

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Appel LJ, Wright JT Jr, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010;363:918-29.

(PDF updated November 16, 2010.)

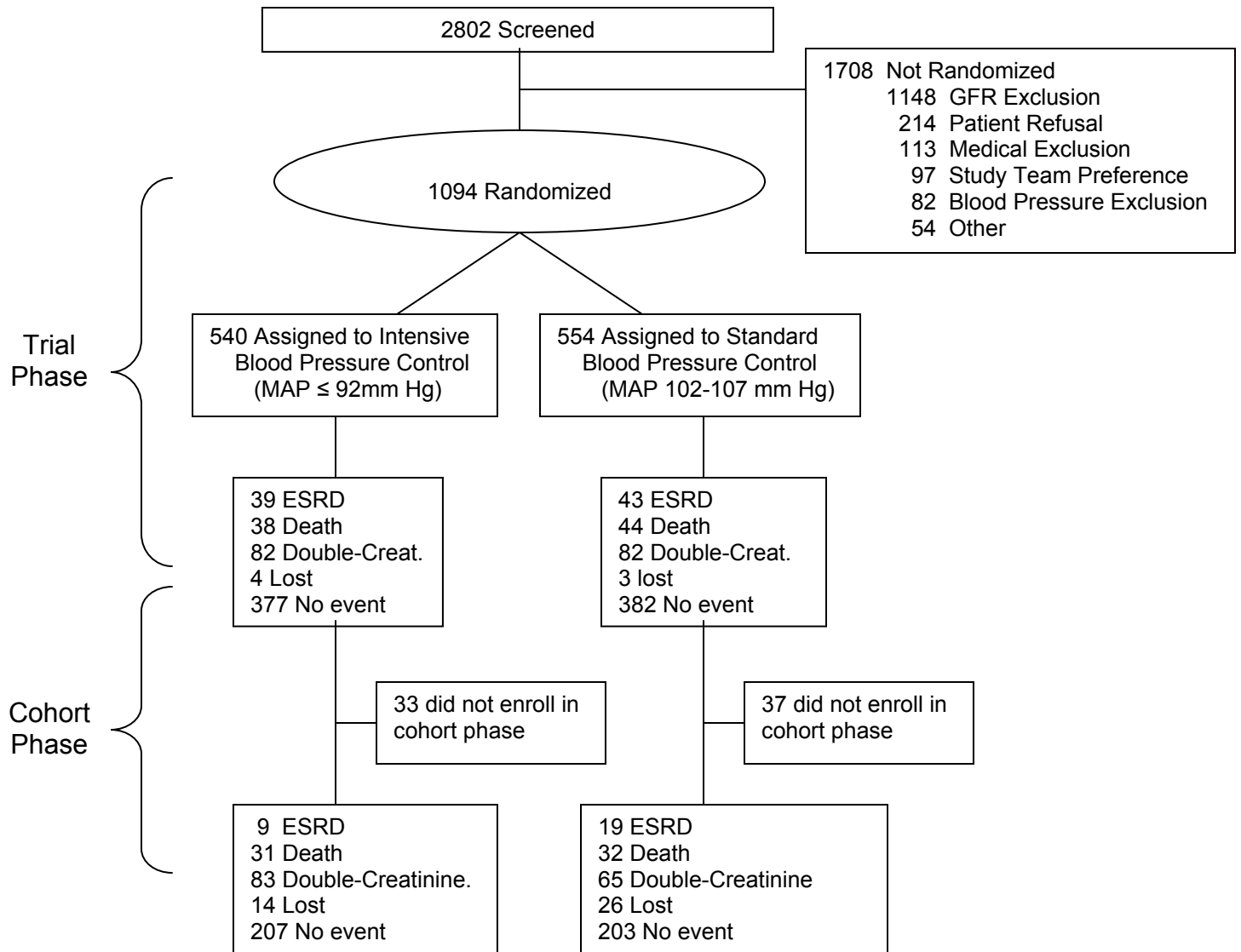
Legend for Appendix Figures

Appendix Figure 1 – Participant flow in the trial and cohort phases of AASK. Event totals during each phase indicate the numbers of patients who experienced the indicated event prior to any of the other components of the primary composite outcome of ESRD, Death, or Doubling of SCR. Once an individual experienced an event (e.g. doubling or serum creatinine), this person was no longer counted for the other events (in this case, ESRD or death), even if one of these events subsequently occurred. For this reason, counts of ESRD and death are less than the total numbers of ESRD and death that occurred in the study. Counts in this figure do not apply to the other composite outcomes (ESRD or death; ESRD or doubling of serum creatinine). In contrast, appendix tables 4-6 display total counts in the study.

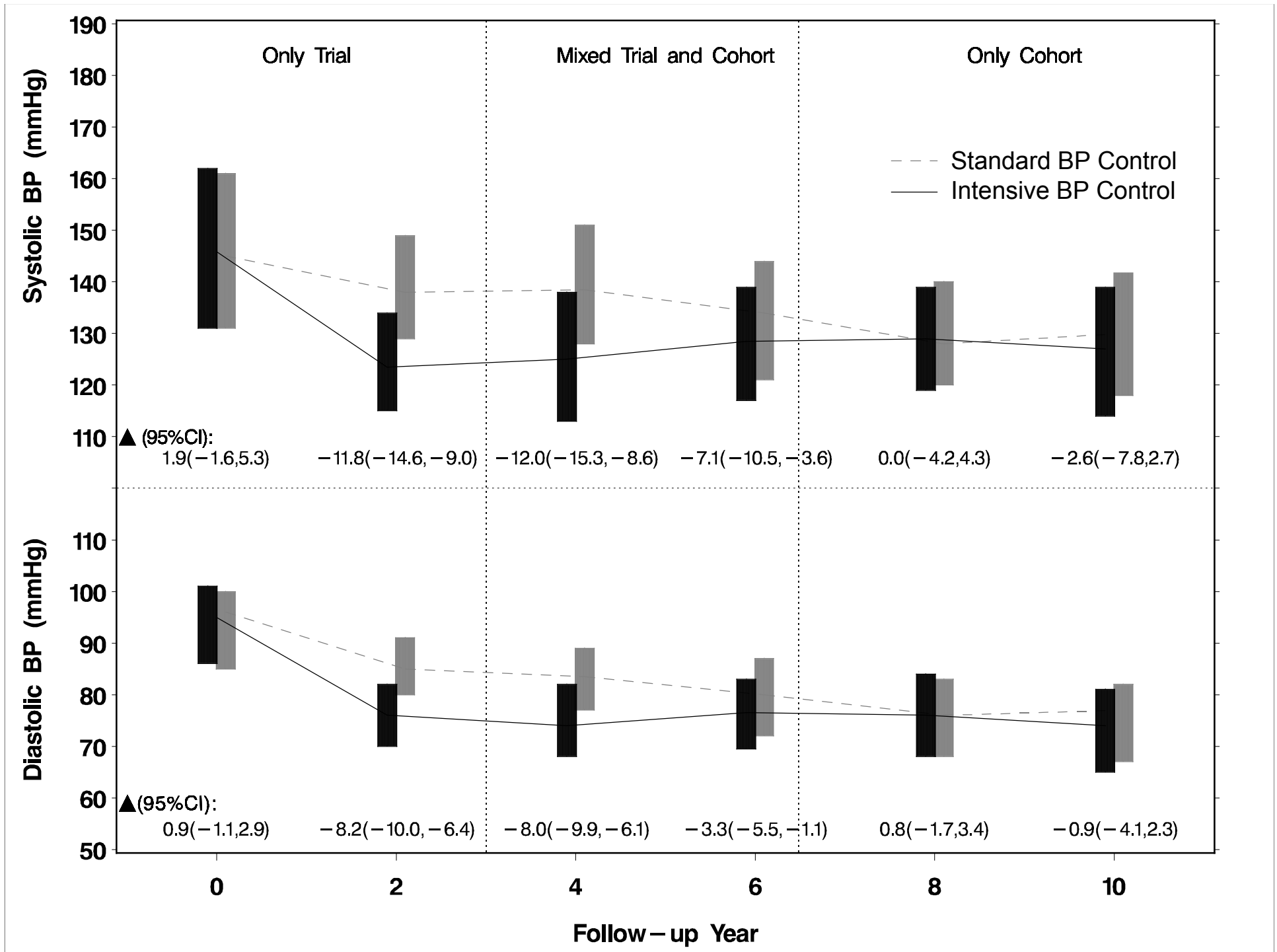
Appendix Figure 2 – Among participants with baseline UP/Cr ≤ 0.22 , BP levels in the standard BP control group (light boxes) and intensive BP control group (dark boxes) over time in the trial and cohort phases of AASK among participants who had not yet experienced the primary study outcome (doubling of serum creatinine level, ESRD or death). Lines connect median BP at each timepoint. For each box, the upper edge corresponds to the 75th percentile and the bottom edge the 25th percentile. Note – During the first 3 years, all participants were in the trial phase. The period between 3 and 6.5 years is a mixed period that is the trial phase for early enrollees and the cohort phase for the late enrollees. After 6.5 years, all data is from the cohort phase.

Appendix Figure 3 – Among participants with baseline UP/Cr > 0.22, BP levels in the standard BP control group (light boxes) and intensive BP control group (dark boxes) over time in the trial and cohort phases of AASK among participants who had not yet experienced the primary study outcome (doubling of serum creatinine level, ESRD or death). Lines connect median BP at each timepoint. For each box, the upper edge corresponds to the 75th percentile and the bottom edge the 25th percentile. Note – During the first 3 years, all participants were in the trial phase. The period between 3 and 6.5 years is a mixed period that is the trial phase for early enrollees and the cohort phase for the late enrollees. After 6.5 years, all data is from the cohort phase. BP estimates at Year 10 are unstable because of small sample size.

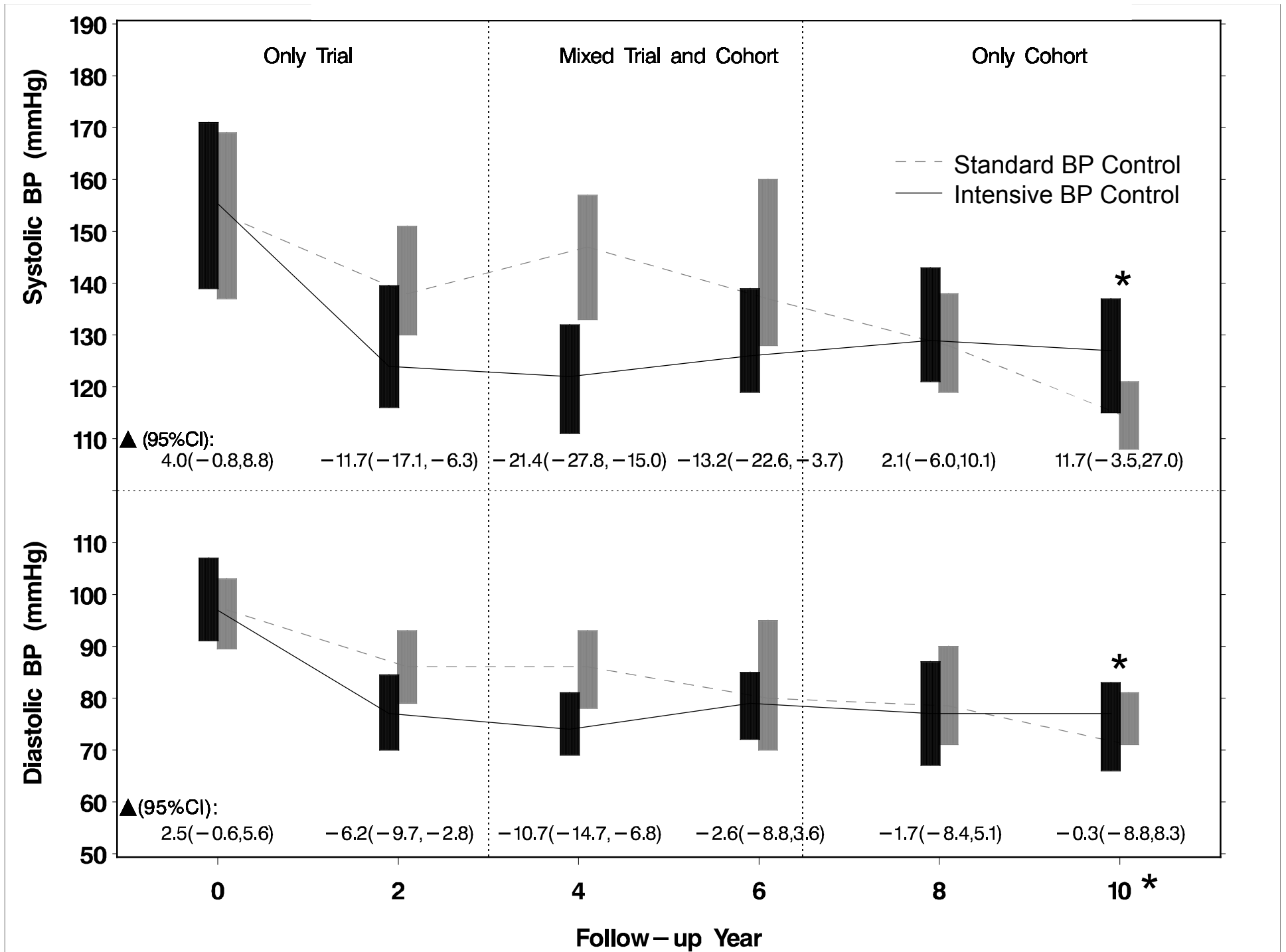
Appendix Figure 1: Participant flow in the trial and cohort phases of AASK



Appendix Figure 2 : BP Levels in Patients with UP/Cr \leq 0.22



Appendix Figure 3 : BP Levels in Patients with UP/Cr > 0.22



* Unstable BP estimates because of small sample size

Appendix Table 1: Characteristics of AASK Participants* at Start of Cohort Phase by Randomized Group, Overall and Stratified by Baseline Urine Protein Excretion at Start of Trial

Variable	All Participants		UP/Cr ≤ 0.22		UP/Cr > 0.22	
	Intensive (N = 377)	Standard (N = 382)	Intensive (N=290)	Standard (N=312)	Intensive (N=86)	Standard (N=68)
Age (yr)	60.5 ± 10.1	59.8 ± 10.3	61.8 ± 9.49	60.7 ± 9.64	56.3 ± 10.9	55.4 ± 12.1
Female	145(38.5%)	152(39.8%)	119 (41.0%)	124 (39.7%)	26 (30.2%)	28 (41.2%)
Current Smoker	119(31.6%)	82 (21.5%)	90 (31.0%)	65 (20.8%)	28 (32.6%)	16 (23.5%)
No High School Education	156(41.4%)	153(40.2%)	124 (42.8%)	134 (43.1%)	32 (37.2%)	18 (26.5%)
Weight(Kg)	91.9 ± 22.7	92.1 ± 21.5	90.4 ± 22.5	91.1 ± 21.4	97.2 ± 22.8	96.6 ± 22.0
Body Mass Index (kg/m ²)	31.4 ± 7.34	31.5 ± 6.86	30.9 ± 7.05	31.3 ± 6.90	33.2 ± 8.11	32.6 ± 6.73
Estimated GFR(ml/min/1.73m ²)	47.0 ± 15.3	47.7 ± 15.0	49.1 ± 15.0	50.1 ± 14.0	39.4 ± 13.9	36.4 ± 14.1
Serum Creatinine (mg/dL)	1.99 ± 0.81	1.98 ± 0.80	1.87 ± 0.73	1.84 ± 0.68	2.44 ± 0.92	2.61 ± 0.98
Urine Protein (g/day)	0.07(0.04,0.25)	0.10(0.04,0.43)	0.06(0.03,0.14)	0.08(0.04,0.25)	0.45(0.16,1.17)	0.51(0.32,1.14)
U.Protein/Creatinine	0.06(0.03,0.20)	0.07(0.03,0.29)	0.04(0.02,0.09)	0.05(0.03,0.17)	0.35(0.11,0.80)	0.42(0.21,0.98)
U.Protein/Creatinine > 0.22	82 (24.0%)	102(30.3%)	39 (14.7%)	61 (21.9%)	43 (58.1%)	41 (70.7%)
Female	32 (24.6%)	38 (29.9%)	16 (15.1%)	21 (20.4%)	16 (66.7%)	17 (70.8%)
Male	50 (23.7%)	64 (30.5%)	23 (14.4%)	40 (22.9%)	27 (54.0%)	24 (70.6%)

*Among participants who had not experienced the primary renal outcome and who therefore remained at risk.

Appendix Table 2: BP Levels and Medication Usage Among AASK Participants with Baseline UP/Cr \leq 0.22*

	Year Post- Randomization					
	Baseline	2	4	6	8	10
# Trial / # Cohort						
Standard BP Control	376/0	326/0	214/32	44/155	0/185	0/107
Intensive BP Control	357/0	314/0	217/29	41/147	0/178	0/111
Mean SBP						
Standard BP Control	147(22)	139(17)	139(17)	135(18)	131(20)	131(20)
Intensive BP Control	149(25)	127(19)	127(20)	128(16)	131(21)	128(20)
Mean DBP						
Standard BP Control	94(13)	85(11)	83(10)	79(12)	76 (12)	75 (12)
Intensive BP Control	95(14)	77(13)	75(11)	76(10)	77 (13)	74 (12)
% with SBP <130 and DBP <80 mmHg						
Standard BP Control	9.8	12.6	16.3	25.1	38.9	40.2
Intensive BP Control	9.5	51	53.7	44.1	39.9	48.6
% with SBP <140 and DBP <90 mmHg						
Standard BP Control	22.9	40.5	43.5	61.8	73	70.1
Intensive BP Control	22.7	77.1	74	70.2	74.7	73
% with SBP \geq 160 and DBP \geq 100 mmHg						
Standard BP Control	16.2	3.4	2	2.5	3.2	0.9
Intensive BP Control	19	2.2	2.8	0.5	3.4	1.8
% on ACEI or ARB						
Standard BP Control	39.7	39.3	47.6	82.9	90.3	82.2
Intensive BP Control	42	40.1	49.6	79.7	88.2	93.6
# of HTN Med Classes						
Standard BP Control	2.3(1.1)	2.6(1.2)	3.0(1.4)	3.6(1.5)	3.9(1.5)	3.8(1.5)
Intensive BP Control	2.4(1.1)	3.4(1.1)	3.5(1.1)	3.6(1.4)	3.7(1.4)	4.1(1.3)

*During the trial phase, mean BP was 128/77 mmHg in the lower BP group and 140/85 mmHg in the usual BP group. During the cohort phase, mean BP was 132/77 mmHg in the lower BP group and 131/77 mmHg in the usual BP group. Sample sizes indicate the number of patients who remained at risk for the primary composite outcome of ESRD, Death, or Doubling of SCR at the indicated time points after randomization.

Appendix Table 3: BP Levels and Medication Usage Among AASK Participants with Baseline UP/Cr > 0.22*

	Baseline	2	Year Post- Randomization				10**
# Trial/ # Cohort			4	6	8		
Standard BP Control	176/0	121/0	56/7	2/28	0/22	0/9	
Intensive BP Control	181/0	140/0	74/8	15/42	0/41	0/22	
Mean SBP							
Standard BP Control	154(22)	141(19)	147(19)	142(28)	129(12)	115(10)	
Intensive BP Control	158(24)	130(25)	125(20)	129(17)	131(17)	127(21)	
Mean DBP							
Standard BP Control	97(15)	86(12)	87(11)	82(17)	78(12)	75(6)	
Intensive BP Control	99(15)	80(16)	76(13)	80(12)	77(13)	74 (12)	
% with SBP <130 and DBP <80 mmHg							
Standard BP Control	5.7	11.6	6.3	23.3	27.3	55.6	
Intensive BP Control	1.1	51.4	59.8	42.1	36.6	45.5	
% with SBP <140 and DBP <90 mmHg							
Standard BP Control	14.2	38	27	46.7	63.6	100	
Intensive BP Control	11.6	72.1	78	77.2	68.3	77.3	
% with SBP ≥160 and DBP ≥100 mmHg							
Standard BP Control	22.2	5.8	7.9	13.3	0	0	
Intensive BP Control	29.3	7.9	4.9	5.3	0	0	
% on ACEI or ARB							
Standard BP Control	39.4	42.1	52.4	76.7	95.5	100	
Intensive BP Control	34.6	42.1	45.1	77.2	87.8	81.8	
# of HTN Med Classes							
Standard BP Control	2.5(1.2)	3.0(1.2)	3.0(1.2)	3.7(1.3)	4.0(1.8)	4.2(1.9)	
Intensive BP Control	2.5(1.2)	3.7(1.1)	3.7(1.1)	4.0(1.2)	4.1(1.2)	4.5(1.2)	

*During the trial phase, mean BP was 132/80 mmHg in the lower BP group and 144/87 mmHg in the usual BP group. During the cohort phase, mean BP was 134/80 mmHg in the lower BP group and 136/81 mmHg in the usual BP group. Sample sizes indicate the number of patients who remained at risk for the primary composite outcome of ESRD, Death, or Doubling of SCR at the indicated time points after randomization.

**Unstable BP estimates because of small sample size.

Appendix Table 4: Mortality, CVD Events, and Hospitalizations by Randomized Group, All Participants

	<u>Intensive Control</u>		<u>Standard Control</u>		<u>Intensive vs Standard</u>	
	<u># events</u>	<u>Rate*</u>	<u># events</u>	<u>Rate*</u>	<u>HR</u>	<u>P-value</u>
Total Mortality Before ESRD						
Trial Phase	38/540	1.6	47/554	2	0.75 (0.49,1.15)	0.19
Cohort Phase	48/412	2.7	44/411	2.6	0.95 (0.63,1.44)	0.81
Both	86/540	2.1	91/554	2.2	0.85 (0.63,1.14)	0.29
CV Death						
Trial Phase	16/540	0.7	15/554	0.6	1.00 (0.49,2.02)	0.99
Cohort Phase	19/350	1.3	9/341	0.6	1.86 (0.84,4.13)	0.13
Both	35/540	0.9	24/554	0.6	1.32 (0.78,2.23)	0.3
CV Composite						
Trial Phase	71/540	3.2	78/554	3.5	0.87 (0.63,1.21)	0.41
Cohort Phase	45/322	3.4	31/307	2.6	1.22 (0.77,1.94)	0.39
Both	116/540	3.3	109/554	3.2	0.98 (0.75,1.27)	0.87
Stroke Event						
Trial Phase	26/540	1.1	29/554	1.3	0.87 (0.51,1.47)	0.6
Cohort Phase	15/337	1.1	15/327	1.1	0.87 (0.43,1.79)	0.71
Both	41/540	1.1	44/554	1.2	0.87 (0.57,1.33)	0.52
Heart Failure Event						
Trial Phase	27/540	1.2	23/554	1	1.11 (0.63,1.94)	0.71
Cohort Phase	22/341	1.5	17/329	1.3	1.13 (0.60,2.14)	0.71
Both	49/540	1.3	40/554	1.1	1.12 (0.73,1.71)	0.6
Major CAD Event						
Trial Phase	19/540	0.8	23/554	1	0.80 (0.44,1.48)	0.48
Cohort Phase	18/339	1.3	7/329	0.5	2.29 (0.95,5.50)	0.06
Both	37/540	1	30/554	0.8	1.16 (0.71,1.88)	0.55
Overall rate of CV Events						
Trial Phase	108/540	4.1	94/554	3.5	1.11 (0.78	0.57
Cohort Phase	70/350	4.7	58/341	4.1	1.08 (0.72	0.74
Both	178/540	4.6	152/554	4	1.03 (0.89,1.20)	0.55
First hospitalization (any cause)						
Trial Phase	256/540	15.3	256/554	14.3	1.05 (0.88,1.24)	0.62
Cohort Phase	84/205	11.8	77/201	11.4	0.99 (0.73,1.35)	0.95
Both	340/540	14.3	332/554	13.4	1.03 (0.89,1.20)	0.67
Overall rate of hospitalization (any cause)						
Trial Phase	518/540	19.9	519/554	19.4	0.98 (0.81 ,1.2)	0.87
Cohort Phase	321/350	21.6	352/341	25.1	0.83 (0.77	0.13
Both	839/540	21.9	870/540	23.1	0.92 (0.78	0.32

*Rate is number of events per 100 person-years. Summarized are CV events and hospitalizations prior to ESRD, and all cause mortality, including deaths prior to and after ESRD. The overall rate of hospitalization and the overall rate of CV Events refer to the rates of all events of the indicated type, including multiple events per patient. For these two outcomes, the # at risk at the start of the cohort phase includes all 691 enrollees into the cohort study. Only the first event is considered for all remaining event categories in the table. For all of these event categories except for mortality, the # at risk at the start of the cohort study was the # of cohort study enrollees in which neither the first event nor ESRD had occurred prior to the start of the cohort. For total mortality, the # at risk at the start of the cohort includes all randomized patients who were known to have survived to the start of the cohort, irrespective of whether they had initiated dialysis by this time.

Appendix Table 5: Mortality, CVD Events, and Hospitalizations by Randomized Group, UP/Cr \leq 0.22

	<u>Intensive Control</u>		<u>Standard Control</u>		<u>Intensive vs Standard</u>	
	<u># events</u>	<u>Rate*</u>	<u># events</u>	<u>Rate*</u>	<u>HR</u>	<u>P-value</u>
Total Mortality Before ESRD						
Trial Phase	22/357	1.4	29/376	1.7	0.74 (0.43,1.30)	0.3
Cohort Phase	38/307	2.7	34/323	2.4	1.10 (0.69,1.75)	0.69
Both	60/357	2	63/376	2	0.94 (0.66,1.34)	0.73
CV Death						
Trial Phase	10/357	0.6	9/376	0.5	1.14 (0.46,2.81)	0.78
Cohort Phase	17/266	1.5	7/274	0.6	2.31 (0.95,5.60)	0.06
Both	27/357	1	16/376	0.5	1.66 (0.89,3.09)	0.11
CV Composite						
Trial Phase	43/357	2.8	49/376	3	0.88 (0.58,1.33)	0.54
Cohort Phase	38/245	3.7	25/247	2.4	1.44 (0.87,2.39)	0.16
Both	81/357	3.1	74/376	2.8	1.07 (0.78,1.47)	0.66
Stroke Event						
Trial Phase	20/357	1.3	22/376	1.3	0.93 (0.50,1.70)	0.8
Cohort Phase	12/254	1.1	13/262	1.2	0.89 (0.40,1.95)	0.77
Both	32/357	1.2	35/376	1.3	0.91 (0.56,1.47)	0.7
Heart Failure Event						
Trial Phase	12/357	0.7	11/376	0.6	1.12 (0.49,2.54)	0.79
Cohort Phase	17/261	1.5	13/268	1.1	1.32 (0.64,2.72)	0.46
Both	29/357	1.1	24/376	0.8	1.23 (0.71,2.11)	0.46
Major CAD Event						
Trial Phase	11/357	0.7	15/376	0.9	0.73 (0.33,1.60)	0.43
Cohort Phase	16/259	1.4	6/264	0.5	2.62 (1.02,6.72)	0.05
Both	27/357	1	21/376	0.7	1.28 (0.72,2.28)	0.39
Overall rate of CV Events						
Trial Phase	66/357	3.8	61/376	3.4	1.11 (0.72)	0.63
Cohort Phase	54/266	4.6	47/266	3.9	1.13 (0.68)	0.63
Both	120/357	4.3	108/376	3.7	1.12 (0.79)	0.52
First hospitalization (any cause)						
Trial Phase	163/357	13.9	168/376	12.8	1.08 (0.87,1.34)	0.5
Cohort Phase	66/158	11.8	61/160	10.7	1.08 (0.76,1.53)	0.67
Both	229/357	13.2	228/376	12.1	1.08 (0.90,1.30)	0.43
Overall rate of hospitalization (any cause)						
Trial Phase	302/357	17.6	336/376	18.5	0.94 (0.73	0.63
Cohort Phase	257/266	22	276/266	23.1	0.94 (0.73	0.66
Both	559/357	20	611/376	20.9	0.94 (0.78	0.55

*Rate is number of events per 100 person-years. Summarized are CV events and hospitalizations prior to ESRD, and all cause mortality, including deaths prior to and after ESRD. The overall rate of hospitalization and the overall rate of CV Events refer to the rates of all events of the indicated type, including multiple events per patient. For these two outcomes, the # at risk at the start of the cohort phase includes all 691 enrollees into the cohort study. Only the first event is considered for all remaining event categories in the table. For all of these event categories except for mortality, the # at risk at the start of the cohort study was the # of cohort study enrollees in which neither the first event nor ESRD had occurred prior to the start of the cohort. For total mortality, the # at risk at the start of the cohort includes all randomized patients who were known to have survived to the start of the cohort, irrespective of whether they had initiated dialysis by this time.

Appendix Table 6: Mortality, CVD Events, and Hospitalizations by Randomized Group, UP/Cr > 0.22

	<u>Intensive Control</u>		<u>Standard Control</u>		<u>Intensive vs Standard</u>	
	# events	Rate*	# events	Rate*	HR	P-value
Total Mortality Before ESRD						
Trial Phase	16/181	2.2	18/176	2.9	0.73 (0.37,1.45)	0.37
Cohort Phase	10/104	2.6	9/86	3.5	0.73 (0.29,1.83)	0.5
Both	26/181	2.4	27/176	3	0.73 (0.42,1.27)	0.27
CV Death						
Trial Phase	6/181	0.8	6/176	1	0.90 (0.28,2.85)	0.86
Cohort Phase	2/83	0.6	2/66	1	0.69 (0.09,5.08)	0.72
Both	8/181	0.8	8/176	1	0.84 (0.31,2.30)	0.73
CV Composite						
Trial Phase	27/181	4.1	29/176	4.9	0.82 (0.48,1.40)	0.46
Cohort Phase	7/76	2.5	6/59	3.3	0.61 (0.20,1.87)	0.39
Both	34/181	3.6	35/176	4.5	0.79 (0.49,1.28)	0.34
Stroke Event						
Trial Phase	6/181	0.9	7/176	1.1	0.69 (0.23,2.09)	0.51
Cohort Phase	3/82	1	2/64	1	0.69 (0.10,4.50)	0.69
Both	9/181	0.9	9/176	1.1	0.71 (0.28,1.84)	0.48
Heart Failure Event						
Trial Phase	14/181	2	12/176	2	1.00 (0.45,2.20)	1
Cohort Phase	5/79	1.7	4/60	2.1	0.68 (0.18,2.64)	0.58
Both	19/181	1.9	16/176	2	0.92 (0.46,1.82)	0.8
Major CAD Event						
Trial Phase	7/181	1	8/176	1.3	0.75 (0.26,2.12)	0.58
Cohort Phase	2/79	0.7	1/64	0.5	0.41 (0.03,6.54)	0.53
Both	9/181	0.9	9/176	1.1	0.76 (0.29,2.00)	0.58
Overall rate of CV Events						
Trial Phase	41/181	4.7	33/176	3.8	1.05(0.6 , 1.83)	0.86
Cohort Phase	16/83	5.1	11/66	5.4	0.95(0.44,2.52)	0.91
Both	57/181	5.5	44/176	5.3	1.01(0.60,1.70)	0.97
First hospitalization (any cause)						
Trial Phase	92/181	18.5	87/176	18.4	1.00 (0.74,1.35)	0.9997
Cohort Phase	17/46	11.4	16/40	15.2	0.67 (0.34,1.35)	0.266
Both	109/181	16.9	103/176	17.8	0.95 (0.72,1.25)	0.7252
Overall rate of hospitalization (any cause)						
Trial Phase	214/181	24.3	182/176	21.2	1.1 (0.8 , 1.52	0.55
Cohort Phase	63/83	20.2	76/66	37.1	0.54 (0.58,2.1)	0.06
Both	277/181	27	258/176	30.9	0.91(0.66,1.26)	0.58

*Rate is number of events per 100 person-years. Summarized are CV events and hospitalizations prior to ESRD, and all cause mortality, including deaths prior to and after ESRD. The overall rate of hospitalization and the overall rate of CV Events refer to the rates of all events of the indicated type, including multiple events per patient. For these two outcomes, the # at risk at the start of the cohort phase includes all 691 enrollees into the cohort study. Only the first event is considered for all remaining event categories in the table. For all of these event categories except for mortality, the # at risk at the start of the cohort study was the # of cohort study enrollees in which neither the first event nor ESRD had occurred prior to the start of the cohort. For total mortality, the # at risk at the start of the cohort includes all randomized patients who were known to have survived to the start of the cohort, irrespective of whether they had initiated dialysis by this time.