1206 Japanese patients and showed that SBP fall≥40 mmHg was associated with 2-year mortality; the association persisted across pre-HD SBP strata. Additionally, Shoji *et al.*[3] showed that lower intradialytic nadir SBP was associated with higher mortality. Notable limitations to this analysis include a low death rate (6.2% per year) and consideration of a single treatment session as the exposure. Tisler *et al.*[4] studied 263 Hungarian patients on HD using time-to-event adjusted analyses and found that patients with frequent IDH (defined as ≥10 episodes per 40-week run-in period of Nadir90 or Fall30+associated symptoms and intervention) had no greater mortality risk than those without IDH. In the study by Tisler *et al.*,[4] patients with as few as one episode of IDH per month met the criteria for frequent IDH, potentially leaving too little separation between the exposure and control groups to detect a clinically important difference. In contrast, our study definition required that patients meet the specified IDH definition in at least 30% of baseline sessions to qualify as (+) IDH; for example, patients with 13 treatments in the LDO cohort's 4-week at-risk period had to have four IDH episodes to qualify, nearly four times the number required in the study by Tisler *et al.*[4]

Despite the plethora of IDH-related studies (a Pubmed search for IDH captured 318 articles[16]) and common allusions to IDH being a cardiovascular risk factor,[17,18] strikingly little data exist to inform a prognostically relevant IDH definition. In publishing its IDH diagnostic criteria, the European guidelines group acknowledged that "no evidence-based recommendation regarding the definition of IDH can be given."[19]

Table 3. Unadjusted and adjusted associations between IDH definitions and mortality on the basis of logistic regression models

Definition	HEMO Cohort (*n*=1409)[a]				LDO Cohort (*n*=10,392)[a]			
	(+) IDH[b]	(−) IDH	Unadjusted OR (95% CI) (+) IDH versus (−) IDH	Adjusted OR[c] (95% CI) (+) IDH versus (−) IDH	(+) IDH[b]	(−) IDH	Unadjusted OR (95% CI) (+) IDH versus (−) IDH	Adjusted OR[d] (95% CI) (+) IDH versus (−) IDH
Nadir90	*n*=167	*n*=1242	2.26[e]	1.56[f]	*n*=1054	*n*=9338	2.10[e]	1.30[f]
	Died: 79 (47.3%)	Died: 353 (28.4%)	(1.63 to 3.14)	(1.05 to 2.31)	Died: 218 (20.7%)	Died: 1035 (11.1%)	(1.78 to 2.47)	(1.07 to 1.57)
Nadir100	*n*=390	*n*=1019	1.97[e]	1.22	*n*=2841	*n*=7551	1.75[e]	1.13
	Died: 162 (41.5%)	Died: 270 (26.5%)	(1.54 to 2.52)	(0.90 to 2.31)	Died: 475 (16.7%)	Died: 778 (10.3%)	(1.54 to 1.98)	(0.97 to 1.31)
Fall20	*n*=1288	*n*=121	0.96	0.76	*n*=9271	*n*=1121	0.65[e]	0.84
	Died: 394 (30.6%)	Died: 38 (31.4%)	(0.64 to 1.44)	(0.47 to 1.24)	Died: 1066 (11.5%)	Died: 187 (16.7%)	(0.55 to 0.77)	(0.69 to 1.02)
Fall30	*n*=1049	*n*=360	1.06	0.94	*n*=7428	*n*=2964	0.78[e]	0.99
	Died: 325 (31.0%)	Died: 107 (29.7%)	(0.82 to 1.38)	(0.68 to 1.31)	Died: 837 (11.3%)	Died: 416 (14.0%)	(0.69 to 0.88)	(0.86 to 1.15)
Fall20Nadir90	*n*=151	*n*=1258	1.95[e]	1.32	*n*=898	*n*=9494	1.83[e]	1.20
	Died: 67 (44.4%)	Died: 365 (29.0%)	(1.38 to 2.75)	(0.88 to 1.97)	Died: 171 (19.0%)	Died: 1082 (11.4%)	(1.53 to 2.19)	(0.98 to 1.47)
Fall30Nadir90	*n*=131	*n*=1278	1.85[f]	1.27	*n*=740	*n*=9652	1.52[e]	1.15
	Died: 57 (43.5%)	Died: 375 (29.3%)	(1.29 to 2.67)	(0.83 to 1.95)	Died: 124 (16.8%)	Died: 1129 (11.7%)	(1.24 to 1.86)	(0.92 to 1.43)
KDOQI	*n*=118	*n*=1291	0.95	1.04	—	—	—	—
	Died: 35 (29.7%)	Died: 397 (30.8%)	(0.63 to 1.43)	(0.65 to 1.66)				
HEMO	*n*=353	*n*=1056	1.46[f]	1.01	—	—	—	—
	Died: 130 (36.8%)	Died: 302 (28.6%)	(1.13 to 1.88)	(0.75 to 1.37)				
Nadir90+Sx[g]	*n*=6	*n*=1403	1.13	0.34	—	—	—	—
	Died: 2 (33.3%)	Died: 430 (30.7%)	(0.21 to 6.20)	(0.06 to 2.04)				
Nadir90+Int[g]	*n*=100	*n*=1309	1.95[f]	1.39	—	—	—	—
	Died: 45 (45.0%)	Died: 387 (29.6%)	(1.29 to 2.94)	(0.86 to 2.23)				

[a]Outcome for the HEMO cohort is 2-year mortality, and outcome for the LDO cohort is 1-year mortality.

[b]IDH defined as ≥30% of exposure period HD sessions meeting the specified definition.

[c]Multivariate logistic models were adjusted for age (per 10 years), sex, race (black or nonblack), ICED (≤1, 2, or 3), smoking status (current smoker or nonsmoker), diabetes, heart failure, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, vintage (≤0.9, 1–1.9, 2–3.9, or ≥4 years or missing), access (graft, fistula, or catheter), postdialysis weight (quartiles; kilograms), delivered treatment time (minutes), albumin (≤2.9, 3–3.9, or ≥4 g/dl or missing), hematocrit (percentage), UF volume (liters), predialysis SBP (≤129, 130–159, or ≥160 mmHg), residual renal function (≤200 or >200 ml/d), hospitalization during exposure period (yes or no), Kt/V group (high or low), flux group (high or low), center, and use of α-adrenergic blocker, renin-angiotensin system blocker, β-blocker, calcium channel blocker, nitrates, or other antihypertensives.

[d]Multivariate logistic models were adjusted for age (per 10 years), sex, race (black, nonblack, or missing), diabetes, heart failure, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, vintage (≤0.9, 1–1.9, 2–3.9, or ≥4 years or missing), access (graft, fistula, or catheter), postdialysis weight (quartiles; kilograms), delivered treatment time (minutes), albumin (≤2.9, 3–3.9, or ≥4 g/dl or missing), hemoglobin (grams per deciliter), UF volume (liters), predialysis SBP (millimeters Hg), equilibrated Kt/V (<1.2, ≥1.2, or missing), missed sessions during exposure period (0, 1, 2, or ≥3), and use of α-adrenergic blocker, renin-angiotensin system blocker, β-blocker, calcium channel blocker, nitrates, and other antihypertensives.

[e]P value<0.001.

[f]P value<0.05.

[g]Given the small n meeting the IDH definition in ≥30% of HD sessions, definition tertiles were examined; point estimates were similar (data not shown).

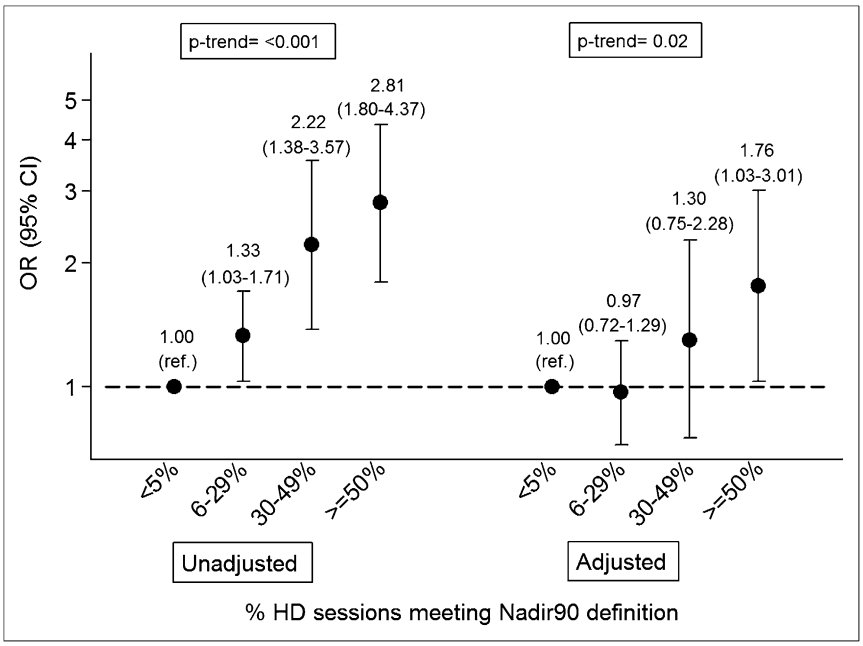

Figure 3. In the HEMO cohort, patients with more frequent episodes of IDH had incrementally greater mortality in both unadjusted and adjusted analyses. Analyses were adjusted for age (per 10 years), sex, race (black or nonblack), ICED (≤1, 2, or 3), smoking status (current smoker or nonsmoker), diabetes, heart failure, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, vintage (≤0.9, 1–1.9, 2–3.9, or ≥4 years or missing), access (graft, fistula, or catheter), postdialysis weight (quartiles; kilograms), delivered treatment time (minutes), albumin (≤2.9, 3–3.9, or ≥4 g/dl or missing), hematocrit (percentage), UF volume (liters), predialysis SBP (≤129, 130–159, or ≥160 mmHg), residual renal function (≤200 or >200 ml/d), hospitalization during exposure period (yes or no), Kt/V group (high or low), flux group (high or low), center, and use of α-adrenergic blocker, renin-angiotensin system blocker, β-blocker, calcium channel blocker, nitrates, or other antihypertensives. Error bars indicate 95% CI.

Lack of an evidence-based IDH definition has led to variation in IDH definitions across studies; we identified 15 different IDH definitions by literature review. Such wide variation renders synthesis of data across studies impossible and prevents the development of meaningful practice recommendations.

In our analysis, we show that nadir SBP-based definitions have greater associations with mortality than non-nadir–based or compound definitions. These findings challenge the oft-cited IDH diagnostic criteria that include the presence of symptoms and/or interventions.[7,19] Our findings in this regard may reflect provider-to-provider variability in intervention thresholds and/or patient-to-patient variability in symptom reporting. The impetus for intervention and the choice of intervention vary from facility to facility and even provider to provider. These practice variations introduce substantial inconsistency into IDH definitions dependent on delivered intervention. Similarly, patient-reported symptoms vary widely. In one survey, Weisbord *et al.*[20] found that 39.0% of patients reported cramping, 23.0% of patients reported dizziness, and 21.0% of patients reported headache with HD. In contrast, HD-related symptom frequency was much higher in another survey, with 74.3% of patients reporting cramping, 63.0% of patients reporting dizziness, and 53.6% of patients reporting headache.[21] Such differences may result from reporting bias but may also reflect differences in physiology, because patients experience symptoms at varying thresholds of BP change and nadir. Patient symptoms may be important factors at the individual level, because they plausibly reflect ischemia, but their use in population-level definitions may be questionable because of wide patient-to-patient variation.

Additionally, we were surprised to find that incrementally larger SBP falls, independent of nadir, were not significantly associated with outcome. Although it is widely held that HD patients suffer from impaired autoregulatory responses to SBP changes, our results may suggest that their compensatory mechanisms are sufficiently active until certain SBP thresholds: <90 mmHg for pre-HD SBP <160 and <100 for pre-HD SBP ≥160 mmHg. Reduction in blood volume to a critical nadir may be necessary to induce enough microcirculatory and microcardiac ischemia to yield reduced cardiac output and associated mortality. Larger SBP falls that do not result in nadirs<90 mmHg may have clinical relevance beyond mortality, and this possibility should be explored in additional analyses examining associations of IDH and morbidities other than death. Our results suggest the need for development of an evidence-based IDH definition that more accurately captures IDH–morbidity and –mortality associations.

Strengths of this study include the use of two cohorts: (*1*) the HEMO Study cohort (notable for its rigorous data collection protocols and detailed information on intradialytic hemodynamics, interventions, and patient symptoms) and (*2*) the LDO cohort (notable for its national representation and a robust number of HD sessions with intradialytic SBP data. Stability in frequency of IDH definitions and IDH definition–mortality associations across both cohorts lends credence to our reported findings.

Our study does have important limitations. First, uncontrolled confounding is an inherent risk of observational research. To minimize this risk, we adjusted our analyses for variables plausibly associated with IDH and mortality; however, we cannot exclude the possibility of residual confounding from these variables or unconsidered variables. Notably, pre-HD SBP is strongly associated with outcome.[22] We attempted

Table 4. Adjusted associations between IDH and 1-year mortality across predialysis SBP strata in the LDO cohort

Definition[a]	Patients Meeting IDH Definition *n* (%)	Adjusted OR[b] (95% CI) for Patients Meeting Versus Not Meeting IDH Definition
Pre-HD SBP≤129 mmHg (6448 patients)		
Nadir90	1393 (21.6%)	1.32 (1.10 to 1.57)[c]
Nadir100	3096 (48.0%)	1.23 (1.05 to 1.44)[c]
Fall20	3018 (46.8%)	1.08 (0.93 to 1.26)
Fall30	1337 (20.7%)	1.02 (0.85 to 1.23)
Fall40	440 (6.8%)	1.30 (0.98 to 1.73)
Fall50	111 (1.7%)	1.34 (0.80 to 2.23)
Fall60	35 (0.5%)	1.51 (0.61 to 3.73)
Fall30Nadir90	847 (13.1%)	1.06 (0.85 to 1.32)
Fall20Nadir90	1136 (17.6%)	1.18 (0.98 to 1.42)
Pre-HD SBP=130–159 mmHg (9759 patients)		
Nadir90	1043 (10.7%)	1.28 (1.05 to 1.55)[c]
Nadir100	2703 (27.7%)	1.14 (0.98 to 1.31)
Fall20	8061 (82.6%)	1.03 (0.86 to 1.24)
Fall30	6176 (63.3%)	1.06 (0.92 to 1.22)
Fall40	3963 (40.6%)	1.11 (0.97 to 1.28)
Fall50	1977 (20.3%)	1.04 (0.88 to 1.22)
Fall60	766 (7.9%)	1.16 (0.92 to 1.46)
Fall30Nadir90	1041 (10.7%)	1.27 (1.05 to 1.54)[c]
Fall20Nadir90	1041 (10.7%)	1.27 (1.05 to 1.54)[c]
Pre-HD SBP≥160 mmHg (8307 patients)		
Nadir90	578 (7.0%)	1.08 (0.83 to 1.41)
Nadir100	1412 (17.0%)	1.29 (1.07 to 1.56)[c]
Fall20	7971 (96.0%)	0.78 (0.55 to 1.11)
Fall30	7386 (88.9%)	1.13 (0.88 to 1.46)
Fall40	6343 (76.4%)	1.06 (0.88 to 1.28)
Fall50	5039 (60.7%)	1.13 (0.96 to 1.33)
Fall60	3659 (44.1%)	1.13 (0.96 to 1.32)
Fall30Nadir90	578 (7.0%)	1.13 (0.86 to 1.48)
Fall20Nadir90	578 (7.0%)	1.13 (0.86 to 1.48)

[a]Positive (+) IDH defined as nadir SBP<90 mmHg in ≥30% of exposure period dialysis sessions (versus not).
[b]Multivariate logistic models were adjusted for age (per 10 years), sex, race (black, nonblack, or missing), diabetes, heart failure, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, vintage (≤0.9, 1–1.9, 2–3.9, or ≥4 years or missing), access (graft, fistula, or catheter), postdialysis weight (quartiles; kilograms), delivered treatment time (minutes), albumin (≤2.9, 3–3.9, or ≥4 g/dl or missing), hemoglobin (grams per deciliter), UF volume (liters), predialysis SBP (millimeters Hg), equilibrated Kt/V (<1.2, ≥1.2, or missing), missed sessions during exposure period (0, 1, 2, or ≥3), and use of α-adrenergic blocker, renin-angiotensin system blocker, β-blocker, calcium channel blocker, nitrates, and other antihypertensives.
[c]*P* value<0.05.

to limit confounding of the IDH–outcome association on the basis of pre-HD BP by stratification on pre-HD BP and inclusion of pre-HD SBP in our stratified multivariable models. We cannot fully exclude the possibility of residual confounding by pre-HD SBP. Second, intradialytic SBPs, intervention, and symptom data were only available from monitored HEMO Study sessions, which were conducted monthly. To ensure that our IDH exposure was representative of patients' broader HD hemodynamic experiences and reduce misclassification error, we aggregated treatment data over a 6-month exposure period. This exposure period duration may have imposed survivor bias; however, only 93 patients (5.0%) were excluded for failing to survive this period, making meaningful bias unlikely. Also, in this regard, it is reassuring that similar findings were observed in the LDO cohort, where only 30-day baseline survival was necessary. Third, HD hemodynamic data were only available for one treatment per month in the HEMO Study, introducing possible misclassification bias. The consistency of IDH frequencies across the HEMO cohort and LDO cohort (where session-to-session hemodynamic data were available) provides reassurance that misclassification in the HEMO cohort was minimal. Fourth, reporting bias may have influenced IDH definitions relying on patient-reported symptoms; however, in as much as individual patients have differing reporting thresholds; this finding represents an inherent limitation of symptoms-based IDH definitions. Fifth, because of data limitations in the LDO cohort, we were unable to consider residual renal function as a confounder, but we did include dialytic vintage as a partial surrogate for this variable. Also, we included residual renal function in our HEMO cohort analyses, and outcomes were similar across cohorts. Sixth, no data were available on antihypertensive medication adherence or timing in either cohort, and therefore, we were unable to assess the influence of these factors on IDH. Finally, there was no systematic attempt to calibrate individual BP devices. However, any resulting bias should have attenuated nadir-based definitions toward the null.

In conclusion, this study shows that, among the definitions considered, an absolute nadir intradialytic SBP<90 mmHg was most potently associated with mortality overall, and for subgroups of patients with pre-HD SBP, it is <160 mmHg. For patients with pre-HD SBP≥160 mmHg, Nadir100 may have a more robust mortality association. IDH defined by SBP fall and IDH symptoms or interventions was not significantly associated with mortality, even when considered across differing pre-HD SBP strata. Additional studies are needed to confirm findings, and prospective studies using consistent IDH definitions are needed to effectively evaluate IDH treatment and preventive strategies.

CONCISE METHODS

Study Population and Data Collection

This study was approved by the Partners Health Care Institutional Review Board. Study data were derived from the HEMO Study and obtained from the National Institute of Diabetes and Digestive and Kidney Diseases data repository and a cohort of prevalent adult patients receiving three times per week in-center HD at one LDO.

The HEMO Study design and methods have been reported.[8,23] Briefly, the HEMO Study was a 2×2 factorial, 15-center, randomized trial to evaluate the outcome effects of HD dose and membrane flux. HEMO participants were enrolled between 1995 and 2000 and ages

18–80 years. Patients were followed until death or December of 2001 and censored at the time of kidney transplant. Notable HEMO exclusion criteria included severe heart failure, unstable angina pectoris, and albumin≤2.6 g/d. Supplemental Figure 1A displays our study timeline. For this analysis, we excluded patients who did not survive the baseline exposure period of prerandomization time+4 months (n=93) and patients who were transplanted or transferred facilities and thus, had <2 years of potential follow-up time barring death (n=344), resulting in 1409 patients. Corroborative time-to-event analysis was conducted in the full cohort of patients who survived the baseline exposure period (n=1753).

The LDO cohort was derived from 12,417 patients on prevalent three times per week in-center HD dialyzing at one LDO between 2005 and 2008. Patients were followed until death or February of 2009. Patients were dialyzed at 1 of 1263 United States ambulatory dialysis facilities located in diverse geographic regions. Supplemental Figure 1B displays our study timeline. We excluded patients who did not survive the 30-day exposure period (n=24) and patients who remained alive but had <1 year of follow-up time kidney because of transplant, care transfer, or dialysis modality change (n=2021), resulting in 10,392 patients.

For the HEMO cohort, all data were obtained by patient interviews, medical chart reviews, and self-reported questionnaires per HEMO protocols; HEMO data collection methods have been previously reported.[8,24] For the LDO cohort, all data were obtained from the electronic medical record of the LDO and collected according to standard protocols as previously reported.[24–26]

Designation of Exposures and Outcome

The exposures of interest were differing IDH definitions selected *a priori* on the basis of prominent definitions identified by literature review (Table 1). In the HEMO cohort, IDH was considered for a baseline period, including treatments incurred during the prerandomization period and the 4 months after randomization. More frequent HD session data were available in the LDO cohort, and therefore, a 30-day exposure period was selected to minimize survivor bias. To account for differences in follow-up time across patients in both cohorts, we divided the number of HD sessions meeting the specified IDH definition by the total number of HD sessions during the exposure period in which IDH defining criteria (intradialytic SBPs, interventions, and symptoms) were considered.

For the HEMO IDH definition, an episode of IDH was defined by an affirmative response to the following question from the monitored HD sessions: "Was there hypotension requiring saline infusion, lowering of the UF rate, or reduced blood flow?" Because the percentage of HD sessions with HEMO-defined IDH was asymmetrically distributed, we divided the HEMO IDH definition exposure into quartiles and identified the 75th percentile (≥30% of exposure HD sessions meeting the definition); patients were then dichotomized on the basis of whether they had met the HEMO-defined IDH at least this number of times. For the KDOQI IDH definition, an episode of IDH was defined as pre-HD SBP − minimum intradialytic SBP≥20 mmHg +intradialytic symptoms of cramping, headache, lightheadedness, vomiting, or chest pain as recorded on the symptom assessment form.[7] Additional *a priori* IDH definitions are shown in Table 1.

To foster interpretability and consistency, a 30% cutpoint of total exposure period HD sessions with events meeting the specified IDH definition was applied to all IDH definitions. This dichotomization threshold was supported by literature precedent[1,27] and felt to be clinically meaningful. Patients with ≥30% exposure period HD sessions meeting the individually specified IDH definition were classified as (+) IDH, and patients not meeting the specified IDH definition in ≥30% of sessions were classified as (−) IDH (the referent group). Lack of symptom and intervention data precluded the examination of HEMO and KDOQI IDH definitions in the LDO cohort. SBP were recorded pre- and post-HD in a seated position using automated devices per routine practice. Intradialytic SBPs were machine-measured in the seated position and typically occurred every 30 minutes during all treatment sessions.

The outcome of interest was 2-year all-cause mortality in the HEMO cohort and 1-year mortality in the LDO cohort. A shorter risk period in the LDO cohort was selected because of limited available follow-up data and desire to maximize the cohort size.

Statistical Analyses

Analyses were performed with STATA 12.0MP (College Station, TX). Baseline subject characteristics were described as counts and proportions for categorical variables and means and SDs for continuous variables. Bivariable comparisons across IDH categories were made using chi-squared and t tests.

In the primary analyses, ORs for 2-year mortality (in the HEMO cohort) and 1-year mortality (in the LDO cohort) across binary IDH definitions were estimated by fitting logistic regression models. Model covariates were selected as those variables hypothesized to be associated with IDH and/or mortality. In the HEMO cohort, multivariable models were adjusted for age (per 10 years); sex; race (black versus nonblack); comorbidities (diabetes, heart failure, peripheral vascular disease, cerebrovascular disease, coronary artery disease, Index of Coexistent Disease [ICED], and smoking status); HD factors, including vascular access type (graft, fistula, or catheter), post-HD weight (quartiles; kilograms), treatment time (minutes), and UF volume (liters); laboratory values (albumin [≤1.9, 3–3.9, or ≥4 g/dl] and hematocrit [percentage]); residual urine output (≤200 versus >200 ml/d); hospitalization during the exposure period; antihypertensive medication use (β-blocker, calcium channel blocker, renin-angiotensin system blocker, nitrate, α-blocker, or other antihypertensives); intervention group (high- or standard-dose HD and high- or low-flux membrane); and clinical center. Postweight, treatment time, UF volume, pre-HD SBP, and laboratory values were considered as mean values during the exposure period. Missing values (smoking [n=2], hematocrit [n=3], and residual urine output [n=16]) were multiply imputed in five replicates using the outcome as a predictor for imputation.

In the LDO cohort, analogous variables were used with the exception of residual urine output, ICED, and smoking, which were not available. Equilibrated Kt/V (<1.2 versus ≥1.2; missing) was used in place of dose randomization group; flux randomization group was nonapplicable. Center was not included because of the large number of centers (n=1263) in the cohort. Missed sessions (0, 1, 2, and ≥3) were used as a surrogate for hospitalization. In both cohorts, the

specification of continuous covariates (linear versus categorical) was guided by each covariate's association with outcome. Individual logistic model fit was examined by Hosmer–Lemeshow testing. Two-tailed P values<0.05 were considered significant.

The Nadir90–mortality association was further explored by analysis of time to death with a Cox proportional hazards model. The proportionality assumption was confirmed by Schoenfeld residual testing. Given the duration of follow-up, the need for time-updated analyses was evaluated by examining IDH frequency over increments of follow-up time. IDH frequencies remained stable over time, and therefore, time-updated analyses were not performed. To examine for a dose–response relationship between IDH and outcome, Nadir90-defined IDH was considered as a categorical exposure ($<$5%, 6%–29%, 30%–49%, and $\geq$50% of sessions with IDH); category thresholds were selected to maximize clinical application. The incremental mortality effects of adding the presence of IDH symptoms and the presence of intervention to the IDH definition Nadir90 were explored (separately) through logistic models with expanded IDH definition criteria. Given the small number of patients who met the Nadir90+symptoms-defined IDH and Nadir90+intervention-defined IDH in $\geq$30% of sessions, we examined the associations considering the top tertile of each exposure and 2-year mortality. No statistically significant associations were observed (data not shown).

Effect modification of the IDH–mortality association on the basis of pre-HD SBP was evaluated using likelihood ratio testing of nested models that did and did not include two-way crossproduct terms. IDH definition–mortality associations were then considered across strata of pre-HD SBP in the LDO cohort. Small numbers within pre-HD SBP strata precluded a parallel analysis in the HEMO cohort. Multivariate logistic models stratified by pre-HD SBP were analogous to those in the primary analyses and further adjusted for mean exposure period pre-HD SBP to account for residual confounding introduced by strata width.

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This manuscript was not prepared in collaboration with the investigators of the HEMO Study and does not necessarily reflect the opinions or views of the HEMO Study or the NIDDK. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University, and its affiliated academic health care centers or the National Institutes of Health.

DISCLOSURES

J.E.F. has received speaking honoraria from Dialysis Clinic Incorporated. G.C.C. has served as a consultant to Allena Pharmaceuticals, AstraZeneca, and Exponent; is an author and section editor for UpToDate; and is the Editor-in-Chief of *CJASN*. When the study began, S.M.B. was employed by Brigham and Women's Hospital. As of September of 2012, the employment of S.M.B. shifted to DaVita Clinical Research, the company that provided the data for this research. The continuation of S.M.B. on the study is as a DaVita Clinical Research employee. Additionally, S.M.B. has received speaking honoraria from Fresenius Medical Care North America and served on advisory boards for Amgen, C.B. Fleet, Keryx, and Otsuka, and his spouse is employed by AstraZeneca.

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