

## **Predialysis Systolic Blood Pressure Variability and Outcomes in Incident Hemodialysis Patients: The DEcide Network Patient Outcomes in ESRD Study**

### **Supplemental Materials**

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### Blood-Pressure Variability Metric

Blood pressure variability (BPV) was assessed using the standard deviation (SD) of the residual from a model fit to the logarithm of a patient's pre-dialysis systolic blood pressure values over time, separately within each 3-month interval from the start of dialysis.

For this BPV-assessment model, assume the  $i$ -th patient has blood pressure measurements  $y_{i1}, \dots, y_{iT}$  over  $T$  successive dialysis sections. The patient's blood pressure change over time can be characterized by the following equation:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij} \quad (1)$$

where  $t_{ij}$  is the time of person  $i$ 's  $j$ -th evaluation,  $\beta_1 t_{ij}$  is the mean trend by which the blood pressure changes over time,  $b_{i1} t_{ij}$  is the deviation between the trend of patient  $i$  and the mean trend. We assume that  $b_{i0}$ ,  $b_{i1}$ , and  $\varepsilon_{ij}$  are normally distributed with mean 0 and  $\varepsilon$ s independent of the  $b$ s.

The observed residual for patient  $i$  at time  $j$ , denoted  $e_{ij}$ , is the vertical distance between the observed and predicted BP measurement. The SD of a subject's residuals from the model fit to a patient's blood pressure measures over time within a time period represent the BPV metric for that patient within that 3-month interval.

Subjects with high blood pressure levels may also exhibit high levels of variability. As we only want to assess the associations of the BPV and not the BP itself, we log-transformed the pre-dialysis systolic blood pressure to equalize the variability measures across overall blood pressure levels. **eFigure 2** demonstrates that the BPV metric is independent of the systolic BP level.

We fit model (1) within rolling 3-month windows for each patient's full person-time. In each case, we specify an unstructured variance-covariance matrix for random effects. Parameter estimation is achieved using the method of maximum-likelihood.

### Assessing factors associated with Blood-Pressure Variability

The effect of covariates on blood-pressure variability was characterized by modeling the 3-6 month window of BPV as a function of covariates using a linear mixed effects model with a random intercept to account for clustering by clinics. We considered patients to be nested within clinics, and referred to the clinics as second-level units and patients as first-level units. The model can be written as follows:

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + u_{0j} + \varepsilon_{ij} \quad (2)$$

where  $y_{ij}$  is the BPV metric and  $x_{ij}$  the value of an explanatory variable for the  $i$ -th patient in the  $j$ -th clinic. The coefficient  $\beta_1$  is assumed to be the same at all the clinics while the random variable  $u_{0j}$  allows the  $j$ -th clinic's intercept to vary from the overall population intercept term  $\beta_0$ . Model (2) is easily extended to include the several subject-level covariates previously described.

### Assessing the impact of Blood-Pressure Variability on overall and cause-specific survival

We modeled overall and cause-specific survival using discrete time Cox models fit by logistic regression with a complementary log-log link. Models were fit using Generalized Estimating Equations (GEE) to allow for clustering by clinic. The discrete time intervals were 30

days. The BPV was calculated as above over rolling 3-month windows for the 3 months prior to the at-risk interval of every month in each patient's person-time. The covariates were partitioned into intervals as per the data section above. For both models (2) and (3), model checking was done by examining residual diagnostic plots. All analyses were conducted using SAS 9.2, with SAS PROC MIXED procedure to fit mixed effect models, and SAS PROC GENMOD to fit the GEE models.

**eTable 1: Comparison of 10,467 Patients Starting Dialysis at Dialysis Clinic, Inc. between 2006-2008 with All Patients Starting Dialysis in the US between 2006-2009**

<b>Demographics</b>		<b>DCI</b>	<b>USRDS</b>
		<b>2006-2008</b>	<b>2006-2009</b>
<b>N</b>		10,467	321,988
<b>Age, years</b>		62.3 ± 15.1	63.0 ± 15.3
<b>Sex, % male</b>		55.6	56.1
<b>Race</b>			
	White, %	62.5	65.7
	Black, %	33.5	28.9
	Other, %	4.0	5.4
<b>Ethnicity, % Hispanic</b>		5.1	13.7
<b>Insurance Status, %</b>			
	Medicare	57.5	56.5
	Medicaid	25.7	25.0
	Other	45.5	49.3
	None	7.8	7.7
<b>Unemployed, %</b>		20.3	20.6
<b>Comorbidities, %</b>			
	Congestive Heart Failure	34.1	33.1
	Atherosclerotic Heart Disease	23.7	21.7
	Other cardiac disease	21.5	16.4
	Cerebrovascular disease	11.9	9.6
	Peripheral Vascular disease	15.4	14.4
	Hypertension	86.4	84.3
	Amputation	3.5	3.2
	Diabetes, currently on insulin	37.6	35.5
	Diabetes, currently on oral medications	12.4	13.4
	Diabetes, without medications	5.5	5.2

	Diabetic retinopathy	10.1	8.7
	Chronic Obstructive Pulmonary Disease	11.5	9.1
	Current Smoker	9.8	6.3
	Malignant Neoplasm	9.3	7.4
	Toxic Nephropathy	0.5	0.5
	Alcohol Dependence	2.1	1.6
	Drug Dependence	1.9	1.4
	Inability to ambulate	5.7	7.0
	Inability to transfer	3.6	3.5
	Needs assistance with daily activities	13.7	11.4
	Institutionalized	8	7.1
	Assisted living	0.8	0.6
	Nursing home	7.7	6.8
	Other	0.5	0.5
<b>Pre-Dialysis Care Parameters</b>			
	Pre-dialysis erythropoietin use, %	31.4	28.5
	Pre-dialysis Nephrology Care, % yes	65.8	56.8
	First Access		
	Arteriovenous Fistula	14.6	12.6
	Graft	3.9	3.5
	Catheter	75	76.8
	Other	0.4	1.1
	Missing/Unknown	6	6.0
	Serum Albumin, g/dL	3.1 ± 0.7	3.1 ± 0.7
	Hemoglobin, g/dL	10.0 ± 1.6	10.0 ± 1.7
	Serum Creatinine, mg/dL	6.6 ± 3.4	6.4 ± 3.4
	eGFR, mL/min/1.73 m <sup>2</sup>	10.4 ± 4.7	10.8 ± 4.9
	HbA1c	7.2 ± 5.4	7.3 ± 6.1
	Total Cholesterol	155.6 ± 60.0	157.1 ± 59.0
<b>ESRD-Related</b>			

	Cause of ESRD, %		
	Diabetes	45.6	45.4
	Hypertension	27.2	28.3
	Glomerulonephritis	9	8.5
	Other	18.2	17.9
	Modality, %		
	Hemodialysis	93.8	94.1
	Peritoneal Dialysis	6	5.8
	Other	0.2	0.1
	Body Mass Index, kg/m <sup>2</sup>	28.7 ± 7.7	28.8 ± 7.7
	Primary Dialysis Setting, % Dialysis Facility/Center	93.8	93.3

Data are presented as mean (standard deviation) or column percent unless otherwise specified.

*Abbreviations:* Dialysis Clinic, Inc., DCI; estimated glomerular filtration rate, eGFR; end-stage renal disease, ESRD

**eTable 2: Baseline Characteristics of 11,291 Incident Hemodialysis Patients by Categories of Predialysis Systolic Blood Pressure**

	Categories of Baseline Systolic Blood Pressure (range, mm Hg)						
	Category 1 (Lowest)	Category 2	Category 3	Category 4	Category 5	Category 6 (Highest)	p <sup>1</sup>
<b>Blood Pressure Range, mm Hg</b>	< 125	125 - 133	133-145	145-155	155-167	> 167	
<b>N (%)</b>	1170 (10.4)	1065 (9.4)	2411 (21.4)	2185 (19.4)	2179 (19.3)	2281 (20.2)	
<b>Demographics</b>							
Age, years	67.9 ± 13.5	65.0 ± 14.7	62.8 ± 15.5	61.6 ± 14.7	60.2 ± 14.6	58.6 ± 14.1	<.0001
Sex, % male	61	58.8	57.2	55.4	53	48.4	<.0001
Race							<.0001
White, %	72.2	66.2	60.7	56.8	54.4	50.8	
Black, %	23.9	30	35.1	38.6	40.5	45.7	
Other, %	3.8	3.8	4.2	4.6	5.1	3.5	
Ethnicity, % Hispanic	4.4	6.3	5.6	5.5	6.2	5.7	0.3126
Race-Ethnicity							<.0001
Black Hispanic, %	0.3	0.1	0.2	0.1	0.2	0.4	
Black Non-Hispanic, %	23.7	29.9	34.9	38.5	40.3	45.3	
Other, %	3.8	3.8	4.2	4.6	5.1	3.5	
White Hispanic, %	3.8	5.7	5.1	5	5.7	5	
White Non-Hispanic, %	68.4	60.5	55.6	51.8	48.7	45.7	
<b>Clinical</b>							
Diabetes, %	59.8	60.1	58.8	63.1	69	73.8	<.0001
Cardiovascular Disease, %	69.1	62.9	54.3	53.2	53.7	52.3	<.0001
Congestive Heart Failure, %	62.5	49	43.9	42.5	42.8	45.5	<.0001
Comorbidity Index, %							<.0001
0-3	26.1	38	42.6	44.6	44.7	43.2	
4-6	23	23.6	25.3	25.4	27.3	30	
7-9	24.8	21.8	19.3	18.9	18	18	
>=10	26.1	16.6	12.8	11.1	9.9	8.7	





%							
Any $\beta$ -blocker Regimen (without RAS)	50.4	41.2	38.2	33.5	28	24.2	
Any RAS Regimen (without $\beta$ -blocker)	11	15.2	15.3	16.8	20.1	20.2	
$\beta$ -blocker +RAS Combination	24.1	27.7	30.2	33.9	38.8	45.4	
Other Medications and Combinations	14.4	15.9	16.3	15.8	13	10.2	

Data are presented as mean (standard deviation) or column percent unless otherwise specified.

*Abbreviations:* end-stage renal disease, ESRD; Renin-Angiotensin System drug (RAS)

Q1.1 to Q5 refers to categories of systolic BP at baseline [quintiles (fifths) of systolic blood pressure with the lowest quintile (Q1) further subdivided into two categories at the median (Q1.1 and Q1.2)].

Conversion Factors: albumin in g/dL to g/L, x10; hemoglobin in g/dL to g/L, x10. No conversion is necessary for ferritin in ng/mL and  $\mu$ g/L.

<sup>1</sup> P-values for continuous variables are p-trend obtained from linear regression and those for categorical variables are obtained from chi-square test.

**eTable 3: Association of Predialysis Systolic Blood Pressure Variability Analyzed as Tertiles and Outcomes among 11,291 Incident Hemodialysis Patients**

	Tertiles	Events	Crude <sup>1</sup>		Minimally Adjusted <sup>2</sup>		Fully Adjusted <sup>3</sup>	
			HR (95% CI)	p	HR	p	HR	p
<b>All-Cause Mortality</b>								
	Lowest	737	Reference		Reference		Reference	
	Middle	999	1.35 (1.23, 1.48)	<.0001	1.36 (1.23, 1.49)	<.0001	1.23 (1.11, 1.35)	<.0001
	Highest	1464	2.06 (1.88, 2.26)	<.0001	2.22 (2.01, 2.44)	<.0001	1.56 (1.41, 1.73)	<.0001
<b>Cardiovascular Mortality</b>								
	Lowest	375	Reference		Reference		Reference	
	Middle	502	1.32 (1.15, 1.51)	<.0001	1.34 (1.17, 1.53)	<.0001	1.21 (1.05, 1.38)	0.0061
	Highest	721	1.97 (1.74, 2.24)	<.0001	2.14 (1.88, 2.43)	<.0001	1.55 (1.36, 1.76)	<.0001
<b>Cardiovascular Events</b>								
	Lowest	1260	Reference		Reference		Reference	
	Middle	1492	1.17 (1.09, 1.25)	<.0001	1.15 (1.08, 1.24)	<.0001	1.08 (1.01, 1.16)	0.0338
	Highest	1779	1.45 (1.34, 1.56)	<.0001	1.48 (1.36, 1.6)	<.0001	1.23 (1.13, 1.33)	<.0001

*Abbreviations:* Hazard Ratio, HR; Confidence Interval, CI

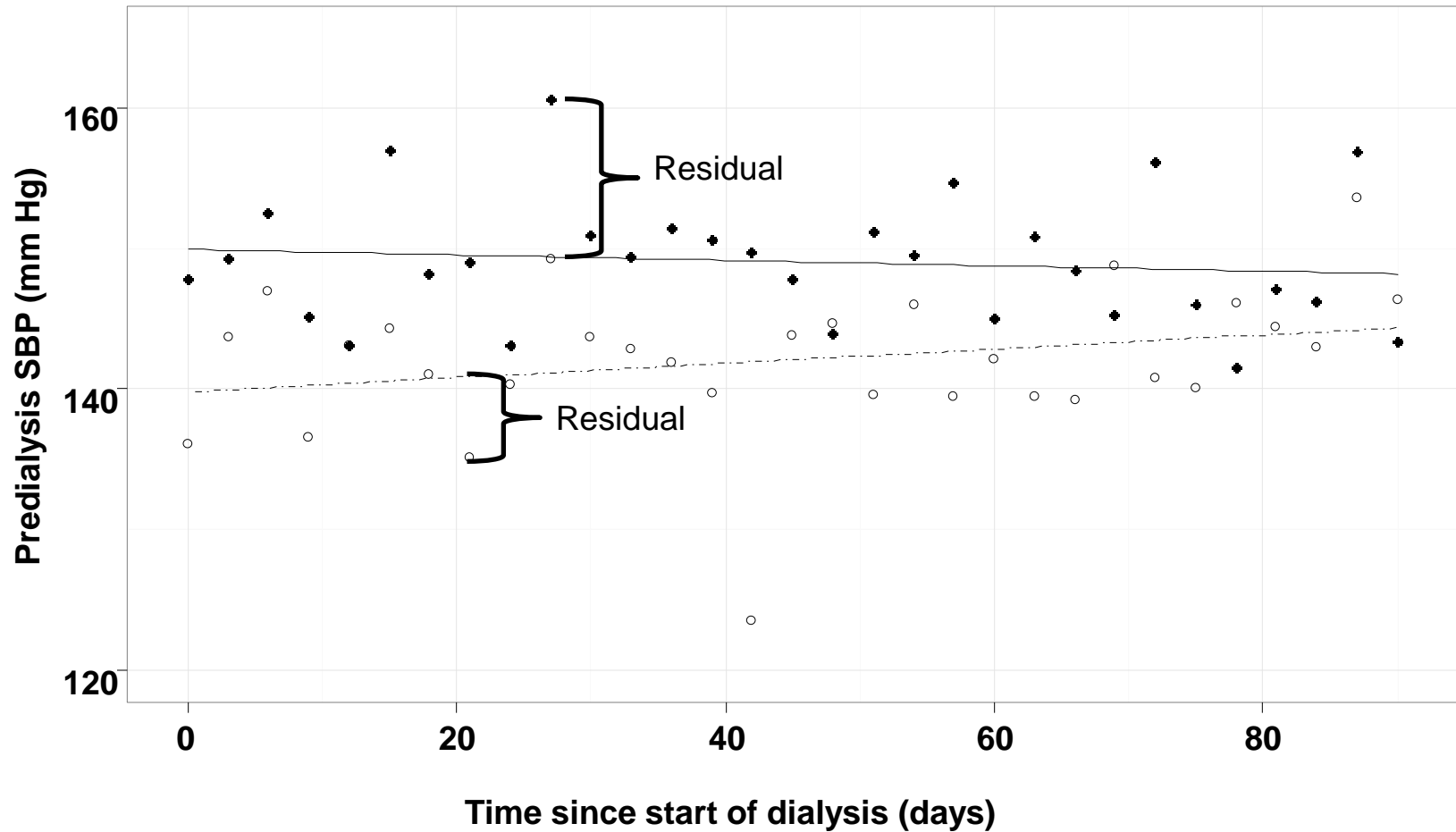
Hazard ratio compared to the lowest tertile of predialysis systolic blood pressure variability metric

<sup>1</sup> Unadjusted model

<sup>2</sup> Adjusted for age, sex, race and ethnicity

<sup>3</sup> Adjusted for demographic characteristics (age, sex, race and ethnicity), clinical factors (history of diabetes, cardiovascular disease, congestive heart failure, comorbidity index and body mass index), end-stage renal disease related factors (cause of end-stage renal disease, Kt/V and relative fluid removal), laboratory measurements (serum albumin, calcium-phosphate product, hemoglobin and ferritin) and antihypertensive medications.

eFigure 1



**eFigure 2**

