**Supplemental Materials**

**Supplemental Table 1**: Definitions of Intradialytic Hypotension.

| | Blood Pressure Parameter(s) | Symptom Parameter(s) | Proportion of Sessions |
|---|---|---|---|
| Nadir | SBP < 90 mmHg | - | 12.41% |
| Nadir + Symptoms | SBP < 90 mmHg | AND any symptoms or intervention | 7.08% |
| KDOQI | Drop in SBP ≥ 20 mmHg or<br>Drop in MAP ≥ 10 mmHg | AND any symptoms or intervention | 35.89% |
| Combination | Pre-dialysis SBP ≥ 100 mmHg: Nadir<br>Pre-dialysis SBP < 100 mmHg: KDOQI | -<br>AND any symptoms or intervention | 11.08% |

Intradialytic hypotension was defined based on different combinations of systolic blood pressure (SBP) or mean arterial blood pressure (MAP) targets, associated symptoms, or interventions. The primary definition of intradialytic hypotension was chosen to be a nadir systolic blood pressure less than 90 mmHg, which has been associated with increased mortality. Alternatively, we used three other definitions: (1) either an SBP < 90 mmHg with any symptoms on chairside clinical notes, change in ultrafiltration rate, or intervention; (2) the KDOQI definition, defined as a drop in SBP ≥ 20 mmHg or a drop in MAP ≥ 10 mmHg with associated symptoms, change in ultrafiltration rate, or intervention; and (3) a split definition using the nadir SBP < 90 mmHg if the pre-treatment SBP was ≥ 100 mmHg or using the KDOQI definition if the pre-treatment SBP was < 100 mmHg. Note that we did not assess IDH defined by a relative reduction in blood pressure alone because we found that over 80% of sessions had a decrease in SBP of 20 mmHg or MAP of 10 mmHg, and thus it was important to combine these parameters with symptoms and interventions because the relative change in blood pressure was a poor discriminator of clinically significant IDH.

**Supplemental Table 2**: Full List of Potential Baseline Covariates.

| Demographic | Laboratory | Pre-Dialysis/Post-Dialysis Data |
|---|---|---|
| Age | Serum hemoglobin | **Blood Pressure subgroup#** |
| Sex | Serum hematocrit | Pre- / post-dialysis systolic blood pressure |
| Race | White blood cell count | Pre- / post-dialysis diastolic blood pressure |
| Ethnicity | Platelet count | |
| Height | Iron level | Pre- / post-dialysis heart rate |
| Weight | Ferritin level | Pre- / post-dialysis respiratory rate |
| Tobacco use | Transferrin saturation | Pre- / post-dialysis temperature |
| Dialysis vintage | Neutrophil-lymphocyte ratio (NLR) | Pre- and post-dialysis weight |
| Vascular access type | Serum glucose | Estimated dry weight |
| Diabetes status | Hemoglobin A1c | |
| Hypertension status | Serum sodium | |
| Cancer (diagnosis within 1 year) | Serum potassium | Ordered dialysis time |
| Chronic obstructive pulmonary disease | Serum calcium | Delivered dialysis time |
| | Serum phosphorus | Ordered dialysate temperature |
| **Cardiovascular disease subgroup#^** | Serum magnesium | Ordered dialysate sodium |
| Heart failure ^ | Intact parathyroid hormone | Ordered dialysate potassium |
| Ischemic heart disease ^ | Serum creatinine | Ordered dialysate calcium |
| Cerebrovascular disease ^ | Serum creatinine index (calculated) | Average blood flow rate |
| Peripheral arterial disease ^ | Serum albumin | Average dialysate flow rate |
| | Alanine transaminase (ALT) | |
| | Aspartate aminotransferase (AST) | **Dialysis clearance markers subgroup#** |
| | Total bilirubin | Dialysis treatment kecn |
| | Direct bilirubin | Dialysis treatment single-pool Kt/V |
| | Uric acid | Dialysis treatment urea reduction ratio |

| Dates of Events | Medications (dose & dates) | Dialysis Events |
|---|---|---|
| Dates of hospitalizations | Amlodipine | Administered iron dose |
| Dates of missed dialysis sessions | Amiloride | Administered Epogen dose |
| Dates of blood culture drawn | Atenolol | Administered vitamin D analog dose |
| Dates of antibiotic administration | Benazepril | Administered clonidine dose |
| Date of death | Bisoprolol | Administered nitroglycerine dose |
| Cause of death | Bumetanide | Administered saline total dose |
| | Carvedilol | |
| | Candesartan | Symptoms and interventions* |
| | Chlorthalidone | |
| | Clonidine | |
| | Diltiazem | |
| | Enalapril | |
| | Eplerenone | |
| | Felodipine | |
| | Fosinopril | |
| | Fosinopril | |
| | Furosemide | |
| | Hydralazine | |
| | Hydrochlorothiazide | |
| | Irbesartan | |
| | Labetalol | |
| | Lisinopril | |
| | Losartan | |
| | Methyldopa | |
| | Metolazone | |
| | Metoprolol | |
| | Minoxidil | |
| | Nicardipine | |
| | Nifedipine | |
| | Olmesartan | |
| | Spironolactone | |
| | Telmisartan | |
| | Torsemide | |
| | Valsartan | |
| | Verapamil | |

The full list of potential variables is listed above, separated by categories. #Variables within the same type are denoted under their subgroups; each variable within each subgroup was evaluated in univariate analyses and the variable with the best fit based on the Akaike Information Criterion (AIC) was chosen for subsequent analyses. ^Of note, the cardiovascular disease factors were excluded from analyses due to a high proportion of missing data. *Symptoms and interventions were adjudicated based on bedside provider notes (listed and explained in further detail in Supplemental Figure 1).

**Supplemental Table 3. Summary of Statistical Models Used in Each Analysis.**

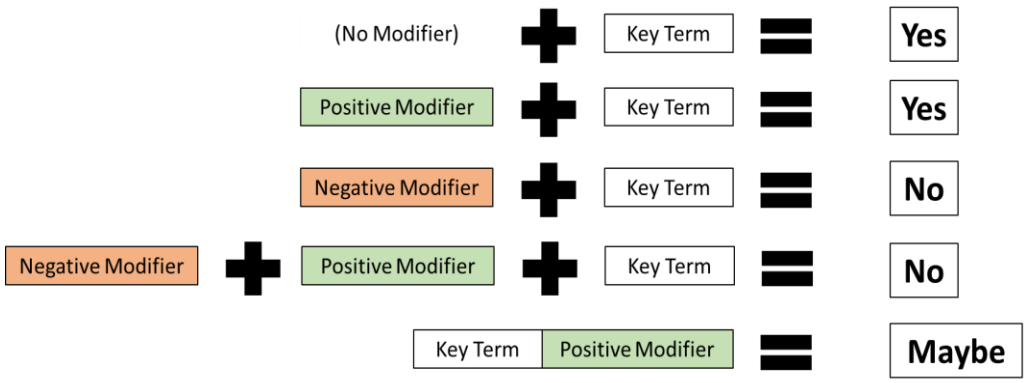
| Main Exposure | Main Outcome | Model | Adjustment and Covariates |
|---|---|---|---|
| Time | PRRi before IDH | Mixed effects linear regression | Time as a quadratic term |
| Clinical Factors | Starting PRRi (low < 0.3) | Simple logistic regression | Baseline covariates |
| Starting PRRi | Intradialytic hypotension | Cox proportional hazard regression | Adjusted for baseline confounding |
| Time-varying PRRi | Intradialytic hypotension | Cox proportional hazard regression with time-varying exposure and covariates | PRRi updated<br>Adjustment for baseline confounding |
| | | Marginal Structural Model<br>(Discrete Time Function) | PRRi updated<br>Covariates: SBP and UFR updated<br>Adjustment for baseline confounding<br>Adjustment for time-varying confounding |

Different statistical models were used to examine the different relationships between time, clinical factors, plasma refill rate index (PRRi), and intradialytic hypotension. The starting PRRi was defined as the ratio of the plasma refill rate to ultrafiltration rate (UFR) first 10-minute interval of each hemodialysis session. Time-varying PRRi was time-updated across each 15-minute interval throughout the full hemodialysis session. Baseline covariates include the following: age at dialysis initiation, sex, race, body mass index at dialysis initiation, dialysis vintage, diabetes status, serum albumin, serum creatinine index, pre-dialysis systolic blood pressure, interdialytic interval, dialysate temperature, average single-pool Kt/V. Time-varying covariates include systolic blood pressure and UFR and were also time-updated across each 15-minute interval throughout the full hemodialysis session. Adjustment for time-varying confounder-mediators refers to the use of inverse probability weighting as part of the methodology behind marginal structural modeling.

**Supplemental Table 3**: Summary of Associations of Plasma Refill Rate Index and Intradialytic Hypotension.

| Intradialytic Hypotension | Definition 1<br>SBP < 90<br>HR [95% CI] | Definition 2<br>SBP < 90 & sx<br>HR [95% CI] | Definition 3<br>ΔSBP ≥ 20 & sx or<br>ΔMAP ≥ 10 & sx<br>HR [95% CI] | Definition 4<br>Def 1 if $SBP_0$ > 100<br>Def 2 if $SBP_0$ < 100<br>HR [95% CI] |
|---|---|---|---|---|
| Baseline Cox Model (Model 1) | | | | |
| Low PRRi | 1.26 [1.18, 1.35] | 1.31 [1.21, 1.43] | 1.14 [1.11, 1.17] | 1.27 [1.19, 1.36] |
| Mid PRRi | Reference | Reference | Reference | Reference |
| High PRRi | 0.79 [0.73, 0.85] | 0.71 [0.65, 0.79] | 0.86 [0.83, 0.89] | 0.78 [0.72, 0.85] |
| Time-Updated Model (Model 2) | | | | |
| Low PRRi | 1.04 [1.02, 1.05] | | | |
| Mid PRRi | Reference | Reference | Reference | Reference |
| High PRRi | 1.07 [1.06, 1.08] | | | |
| Marginal Structural Models (Model 3A) | | | | |
| Low PRRi | 1.09 [1.02, 1.16] | 1.73 [1.62, 1.85] | 1.51 [1.46, 1.55] | 1.23 [1.16, 1.30] |
| Mid PRRi | Reference | Reference | Reference | Reference |
| High PRRi | 1.38 [1.30, 1.45] | 2.40 [2.25, 2.57] | 1.76 [1.71, 1.82] | 1.52 [1.44, 1.60] |
| Marginal Structural Models (Model 3B) | | | | |
| Drop in PRRi | 1.71 [1.57, 1.86] | 2.33 [2.14, 2.55] | 1.87 [1.79, 1.96] | 1.71 [1.57, 1.86] |
| Stable PRRi | Reference | Reference | Reference | Reference |
| Rise in PRRi | 1.52 [1.40, 1.65] | 2.62 [2.41, 2.84] | 1.96 [1.89, 2.05] | 1.55 [1.44, 1.68] |

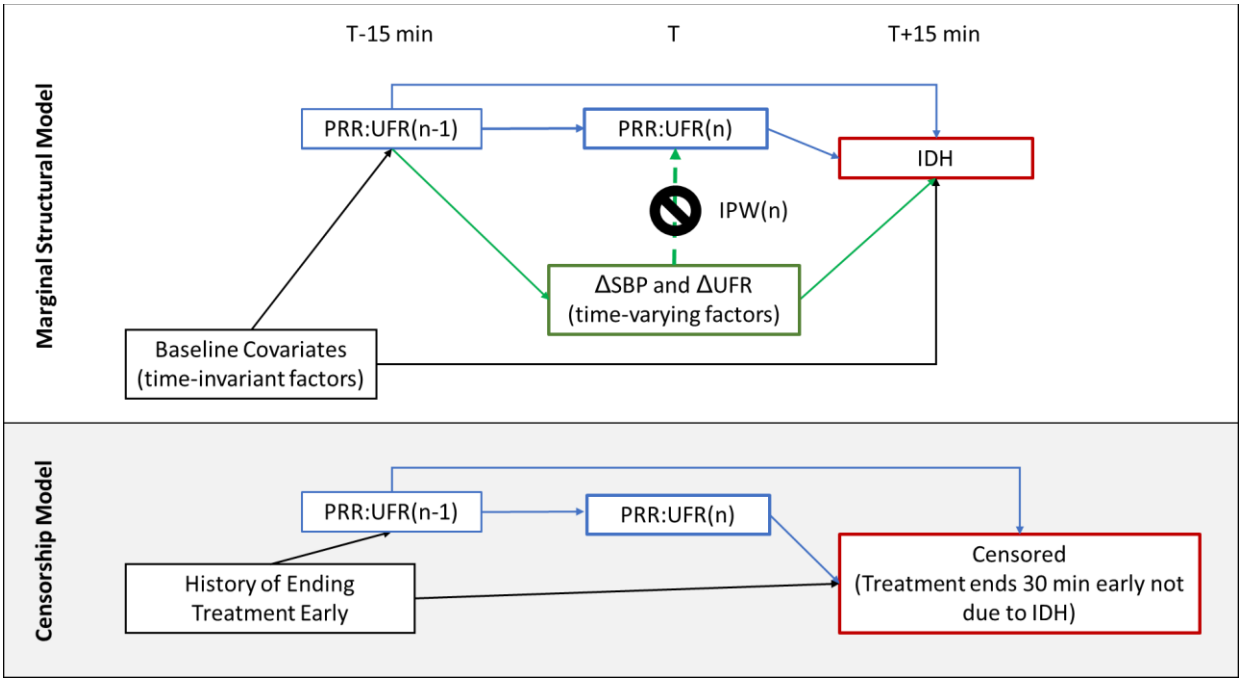
Summary of results from various models examining the relationship between plasma refill rate index (PRRi) and intradialytic hypotension (IDH) across various definitions of IDH. The baseline model (model 1) is a Cox proportional hazard regression using the starting PRRi and covariates defined at study entry and at the start of each hemodialysis session. The starting PRRi was defined as the ratio of plasma refill rate (PRR) to ultrafiltration rate (UFR) within the first 10-minute interval of each hemodialysis session, with low PRRi < 0.3 (bottom $25^{th}$ percentile) and high PRRi > 0.9 (top $25^{th}$ percentile) in reference to moderate PRRi ($0.3 \leq PRRi \leq 0.9$). The time-varying model (model 2) includes time-updated PRRi but only accounts for baseline confounding effects. Model 3A and 3B uses inverse probability weighting to account for the time-varying confounder-mediator effects from the time-updated changes in UFR and SBP through marginal structural modeling. Model 3A examined PRRi across each time interval, while Model 3B examined the interval change in PRRi between each interval. All effects are reported as hazard ratios (HR) with 95% confidence intervals (CI) and p-values. Of note*, model 3 (marginal structural model) forms a discrete time function which produces an odds ratio whose estimates approximate an HR. All models were adjusted for the following baseline confounders: age at dialysis initiation, sex, race, body mass index at dialysis initiation, dialysis vintage, diabetes status, serum albumin, serum creatinine index, pre-dialysis systolic blood pressure, interdialytic interval, dialysate temperature, average single-pool Kt/V. The definition of IDH were as follows: (1) nadir systolic blood pressure < 90 mmHg; (2) either an SBP < 90 mmHg with any symptoms on chairside clinical notes, change in ultrafiltration rate, or intervention; (3) the KDOQI definition, defined as a drop in SBP ≥ 20 mmHg or a drop in MAP ≥ 10 mmHg with associated symptoms, change in ultrafiltration rate, or intervention; and (4) a split definition using the nadir SBP < 90 mmHg if the pre-treatment SBP was ≥ 100 mmHg or using the KDOQI definition if the pre-treatment SBP was < 100 mmHg.



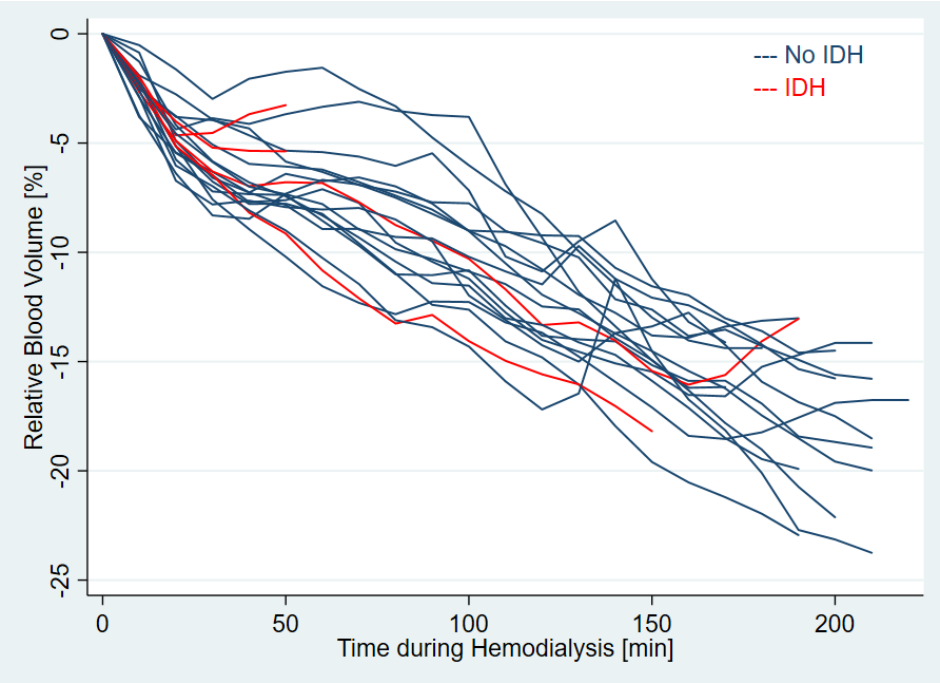

**Summary of Modifying and Key Terms used for Symptom and Intervention Adjudication Algorithm.**

| Symptom Adjudication | | Fluid Administration | | Other Intervention Terms | |
|---|---|---|---|---|---|
| **Associated Modifiers** | **Key Terms** | **Associated Modifiers** | **Key Terms** | **Associated Modifiers** | **Key Terms** |
| **Positive**:<br>• "c/o"<br>• "complaint of"<br>• "with"<br>• "due to"<br>• "d/t"<br>• " dt "<br>• "(+)"<br>• "experienced"<br><br>**Negative**:<br>• "no"<br>• "not"<br>• "without"<br>• "w/o"<br>• "w.o."<br>• "absence of"<br>• "(-)"<br>• "denies"<br>• "denied" | **Symptoms**:<br>• "nausea"<br>• "nauseous"<br>• "nauseated"<br>• "emesis"<br>• "vomit"<br>• "n/v"<br>• "n.v."<br>• "lightheaded"<br>• "light headed"<br>• "light-headed"<br>• "syncope"<br>• "seize"<br>• "altered"<br>• "unresponsive"<br>• "not responsive"<br>• "los"<br>• "cramp"<br>• "orthostatic"<br>• "symptomatic hypotension"<br>• "intradialytic hypotension" | **Positive:**<br>• "give"<br>• "given"<br>• "gave"<br>• "received"<br>• "repleted"<br>• "replaced"<br>• "administered"<br>• "improved w"<br>• "managed w"<br>• "treated w"<br>• "rx w"<br>• "relieved w"<br>• "paused"<br><br>**Negative:**<br>• "refused"<br>• "declined"<br>• "did not want" | **Included**:<br>• "n/s"<br>• "00cc"<br>• "00 cc"<br>• "00ml"<br>• "00 ml"<br>• "bolus"<br>• "saline"<br>• "fluid"<br><br>**Excluded**:<br>• "00 cc/m"<br>• "00 ml/m" | **Positive**:<br>• "altered"<br>• "adjusted"<br>• "goal unmet"<br>• "not able to meet"<br>• "not able to achieve"<br>• "unable to meet"<br>• "unable to tolerate"<br>• "unable to achieve"<br>• "unable to pull"<br>• "lowered"<br>• "decreased"<br>• "drop"<br>• "reduce"<br>• "turned off"<br><br>**Negative:**<br>• "tolerated"<br>• "goal met" | **Ultrafiltration**:<br>• "uf"<br>• "goal"<br>• "uf goal"<br>• "ufr goal"<br><br>**Others**:<br>• "midodrine"<br>• "trendelenburg" |

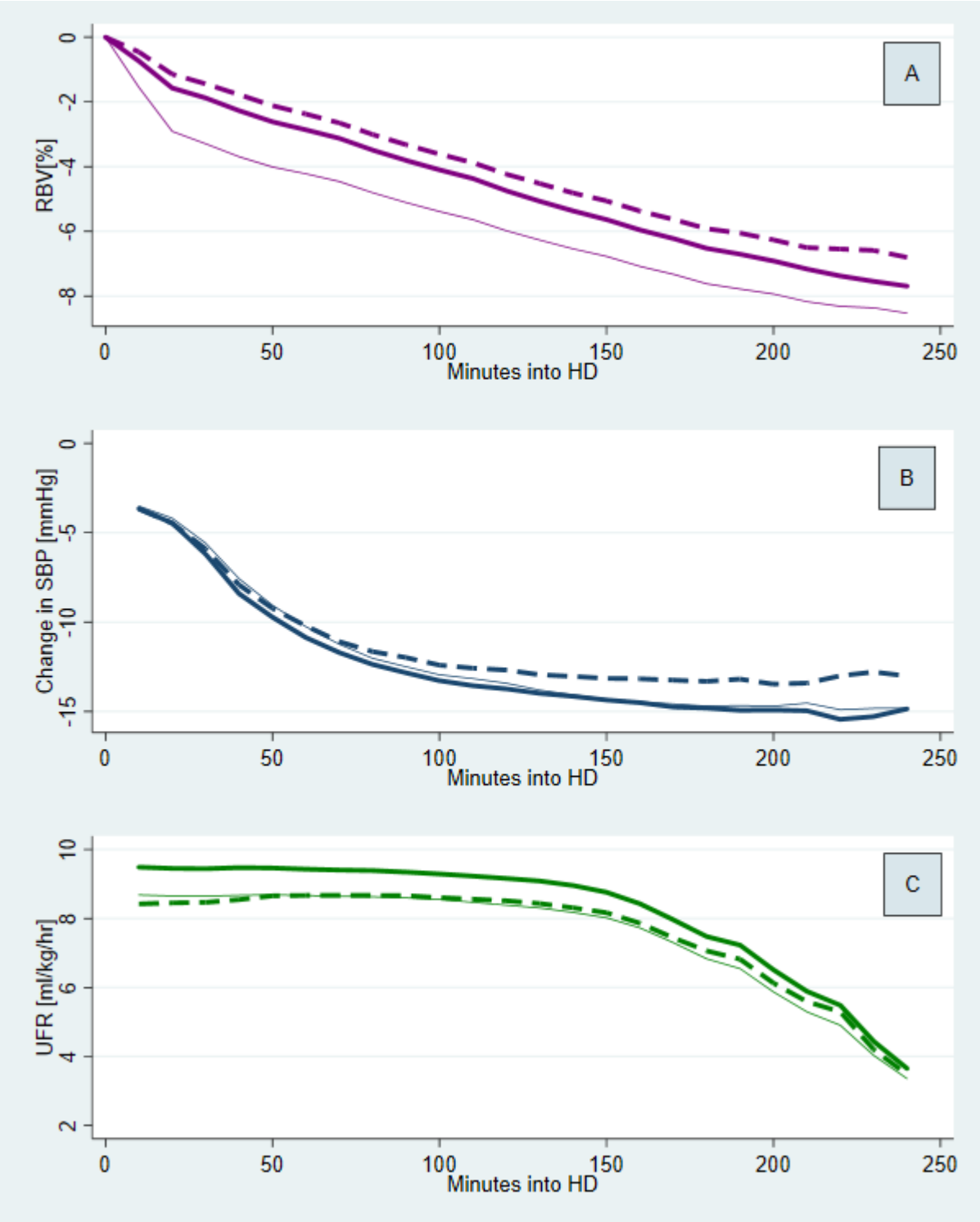
**Supplemental Figure 1: Details of Algorithm Used for Symptom Adjudication and Interventions**. All text was stored as string variables in STATA and converted to lowercase and parsed into phrases by commas, periods, and semi-colons. Leading, training, and consecutive internal blanks were removed. Each phrase was then searched for matches to key phrases (defined for each symptom and intervention) as well as for modifying and administration terms. The index location of each symptom or intervention in relation to modifying and administration terms were then used to determine whether a symptom or intervention occurred. If a key term was an intervention and the modifier was immediately following (for instance, "fluid administered") and no other negative modifiers were present, an intervention was deemed to have occurred; however, if the key term was a symptom, a symptom was deemed not to have occurred. Manual review of a random sample of 2% of the notes yielded a positive predictive value of 90% and negative predictive value of 96-98% for the algorithm-derived symptom and intervention ascertainment. Additionally, using the documented ultrafiltration data, we identified sessions with fluid administration or with cumulative fluid removed > 500 ml less than goal ultrafiltration volume.




**Supplemental Figure 2: Conceptual Diagram of the Marginal Structural Model**. The main marginal structural analysis is shown in the top panel. At any timepoint, the current plasma refill rate index (PRRi, or PRR:UFR) is informed by the preceding PRRi, which is also associated with the outcome of intradialytic hypotension (IDH(=). At each time point, factors such as changes in systolic blood pressure (ΔSBP) and ultrafiltration rate (ΔUFR) may be both a consequence of previous PRRi and a cause of changes in the current PRR. As a result, these factors introduce time-varying confounding and mediating effects on the relationship between the exposure of PRRi and outcome of IDH. We can adjust for these time-varying effects through the use of inverse probability weights (IPW) of each PRRi at each time interval. By incorporating the IPW, we can form a pseudopopulation in which these intermediate effects are no longer associated with the current exposure. This way, the time-varying confounders can be adjusted for similarly to baseline confounders after re-weighting. In the bottom panel, a censorship model was generated to estimate the probability of any given hemodialysis session ending at least 30 minutes early but not due to IDH (for instance due to patient request or vascular access complications). Predictors of censorship included baseline demographics and the history of prior treatments with early cessation of treatment. The probabilities generated from the censorship model were then incorporated with the IPW from the original marginal structural model to form the final weights for the analysis.




**Supplemental Figure 3: Illustrative Example of Relative Blood Volume Trajectories Between Different Hemodialysis Sessions Within the Same Patient**. Each line represents the relative blood volume (expressed as a percentage) reduction over time during a single hemodialysis session, with lines in blue representing sessions without intradialytic hypotension (IDH) and lines in red representing sessions with IDH (defined as a systolic blood pressure < 90 mmHg and truncated at the time of IDH).




**Supplemental Figure 4: Summary of Intradialytic Metrics During Hemodialysis Across the Study Population, Stratified by Starting Plasma Refill Rate Index Category**. The population was grouped into three categories based on the starting plasma refill rate index (PRRi): low (PRRi < 0.3) shown as a thin solid line, middle (PRRi 0.3-0.9) shown as a thick solid line, and high (PRRi > 0.9) shown as a thick dashed line. The panels provide the population-average for four different intradialytic measures throughout hemodialysis: (A) relative blood volume (RBV), (B) change in systolic blood pressure (SBP), and (C) ultrafiltration rate (UFR).