

Supplementary Table 1. The Effect of Residual Function on Plasma Solute Levels

Solute	All Subjects				Subjects Without Residual Kidney Function				p value Interaction RKF and Group
	Plasma Level Standard Kt/V <sub>urea</sub> n=643	Plasma Level High Kt/V <sub>urea</sub> n=638	Relative Difference and Confidence Interval (%)	p value	Plasma Level Standard Kt/V <sub>urea</sub> n=469	Plasma Level High Kt/V <sub>urea</sub> n=460	Relative Difference and Confidence Interval (%)	p value	
Urea Nitrogen (mg/dl)	63 ± 19	57 ± 18	-9.4 (-12.5, -6.3)	<0.001	62 ± 19	57 ± 19	-8.6 (-12.3, -4.8)	<0.001	0.408
p-Cresol Sulfate (mg/dl)	3.3 ± 1.7	3.4 ± 1.7	2.2 (-3.6, 7.8)	0.463	3.2 ± 1.8	3.4 ± 1.7	4.3 (-2.8, 11.3)	0.235	0.254
Indoxyl Sulfate (mg/dl)	2.7 ± 1.3	2.4 ± 1.1	-11.0 (-15.7, -6.4)	<0.001	2.7 ± 1.3	2.5 ± 1.1	-8.0 (-13.5, -2.4)	0.005	0.063
Hippurate (mg/dl)	5.5 ± 4.6	5.3 ± 4.0	-4.1 (-12.4, 4.3)	0.338	6.0 ± 4.7	5.7 ± 4.1	-5.3 (-14.6, 4.1)	0.269	0.467
Phenylacetylglutamine (mg/dl)	4.6 ± 3.0	4.3 ± 2.6	-6.8 (-13.3, -0.2)	0.04	4.9 ± 3.2	4.4 ± 2.6	-8.7 (-16.1, -1.3)	0.021	0.233
TMAO (µM)	107 ± 63	97 ± 65	-8.9 (-15.3, -2.4)	0.007	109 ± 63	99 ± 68	-9.0 (-16.4, -1.5)	0.018	0.849
Methylguanidine (µM)	8.7 ± 4.7	6.7 ± 3.8	-22.5 (-27.3, -17.8)	<0.001	8.9 ± 4.9	7.0 ± 4.1	-21.4 (-27.0, -15.9)	<0.001	0.839
ADMA (µM)	0.92 ± 0.24	0.92 ± 0.23	0.5 (-2.2, 3.2)	0.735	0.93 ± 0.23	0.93 ± 0.23	0 (-3.3, 3.3)	0.989	0.545
SDMA (µM)	4.4 ± 1.4	4.2 ± 1.3	-4.0 (-7.4, -0.7)	0.018	4.5 ± 1.5	4.2 ± 1.3	-5.1 (-9.0, -1.3)	0.009	0.234

RKF, residual kidney function. Values for all subjects (as reported in Table 2 in the body of the report) are compared with values in subjects reported to have no residual renal function. In both cases, the observed relative differences are calculated as:  $((\text{High Kt/V}_{\text{urea}} \text{ group} / \text{standard Kt/V}_{\text{urea}} \text{ group}) - 1) * 100$ . Confidence intervals and p values are calculated using bootstrapping with 2000 replicates. Negative values represent lower concentration in the higher Kt/V<sub>urea</sub> group. The 352 patients classified as having residual function were those for whom values for pre- and post-BUN, urine volume, urine ureaN, and urine collection interval were recorded. Results were no different when comparison were made classifying a total of 444 patients as having residual function including patients who had missing values for some of these parameters.

**Supplementary Table 2. The Effect of A Higher Kt/V<sub>urea</sub> on Pretreatment Plasma Solute Levels with and without Adjustment for Demographic Variables and Plasma Albumin**

	Relative Difference, % (95% CI)		Relative Difference, % (95% CI)	
	Unadjusted	p value	Adjusted for age, sex, race, vintage, diabetes, and plasma albumin	p value
Urea Nitrogen	- 9.4 (-12.5, -6.3)	<0.001	-9.6 (-12.7, -6.6)	<0.001
p-Cresol Sulfate	2.2 (-3.6, 8.0)	0.463	2.5 (-3.1, 8.0)	0.383
Indoxyl Sulfate	- 11.0 (-15.6, -6.4)	<0.001	-11.1 (-15.5, -6.8)	<0.001
Hippurate	- 4.1 (-12.4, 4.2)	0.338	-4.4 (-12.7, 3.9)	0.298
Phenylacetylglutamine	- 6.8 (-13.3, -0.2)	0.042	-6.5 (-12.9, -0.02)	0.049
TMAO	- 8.9 (-15.3, -2.4)	0.007	-8.6 (-14.7, -2.5)	0.006
Methylguanidine	- 22.5 (-27.3, -17.7)	<0.001	-22.4 (-26.6, -18.2)	<0.001
ADMA	+ 0.5 (-2.2, 3.2)	0.735	0.4 (-2.4, 3.1)	0.793
SDMA	- 4.0 (-7.4, -0.7)	0.018	-4.2 (-7.3, -1.1)	0.008

The relative differences are calculated as:  $((\text{High Kt/V}_{\text{urea}} \text{ group} / \text{standard Kt/V}_{\text{urea}} \text{ group}) - 1) * 100$ . Confidence intervals and p values are calculated using bootstrapping with 2000 replicates. Negative values represent lower concentration in the higher Kt/V<sub>UREA</sub> group. The unadjusted differences are the same as those presented in Table 2 in the body of the report. The relative difference in the adjusted model represents modeled solute concentrations at average levels of covariates. Adjustment for demographic factors and plasma albumin did not alter the differences between the High Kt/V<sub>urea</sub> and Standard Kt/V<sub>urea</sub> groups.

**Supplementary Table 3. The Effect of A Higher  $Kt/V_{urea}$  on Pre-Treatment Plasma Free Solute Levels**

<b>Solute</b>	<b>Plasma Level Standard <math>Kt/V_{urea}</math></b>	<b>Plasma Level High <math>Kt/V_{urea}</math></b>	<b>Relative Difference and Confidence Interval (%)</b>	<b>p value</b>
p-Cresol Sulfate free (mg/dl)	0.36 ± 0.30	0.40 ± 0.35	10.0 (-0.09, 20.1)	0.052
p-Cresol Sulfate % free	10.7 ± 5.9	11.6 ± 7.1	7.7 (0.6, 14.8)	0.033
p-Cresol Sulfate free selected (mg/dl)	0.32 ± 0.21	0.33 ± 0.21	2.4 (-5.5, 10.2)	0.551
p-Cresol Sulfate % free selected	9.3 ± 2.7	9.5 ± 2.8	1.6 (-1.9, 5.2)	0.370
Indoxyl Sulfate free (mg/dl)	0.28 ± 0.19	0.27 ± 0.19	-5.1 (-12.3, 2.2)	0.169
Indoxyl Sulfate % free	10.2 ± 4.9	11.0 ± 5.8	7.6 (1.4, 13.7)	0.016
Indoxyl Sulfate free selected (mg/dl)	0.27 ± 0.18	0.24 ± 0.15	-10.2 (-16.6, -3.7)	0.002
Indoxyl Sulfate % free selected	9.6 ± 3.4	10.0 ± 3.8	4.1 (-0.4, 8.5)	0.073
Hippurate free all values (mg/dl)	3.8 ± 3.5	3.7 ± 3.2	-2.5 (-12.3, 7.3)	0.614
Hippurate free % free all values	67 ± 23	67 ± 17	0.1 (-3.2, 3.3)	0.976

The observed relative differences are calculated as:  $((\text{High } Kt/V_{urea} \text{ group} / \text{standard } Kt/V_{urea} \text{ group}) - 1) * 100$ . Confidence intervals and p values are calculated using bootstrapping with 2000 replicates. Negative values represent lower concentration in the high  $Kt/V_{urea}$  group. The measured free fractions for PCS and IS in some HEMO samples were greatly in excess of those seen in samples obtained locally. We suspect that some high free fractions were caused by sample collection after administration of heparin, which has been shown to

elevate solute free fractions by releasing free fatty acids from triglycerides in vitro.<sup>1</sup> A change in albumin properties in stored samples could also have effected solute binding. For comparison, the analysis was performed again on selected values for p-cresol sulfate and indoxyl sulfate which were obtained by removing samples for which free fractions exceeded the average plus 4 standard deviations. Excluded samples numbered 58 and 85 for free PCS and 24 and 38 for free IS in the standard and high  $Kt/V_{\text{urea}}$  groups, respectively.

**Supplementary Table 4. Associations of Solute Levels with Demographic Factors and Plasma Albumin**

Outcome Variables	Predictor Variables											
	Age Per 10 years higher		Male vs. Female		Black vs. Non-Black		DM vs. No DM		Vintage Per 1 year higher		Albumin Per 1 g/dL higher	
	Natural Scale	Log-Std (SE=0.02)	Natural Scale	Log-Std (SE=0.06)	Natural Scale	Log-Std (SE 0.06)	Natural Scale	Log-Std (SE 0.06)	Natural Scale	Log-Std (SE=0.01)	Natural Scale	Log-Std (SE=0.07)
<b>UN</b> mg/dl	-1.26 (0.37)**	-0.06**	2.51 (1.1)*	0.13*	-3.72 (1.08)***	-0.22***	-1.40 (1.05)	-0.06	-0.05 (0.13)	0.0001	8.02 (1.34)***	0.50***
<b>PCS</b> mg/dl	0.06 (0.03)	0.03	-0.05 (0.10)	0.001	0.20 (0.10)*	0.12*	0.60 (0.09)***	0.27***	-0.05 (0.01)***	-0.03***	0.69 (0.12)***	0.43***
<b>IS</b> mg/dl	-0.09 (0.02)***	-0.05*	0.31 (0.07)***	0.25***	0.08 (0.07)	0.05	-0.33 (0.07)***	-0.17**	0.04 (0.01)***	0.02*	0.85 90.09)***	0.70***
<b>HIPP</b> mg/dl	-0.25 (0.08)**	-0.08***	0.32 (0.24)	0.10	-0.82 (0.25)**	-0.19**	-0.66 (0.24)**	-0.18**	0.14 (0.03)***	0.05***	1.91 (0.30)***	0.52***
<b>PAG</b> mg/dl	0.05 (0.06)	0.02	-0.23 (0.16)	-0.11	-0.06 (0.16)	0.01	0.59 (0.16)***	0.18**	0.04 (0.02)*	0.01*	0.12 (0.21)	0.13
<b>TMAO</b> $\mu$ M	1.32 (1.28)	0.02	-0.34 (3.60)	0.05	4.45 (3.69)	0.02	8.40 (3.58)*	0.23***	0.58 (0.43)	0.001	4.70 (4.63)	0.17*
<b>MG</b> $\mu$ M	-0.91 (0.08)***	-0.18***	1.00 (0.25)***	0.20***	0.94 (0.25)***	0.27	-2.09 (0.24)***	-0.49***	0.20 (0.03)***	0.05***	2.43 (0.31)***	0.67***
<b>ADMA</b> $\mu$ M	-0.01 (0.005)*	-0.05**	-0.03 (0.01)*	-0.15**	-0.05 (0.01)***	-0.24	0.01 (0.01)	0.07	0.01 (0.01)***	0.04***	-0.03 (0.02)	-0.14
<b>SDMA</b> $\mu$ M	-0.28 (0.03)***	-0.20***	0.22 (0.08)**	0.19**	0.01 (0.08)	0.05	-0.76 (0.07)***	-0.58***	0.07 (0.01)***	0.05***	0.55 (0.10)***	0.44***

Values are  $\beta$  coefficients (SE). \*  $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .  $\beta$  coefficients from "Log-Std" models represent changes in natural log-standardized solute concentrations with changes in age, sex, race, diabetes, vintage and albumin as indicated in the Table.

**Supplementary Table 5. The Effect of Adjustment for nPCR on the Effect of A Higher Kt/V<sub>urea</sub>**

	<b>Unadjusted</b>	<b>Adjusted for nPCR</b>
<b>Solute</b>	<b>Relative Difference Pre-Treatment and Confidence Interval (%)</b>	<b>Relative Difference Pre-Treatment and Confidence Interval (%)</b>
Urea Nitrogen	-9 (-12, -6)	-16 (-17, -14)
p-Cresol Sulfate	2 (-4, 8)	0 (-6, 5)
Indoxyl Sulfate	-11 (-16, -6)	-14 (-18, -9)
Hippurate total	-4 (-12, 4)	-7 (-15, 1)
Phenylacetylglutamine	-7 (-13, -0)	-9 (-15, -3)
TMAO	-9 (-15, -2)	-11 (-17, -6)
Methylguanidine	-22 (-27, -18)	-26 (-30, -21)
ADMA	0 (-2, 3)	1 (-2, 4)
SDMA	-4 (-7, -1)	-5 (-8, -2)

Observed relative difference is calculated as:  $((\text{High Kt/V}_{\text{UREA}} \text{ group} / \text{standard Kt/V}_{\text{UREA}} \text{ group}) - 1) * 100$ . Confidence interval and p values are calculated using bootstrapping with 2000 replicates. Negative values represent lower concentration in the higher Kt/V<sub>urea</sub> group. The changes resulting from adjustment for nPCR reflect slightly higher nPCR calculated in the high Kt/V<sub>urea</sub> group at the time of study. The adjustment must be interpreted with caution. In particular, the nPCR values are derived from plasma urea nitrogen values in a way that tends to associate urea nitrogen with nPCR independent of the biologic association of plasma urea nitrogen with protein catabolism.<sup>2</sup> The extent to which the increase in nPCR in the high dose group reflected an increase in protein catabolism in HEMO subjects is uncertain.<sup>3</sup> It is notable that there was no increase in protein ingestion as assessed by dietary record at one year or other intervals.

**Supplementary Table 6. Plasma Solute Levels in High and Low Flux Groups**

<b>Solute</b>	<b>Plasma Level Low Flux n=642</b>	<b>Plasma Level High Flux n=639</b>	<b>Relative Difference and Confidence Interval (%)</b>	<b>p value for relative difference</b>
Urea Nitrogen (mg/dl)	60 ± 19	59 ± 19	-1.2 (-4.6, 2.1)	0.48
p-Cresol Sulfate (mg/dl)	3.4 ± 1.7	3.3 ± 1.7	-0.8 (-6.4, 4.8)	0.78
Indoxyl Sulfate (mg/dl)	2.6 ± 1.2	2.5 ± 1.2	-2.9 (-7.9, 2.2)	0.27
Hippurate (mg/dl)	5.6 ± 4.3	5.3 ± 4.2	-5.7 (-14.0, 2.7)	0.18
Phenylacetylglutamine (mg/dl)	4.7 ± 2.8	4.3 ± 2.8	-7.6 (-14.0, -1.3)	0.02
TMAO (μM)	100 ± 60	104 ± 68	3.6 (-3.4, 10.7)	0.32
Methylguanidine (μM)	8.1 ± 4.7	7.4 ± 4.1	-8.7 (-14.7, -2.8)	0.004
ADMA (μM)	0.93 ± 0.25	0.91 ± 0.21	-2.3 (-5.0, 0.3)	0.08
SDMA (μM)	4.4 ± 1.4	4.1 ± 1.3	-7.6 (-10.9, -4.4)	<0.001

The relative differences for the two treatment groups are calculated as: ((High Flux group /Low Flux group) – 1) \*100. Confidence intervals and p values are calculated using bootstrapping with 2000 replicates. Negative values represent lower concentration in the high flux group.



**Supplementary Table 7. Measurements in Local Hemodialysis Subjects**

<b>Solute</b>	<b>Clearance ml/min</b>	<b>Reduction Ratio %</b>	<b>Vd / Body Weight l/kg</b>
p-Cresol Sulfate	23 ± 5	31 ± 13	0.17 ± 0.08
Indoxyl Sulfate	32 ± 6	36 ± 13	0.18 ± 0.05
Hippurate	125 ± 10	71 ± 5	0.25 ± 0.03
Phenylacetylglutamine	174 ± 19	80 ± 5	0.27 ± 0.04
TMAO	204 ± 26	82 ± 5	0.30 ± 0.05
Methylguanidine	191 ± 16	60 ± 6	0.54 ± 0.17
ADMA	188 ± 22	40 ± 11	1.02 ± 0.41
SDMA	188 ± 23	49 ± 9	0.74 ± 0.20

Values for PCS, IS, HIPP, and PAG are from n=8 hemodialysis patients studied at the VA Palo Alto as reported by Sirich et al.<sup>4</sup> Values for TMAO, MG, ADMA, and SDMA were obtained by reanalyzing stored samples from 6 of these 8 patients. Urea clearance averaged 292 ± 52 ml/min in the 8 patients and 312 ± 52 in those in whom TMAO, MG, ADMA, and SDMA were assayed.

**Supplementary Table 8. Association of Solute Levels with Session Duration  
and Blood Flow Rate Adjusted for  $Kt/V_{urea}$**

Solute	Association with Duration log standardized			Association with Blood Flow log standardized			Association with Ratio of Treatment Time to Blood flow log standardized		
	$\beta$ (95% CI)	p	R <sup>2</sup>	$\beta$ (95% CI)	p	R <sup>2</sup>	$\beta$ (95% CI)	p	R <sup>2</sup>
Urea Nitrogen	-0.04 (-0.09, 0.02)	0.23	0.0047	-0.11 (-0.17, -0.05)	<0.001	0.0135	0.07 (0.01, 0.12)	0.02	0.0082
p-Cresol Sulfate	0.01 (-0.05, 0.07)	0.40	0.0002	0.07 (0.01, 0.13)	0.02	0.0043	-0.05 (-0.11, 0.004)	0.07	0.0026
Indoxyl Sulfate	-0.01 (-0.06, 0.05)	0.82	0.0063	0.03 (-0.03, 0.09)	0.37	0.0069	-0.03 (-0.08, 0.03)	0.34	0.0070
Hippurate	0.03 (-0.03, 0.09)	0.37	0.0010	-0.03 (-0.09, 0.03)	0.31	0.0012	0.04 (-0.01, 0.10)	0.14	0.0021
Phenylacetylglutamine	-0.04 (-0.10, 0.02)	0.16	0.0024	-0.07 (-0.14, -0.01)	0.02	0.0054	0.03 (-0.02, 0.09)	0.22	0.0020
TMAO	-0.02 (-0.08, 0.03)	0.42	0.0052	0.01 (-0.05, 0.07)	0.85	0.0047	-0.02 (-0.08, 0.04)	0.49	0.0050
Methylguanidine	-0.01 (-0.07, 0.05)	0.70	0.0324	-0.06 (-0.12, 0.001)	0.06	0.0351	0.04 (-0.01, 0.10)	0.14	0.0339
ADMA	0.01 (-0.05, 0.07)	0.78	0.0006	-0.11 (-0.17, 0.05)	<0.001	0.0108	0.10 (0.04, 0.15)	0.001	0.0097
SDMA	-0.10 (-0.16, -0.04)	0.001	0.0093	-0.11 (-0.17, -0.05)	<0.001	0.0109	0.03 (-0.02, 0.09)	0.28	0.0011

All values were natural log transformed and standardized (mean =0 and standard deviation =1).  $\beta$  is obtained from multivariable linear regression of solute concentrations on the duration of dialysis session, the blood flow rate, and the ratio treatment time to blood flow rate and  $Kt/V_{urea}$ . Patients with recorded urea reduction ratio >94% (n=17) or <5% (n=2) were excluded as it was presumed that they represented error in sample collection or labeling. Treatment time averaged  $207 \pm 29$  min (range, 146 to 300 minutes), blood flow averaged  $207 \pm 29$  ml/min (range, 150 to 421 ml/min), and the ratio of treatment time to blood flow averaged  $0.62 \pm 0.14$  (range, 0.37 to 1.36).

**Supplementary Table 9. Timing of Repository Sample Collection**

	<b>Standard Kt/V<sub>urea</sub></b>	<b>High Kt/V<sub>urea</sub></b>
Total Number of Samples	643	638
D1 (Monday or Tuesday)	190	197
D2 (Wednesday or Thursday)	382	385
D3 (Friday or Saturday)	71	56
F3	9	11
F4	549	537
F5	75	84
F6, 7, or 8	10	6

F3 denotes the third month after randomization, F4 the fourth month, and so forth. Samples were obtained at varying points in the study but all solutes were measured in a single sample and thus obtained on the same day in each patient.

**Supplementary Table 10. Effect of Compartmentalization on Predicted Differences in Solute Concentration**

**Assuming No Non-Dialytic Clearance and Equal Solute Production in Standard and High  $Kt/V_{urea}$  Groups**

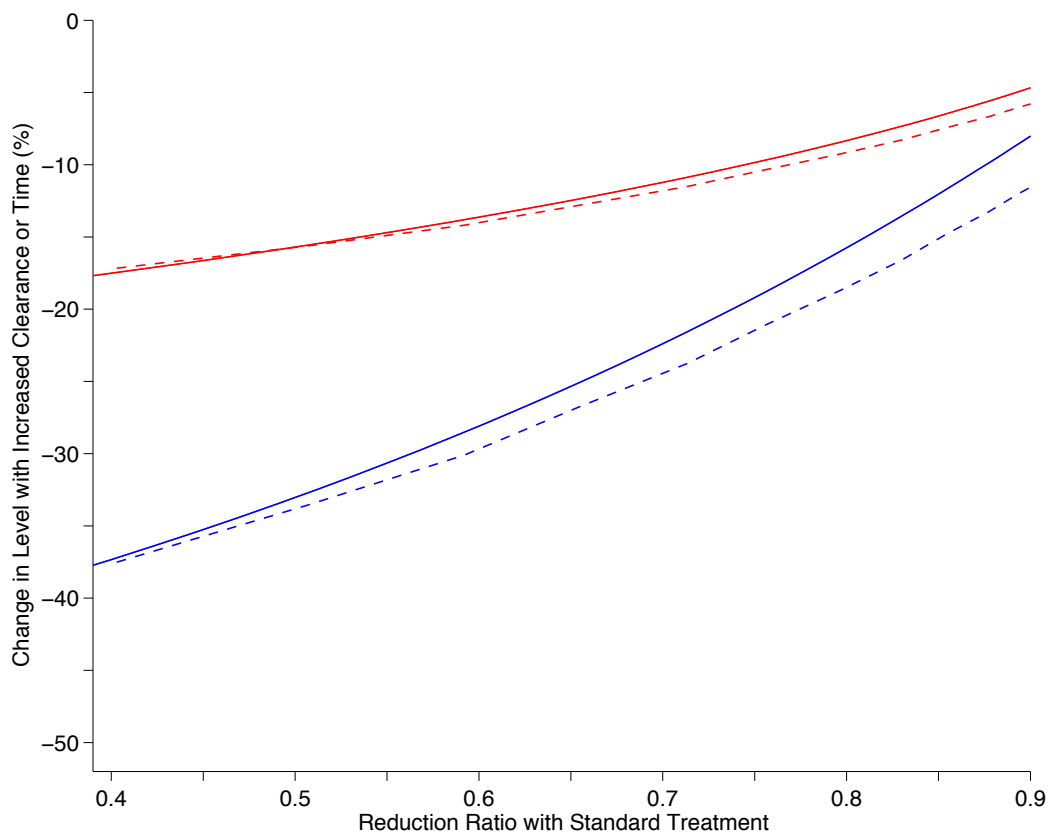
	Methylguanidine				p-Cresol Sulfate					
	One Compartment		Two Compartment		One Compartment		Two Compartment		Two Compartment	
	Standard $Kt/V_{urea}$	High $Kt/V_{urea}$	Standard $Kt/V_{urea}$	High $Kt/V_{urea}$	Standard $Kt/V_{urea}$	High $Kt/V_{urea}$	Standard $Kt/V_{urea}$	High $Kt/V_{urea}$	Standard $Kt/V_{urea}$	High $Kt/V_{urea}$
<b>Time (min)</b>	193	221	193	221	193	221	193	221	193	221
<b><math>K_{Dialytic}</math> (ml/min)</b>	195	219	195	219	28	31	28	31	28	31
<b>Volume C1 (l)</b>	52	51	7.6	7.4	12.2	11.9	3.0	2.9	3.0	2.9
<b>Volume C2 (l)</b>	-	-	89	88	-	-	12.0	11.7	24	23.5
<b><math>K_{IC}</math> (ml/min)</b>	-	-	968	950	-	-	140	137	75	74
<b>Predicted % Difference APC</b>		-14.5		-16.8	-	-16.2		-16.3		-17.0

$K_{Dialytic}$ , dialytic clearance;  $K_{IC}$ , intercompartmental clearance; Predicted % Difference APC, predicted percentage by which the average pre-treatment concentration would be lower in the High  $Kt/V_{urea}$  group if solute production were constant and there were no non-dialytic clearance. Solute clearances were estimated as described in the Methods. Modeling was initially performed assuming a single compartment with volume determined by dividing the amount of solute removed by the

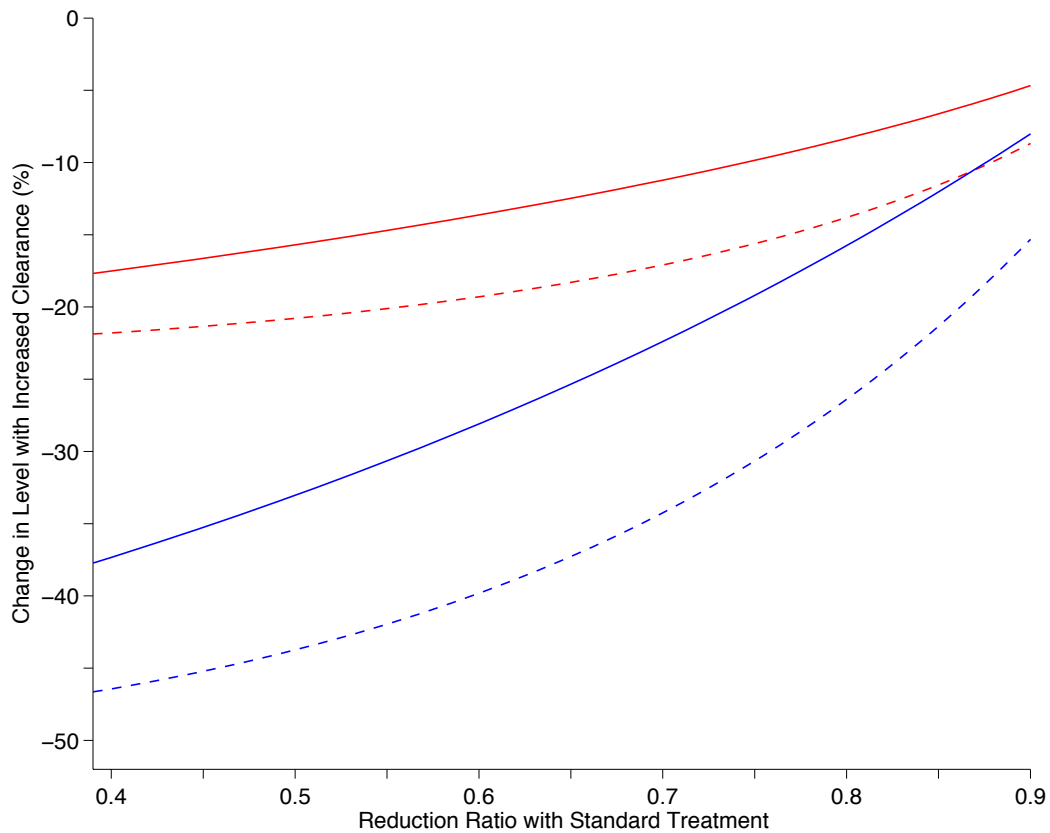
change in solute concentration in locally studied patients (Supplementary Table 7) and adjusting for body weight. Modeling was then performed assuming two compartments as described by Eloit et al.<sup>5</sup> Values for the compartmental volumes and  $K_{IC}$  for methylguanidine were obtained by adjusting values reported by Eloit et al.<sup>5</sup> for the body weight of HEMO subjects. Because estimates of  $K_{IC}$  along with multicompartments volumes are not available for PCS and other solutes, we entered a variety of values for these parameters, and found that wide variation in the assumed values had little effect on the modeled relative difference in pre-treatment concentrations between the Standard and High  $Kt/V_{urea}$  groups.

## References to Supplementary Tables

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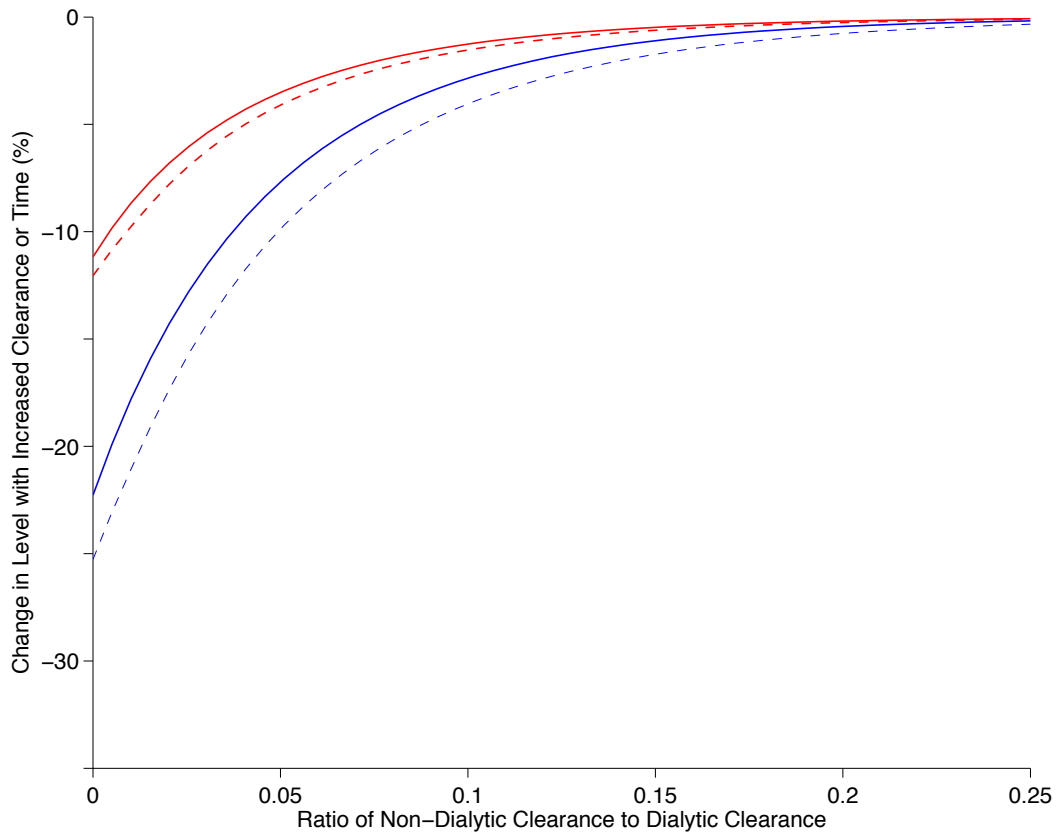


Supplementary Figure 1A. Intermittency limits our ability to reduce solute levels by increasing dialytic clearance and/or time. The figure compares the predicted effects on average pretreatment solute levels of increasing  $Kt/V$  by increasing clearance and time plotted as a function of the reduction ratio achieved by standard thrice-weekly treatment. The effect of increasing time (broken lines) by 30 percent (red lines) and 100 percent (blue lines) is little different from the effect of increasing clearance (solid lines) by the same proportions. Values are modeled for an initial treatment time of 200 minutes and assuming no non-dialytic clearance and a continuously generated solute distributed in a single compartment.

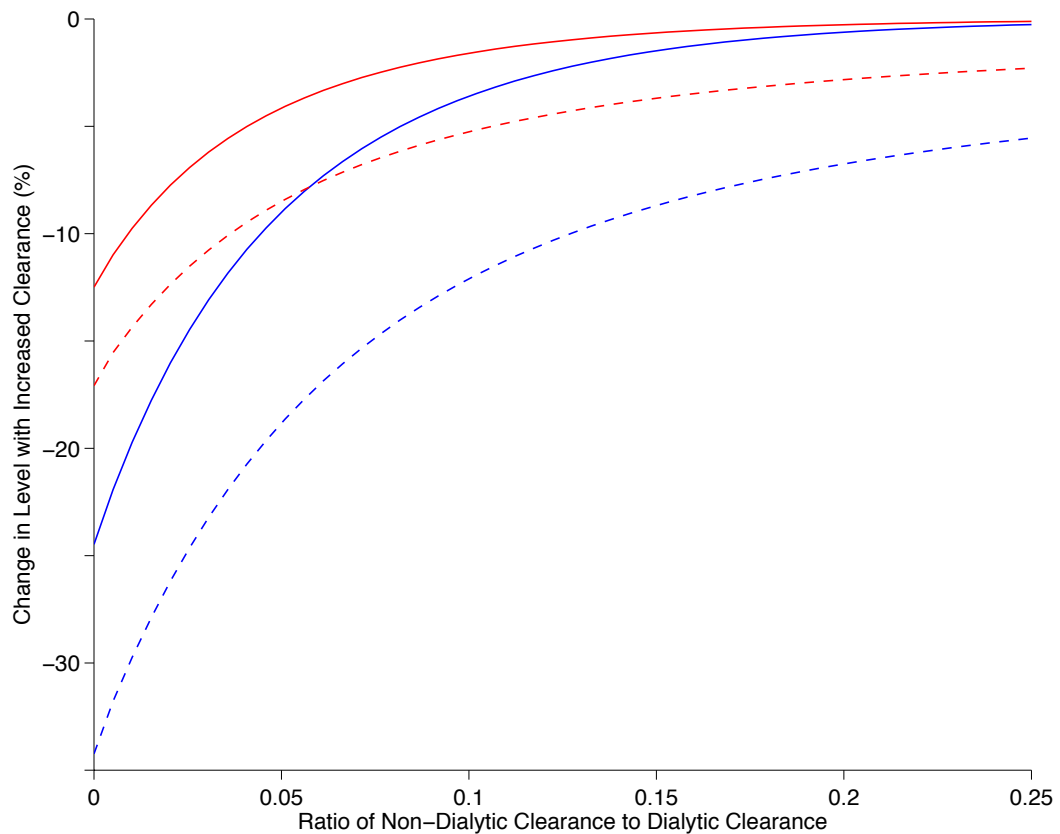


Supplementary Figure 1B. Intermittency limits our ability to reduce solute levels by increasing dialytic clearance and/or time. The figure compares the predicted effect on time averaged concentration (broken lines) and pretreatment concentration (solid lines) of increasing  $Kt/V$  by increasing clearance by 30 percent (red lines) and 100 percent (blue lines). Increasing  $Kt/V$  lowers the time average concentration slightly more than the pretreatment concentration. Values are modeled for an initial treatment time of 200 minutes and assuming no non-dialytic clearance and a continuously generated solute distributed in a single compartment.

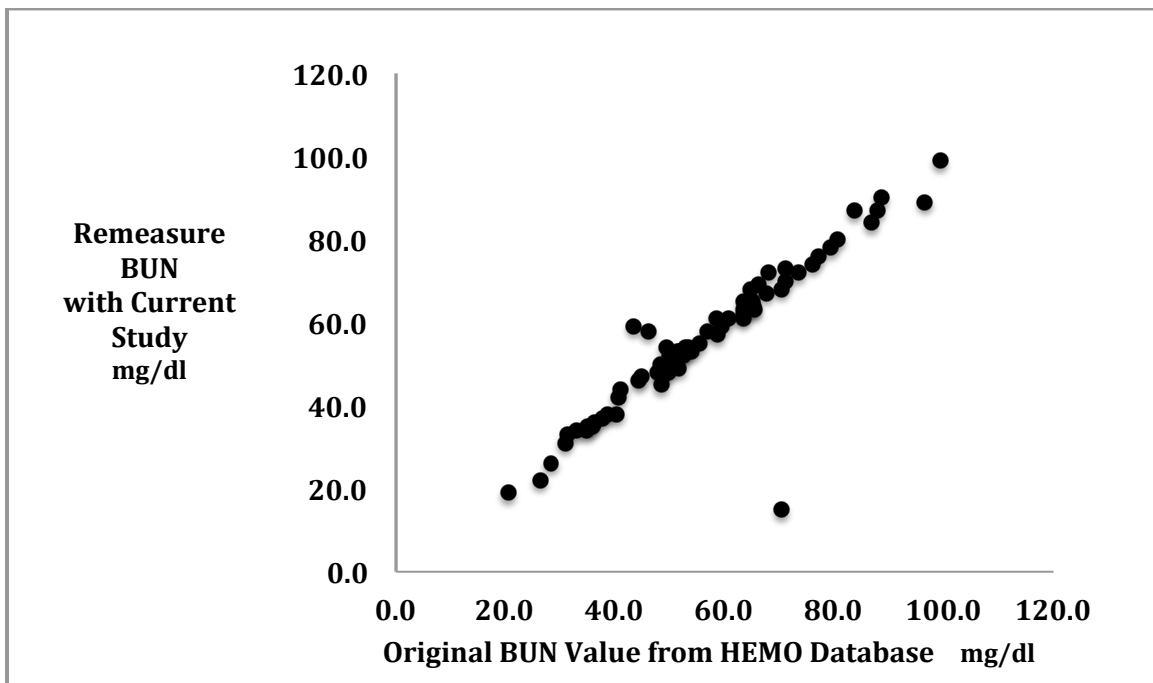




Supplemental Figure 2A. The presence of a non-dialytic clearance limits our ability to reduce solute levels by increasing dialytic clearance and/or time. The figure compares the predicted effect on average pretreatment solute levels of increasing  $Kt/V$  by increasing clearance and time in the presence of a continuous non-dialytic clearance. The effect of increasing time (broken lines) by 30 percent (red lines) and 100 percent (blue lines) is little different from the effect of increasing clearance (solid lines) by the same proportions. Values are modeled for a treatment time of 200 minutes and an initial  $Kt/V$  of 1.3 with a continuously generated solute distributed in a single compartment.



Supplemental Figure 2B. The presence of a non-dialytic clearance limits our ability to reduce solute levels by increasing dialytic clearance and/or time. The figure compares the effect of increasing  $Kt/V$  by increasing clearance on average peak concentration (solid lines) and time-averaged concentration (broken lines). The time averaged concentration is reduced more than the average peak concentration but increases of 30 percent (red lines) and 100 percent (blue lines) in clearance still result in comparatively small reductions in plasma solutes levels when non-dialytic clearance is present. Values are modeled for a treatment time of 200 minutes and an initial  $Kt/V$  of 1.3 with a continuously generated solute distributed in a single compartment.



Supplemental Figure 3. Stability of urea values in n=68 stored samples. Remeasured values were in overall good agreement with original values except for a single sample where the remeasured value of 15 mg/dl corresponded with the originally measured post-treatment BUN values rather than the originally measured pre-treatment BUN value of 70 mg/dl. Without this sample, regression was  $y=0.77x + 2.0$ ,  $R^2=0.97$ .