Supplementary Table 1. Comparison of Biomarkers of Renal Function During Follow-Up According to Development of End-Stage Renal Disease

Biomarker	\multicolumn{4}{l	}{Time Prior to ESRD/Modified End of Follow-up}	Estimated Time of Divergence[a]	P-values Equality	Interaction
	3 years	2 years	1 year	Time of ESRD/mEnd of Follow-up			

Supplementary Table 1. Comparison of Biomarkers of Renal Function During Follow-Up According to Development of End-Stage Renal Disease

Biomarker	3 years	2 years	1 year	Time of ESRD/mEnd of Follow-up	Estimated Time of Divergence[a]	Equality	Interaction
Comparison of Biomarkers in those that develop ESRD vs. Not							
	\multicolumn{4}{}{Time Prior to ESRD/Modified End of Follow-up}		P-values		
Placebo Group							
	ESRD vs. not (P-difference)	ESRD vs. not (P-difference)	ESRD vs. not (P-difference)	ESRD vs. not (P-difference)			
Creatinine (mg/dL)[b]	2.0 vs 1.7; p<0.001	2.4 vs 1.8; p<0.001	2.8 vs 1.9; p<0.001	4.3 vs 1.9; p<0.001	>3 years	<0.001	<0.001
eGFR (mL/min/1.73m^2)	33.5 vs 38.2; p<0.001	28.1 vs 36.7; p<0.001	23.3 vs 35.4; p<0.001	15.6 vs 34.9; p<0.001	>3 years	<0.001	<0.001
Urine Protein/Creatinine Ratio[b]	1.4 vs 0.4; p<0.001	1.7 vs 0.4; p<0.001	2.1 vs 0.4; p<0.001	2.5 vs 0.5; p<0.001	>3 years	<0.001	<0.001
Darbepoetin Group							
	ESRD vs. not (P-difference)	ESRD vs. not (P-difference)	ESRD vs. not (P-difference)	ESRD vs. not (P-difference)			
Creatinine (mg/dL)[b]	2.0 vs 1.7; p<0.001	2.3 vs 1.8; p<0.001	2.7 vs 1.8; p<0.001	4.6 vs 1.9; p<0.001	>3 years	<0.001	<0.001
eGFR (mL/min/1.73m^2)	32.5 vs 38.2; p<0.001	28.6 vs 37.7; p<0.001	24.1 vs 37.0; p<0.001	14.7 vs 35.9; p<0.001	>3 years	<0.001	<0.001
Urine Protein/Creatinine Ratio[b]	1.7 vs 0.4; p<0.001	2.1 vs 0.4; p<0.001	2.7 vs 0.4; p<0.001	3.1 vs 0.5; p<0.001	>3 years	<0.001	<0.001

P for Equality tests the null hypothesis that the curves are superimposable; P for Interaction tests the null hypothesis that the curves are parallel.

[a] Estimated time of divergence of biomarkers of interest (developed ESRD vs. not) was defined as the latest time at which the difference in point estimates became significant at α=0.01.

[b] Groups are summarized and compared using geometric means

eGFR, estimated glomerular filtration rate

Supplementary Table 2. Comparison of Biomarkers During Follow-Up According to Development of End-Stage Renal Disease Using a Refined Non-ESRD Comparator Group

Comparison of Biomarkers in those who develop ESRD (n=668) vs. Propensity Score Matched Sample of Non-ESRD (n=670)						
	Time Prior to ESRD/Modified End of Follow-up				P-values	
Biomarker	3 years	2 years	1 year	Time of ESRD/mEnd of Follow-up	Equality	Interaction
	Placebo Group					
	ESRD vs. not (P-difference)	ESRD vs. not (P-difference)	ESRD vs. not (P-difference)	ESRD vs. not (P-difference)		
Hemoglobin (g/dL)	10.4 vs 10.1; p<0.001	10.3 vs 10.2; p=0.36	10.2 vs 10.4; p=0.005	9.5 vs 10.4; p<0.001	<0.001	<0.001
Darbepoetin (Mean Dose in mcg/month)	1.3 vs 6.0; p=0.009	3.2 vs 5.9; p=0.037	7.4 vs 6.7; p=0.54	18.5 vs 8.0; p<0.001	<0.001	<0.001
Darbepoetin Dose Difference ([ESRD – non-ESRD] in mcg/month)	-4.8	-2.7	+0.7	+10.5	<0.001	<0.001
Ferritin (mcg/L)[b]	147 vs 144; p=0.81	148 vs 143; p=0.52	172 vs 151; p=0.047	204 vs 169; p=0.013	0.002	0.004
Transferrin Saturation (%)	24.9 vs 25.7; p=0.44	24.5 vs 25.6; p=0.14	26.1 vs 25.8; p=0.74	24.3 vs 26.1; p=0.036	0.14	0.10
CRP (mg/L)[b, c]	3.7 vs 2.7; p=0.030	3.9 vs 2.9; p=0.001	3.9 vs 3.4; p=0.057	5.8 vs 3.3; p<0.001	<0.001	0.028
	Darbepoetin Group					
	ESRD vs. not (P-difference)	ESRD vs. not (P-difference)	ESRD vs. not (P-difference)	ESRD vs. not (P-difference)		
Hemoglobin (g/dL)	11.2 vs 11.1; p=0.16	11.7 vs 11.6; p=0.76	11.9 vs 11.9; p=0.27	11.5 vs 12.4; p<0.001	<0.001	<0.001
Darbepoetin (Mean Dose in mcg/month)	131 vs 153; p=0.010	138 vs 146; p=0.28	162 vs 167; p=0.48	232 vs 197; p=<0.001	<0.001	<0.001

Darbepoetin Dose Difference ([ESRD – non-ESRD] in mcg/month)	-23	-8	-5	+36	<0.001	<0.001
Ferritin (mcg/L)[b]	92 vs 107; p=0.10	119 vs 120; p=0.90	151 vs 144; p=0.46	179 vs 183; p=0.75	0.09	0.047
Transferrin Saturation (%)	22.0 vs 21.6; p=0.73	25.6 vs 27.2; p=0.12	29.8 vs 29.4; p=0.62	29.5 vs 34.0; p<0.001	<0.001	<0.001
CRP (mg/L)[b, c]	2.9 vs 3.7; p=0.08	3.5 vs 3.4; p=0.80	3.6 vs 4.0; p=0.22	5.3 vs 3.7; p=0.002	0.002	<0.001

Supplementary Figure 1. TREAT Study Darbepoetin Management Protocol

Darbepoetin alfa Dosing Algorithm

| Hb (g/dL)	Hb rate of rise (g/dL/2 weeks)	Dose Adjustment
< 12.5	< 0.5	Increase to next higher dose
	≥ 0.5 - < 1.0	Maintain dose
	≥ 1.0	Decrease to next lower dose
12.5 - < 13.5	< 0.5	Maintain dose
	≥ 0.5 - < 1.0	Maintain dose
	≥ 1.0	Decrease to next lower dose
13.5-14.0	Any	Decrease to next lower dose
> 14.0	Any	Administer placebo until Hb value is below 13.0, then resume darbepoetin alfa at next lower dose

Rescue Therapy Dosing Algorithm

| Hb (g/dL)	Hb rate of rise (g/dL/2 weeks)	Dose Adjustment
< 9.0	< 0.5	Initiate or increase to next higher dose
< 9.0	≥ 0.5, but < 1.0	Maintain dose
< 9.0	≥ 1.0	Decrease to next lower dose
≥ 9.0	Any	Resume placebo administration

Supplementary Figure 2. TREAT Study Iron Management Protocol
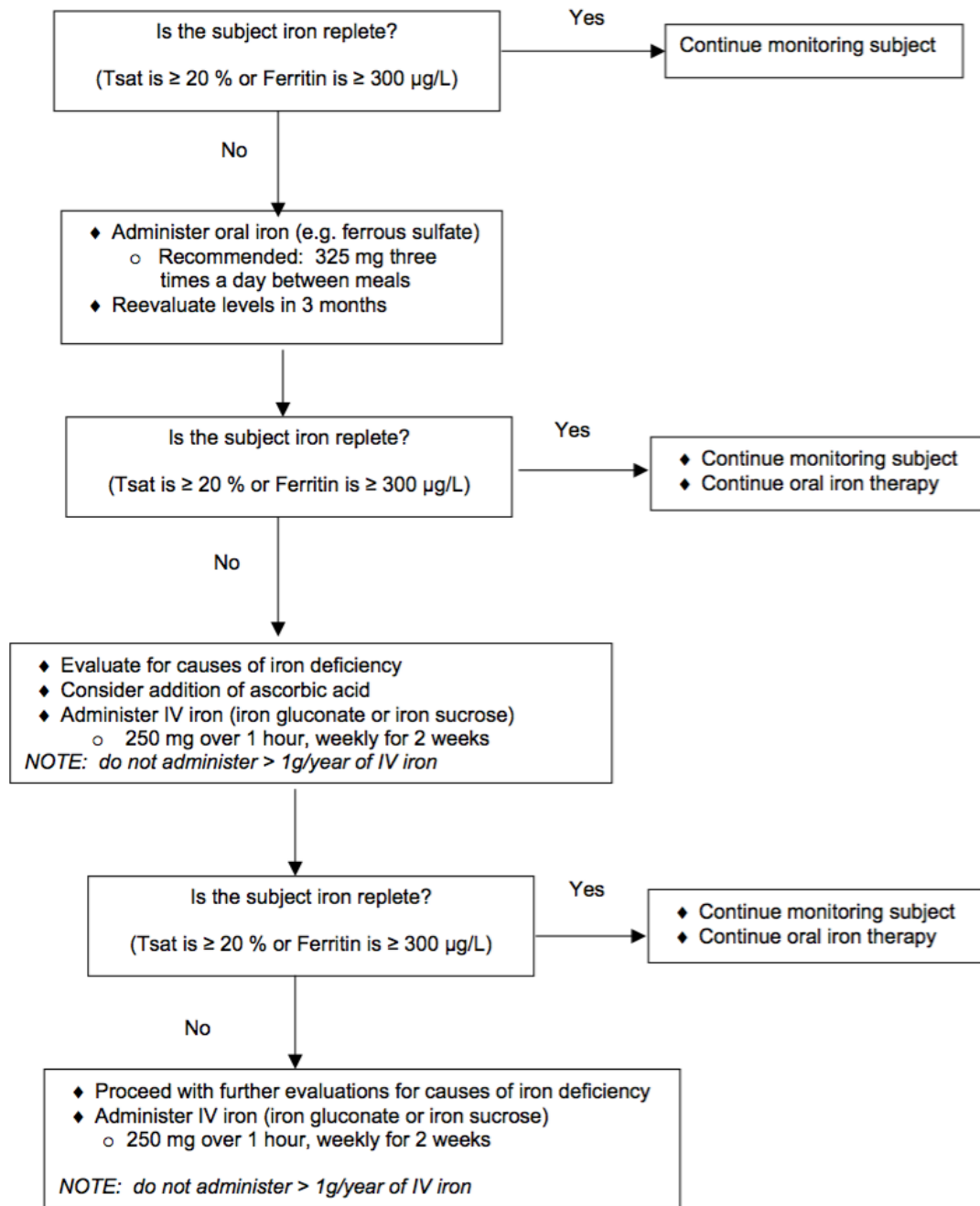
Supplementary Figure 3. Trajectory of Hemoglobin According to Development of ESRD in Subgroups of Participants With and Without Baseline ACEi/ARB Use
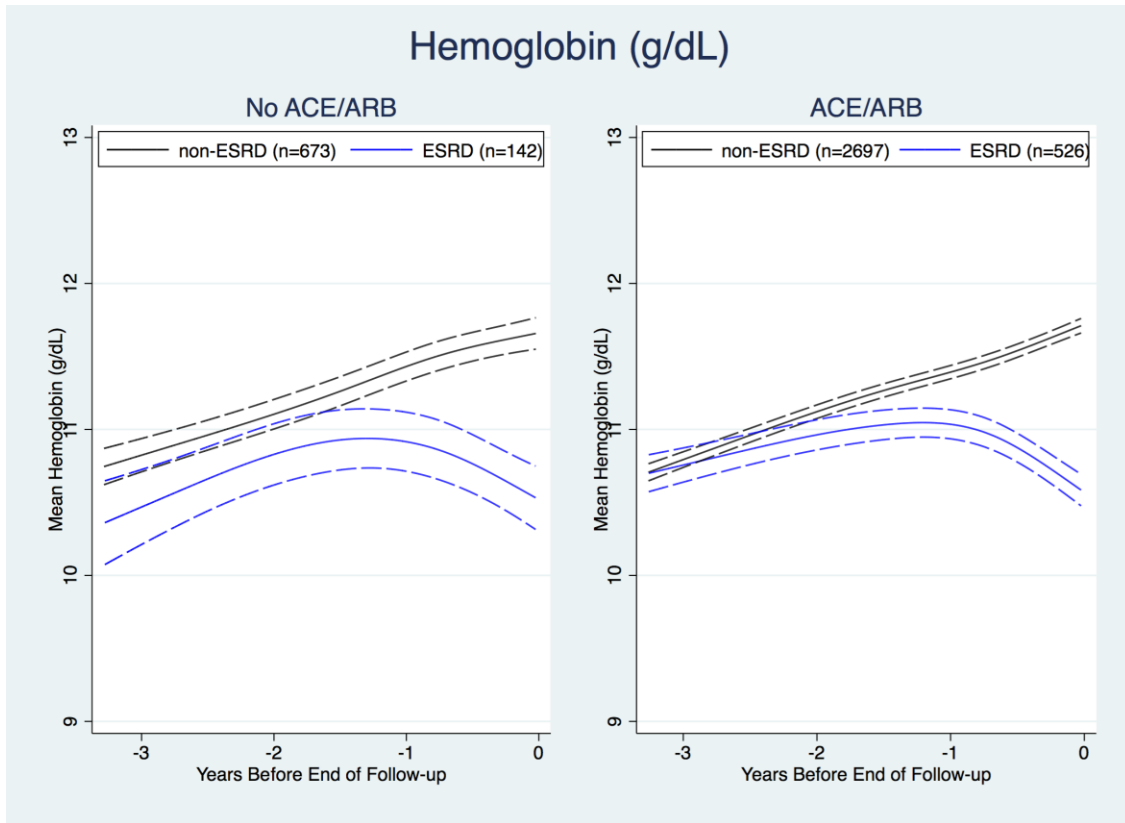
Supplementary Figure 4. Trajectory of Serum Creatinine According to Development of ESRD
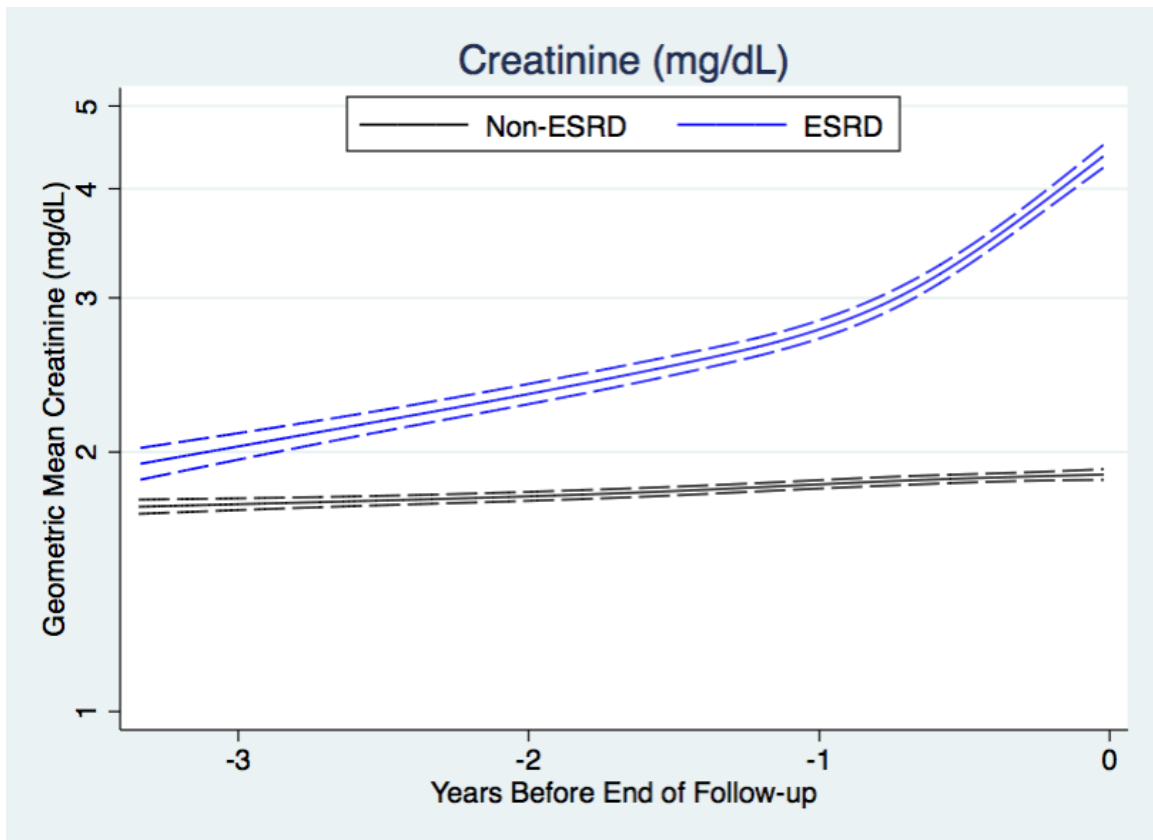
Supplementary Figure 5. Trajectory of Estimated Glomerular Filtration Rate According to Development of ESRD