SUPPLEMENTAL MATERIAL

Table S1. Model selection.

Model	-2Log-likelihood	BIC*	Proportion in class (%)			
			1	2	3	4
1 class	485795	486185				
2 classes	483155	483622	61.6	38.4		
3 classes	482801	483313	18.1	73.3	8.6	
4 classes	482731	483288	3.4	47.4	46.4	2.8

* BIC denotes the Bayesian Information Criteria.

Table S2. Participant characteristics by visit-to-visit variability of systolic blood pressure (SBP).*

Characteristic	SPRINT				ACCORD			
	Class of visit-to-visit variability							
	5.7 mmHg (N=1642)	10.8 mmHg (N=6449)	17.9 mmHg (N=936)	p value for trend	5.7 mmHg (N=825)	10.8 mmHg (N=3519)	17.9 mmHg (N=231)	p value for trend
Intensive group—no. (%)	899 (54.8)	3196 (49.6)	431 (46.0)	<0.001	457 (55.4)	1688 (48.0)	142 (61.5)	0.248
Baseline characteristics								
Age—yr	66.6±8.9	67.9±9.3	69.4±10.0	<0.001	61.9±7.1	62.8±6.5	64.0±6.9	<0.001
White—no. (%)	952 (58.0)	3784 (58.7)	481 (51.4)	0.011	504 (61.1)	2068 (58.8)	112 (48.5)	0.005
Female—no. (%)	428 (26.1)	2331 (36.1)	453 (48.4)	<0.001	347 (42.1)	1701 (48.3)	131 (56.7)	<0.001
Body-mass index—kg/m^2	30.1±5.4	29.9±5.8	29.4±6.2	0.006	31.6±5.6	32.3±5.4	32.3±5.7	0.006
Framingham Risk Score—%	23.9±11.4	24.6±12.4	26.6±13.9	<0.001	33.3±16.1	35.0±16.7	40.0±18.7	<0.001
Estimated GFR—$ml/min/1.73\ m^2$	74.3±18.9	71.7±20.5	68.7±22.6	<0.001	91.9±23.4	90.8±22.9	85.1±24.3	0.001
Cholesterol—mg/dl								
Total	189.4±41.8	190.2±40.4	191.7±44.1	0.185	187.5±40.7	192.3±42.2	198.4±41.6	<0.001
High-density lipoprotein	51.2±13.4	53.0±14.5	55.1±15.7	<0.001	45.3±12.5	46.3±13.0	46.1±13.8	0.090
Triglycerides—mg/dl	127.4±83.1	126.2±94.1	120.3±75.1	0.088	185.3±130.1	183.7±128.6	181.9±124.2	0.690
Glucose—mg/dl	99.4±12.5	98.8±13.7	97.9±14.5	0.009	172.3±51.5	174.2±54.9	172.4±63.1	0.596
Ratio of urinary albumin (mg) to creatinine (g)	32.2±151.0	40.2±165.1	58.4±179.8	<0.001	52.4±174.8	84.3±246.0	170.6±411.8	<0.001
Aspirin use—no. (%)	821 (50.0)	3317 (51.4)	160 (49.1)	0.995	420 (50.9)	1867 (53.1)	112 (48.5)	0.930
Statin use—no. (%)	717 (43.7)	2810 (43.6)	394 (42.1)	0.574	552 (66.9)	2287 (65.0)	145 (62.8)	0.168
Antihypertensive medication use—no. (%)	1461 (89.0)	5849 (90.7)	861 (92.0)	0.008	711 (86.2)	3087 (87.7)	215 (93.1)	0.015
Smoking—no. (%)	182 (11.1)	845 (13.1)	158 (16.9)	<0.001	90 (10.9)	410 (11.7)	28 (12.1)	0.512
Cardiovascular disease—no. (%)	269 (16.4)	1272 (19.7)	239 (25.5)	<0.001	288 (34.9)	1125 (32.0)	94 (40.7)	0.910
Blood pressure—mmHg								
Systolic	136.3±10.6	139.5±15.1	146.5±22.2	<0.001	136.7±10.7	139.0±15.7	146.1±19.3	<0.001
Diastolic	77.9 (10.3)	78.1 (11.7)	79.3 (15.0)	0.014	75.6 (8.9)	75.8 (10.1)	77.0 (11.1)	0.158
Characteristics 0-1 year post-randomization								
No. antihypertensive medications	2.0±1.0	2.2±1.0	2.5±1.0	<0.001	2.4±1.0	2.6±1.1	3.3±1.1	<0.001
No. changes in no. antihypertensive medications	0.7±0.9	1.2±1.1	1.8±1.3	<0.001	1.3±1.3	1.7±1.3	2.4±1.4	<0.001
Visit adherence—no. (%)†	89.9	82.9	81.0	<0.001	81.2	77.2	75.3	0.010

* Plus-minus values are means ±SD. GFR denotes glomerular filtration rate.

† Visit adherence was defined as not missing any visit during the first year post-randomization. SPRINT required the intensive and standard groups to have visits at 1, 3, 6, 9, and 12 months. ACCORD required the intensive group to have visits at 1, 2, 3, 4, 6, 8,10, and 12 months and the standard group at 1, 4, 8, and 12 months.

Table S3. Post 1-year outcomes associated with visit-to-visit variability classes.

Variable	Participants	Class of visit-to-visit variability			P value for trend	P value for trial heterogeneity of hazard ratio
		5.7 mmHg	10.8 mmHg	17.9 mmHg		
SPRINT primary outcome						
No. events (%)	SPRINT	53 (3.2)	267 (4.1)	60 (6.4)	<0.001	
	ACCORD	39 (4.7)	365 (10.4)	37 (16.0)	<0.001	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.75 (1.41-2.18)	2.83 (2.12-3.77)	<0.001	0.032
	SPRINT†	1.00	1.32 (0.99-1.78)	2.09 (1.44-3.02)	<0.001	
	ACCORD†	1.00	2.33 (1.68-3.25)	4.06 (2.59-6.37)	<0.001	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.54 (1.24-1.92)	2.05 (1.53-2.76)	<0.001	0.019
	SPRINT†	1.00	1.13 (0.84-1.51)	1.51 (1.03-2.19)	0.034	
	ACCORD†	1.00	2.11 (1.51-2.94)	2.90 (1.83-4.59)	<0.001	
ACCORD primary outcome						
No. events (%)	SPRINT	37 (2.3)	185 (2.9)	44 (4.7)	0.001	
	ACCORD	31 (3.8)	296 (8.4)	25 (10.8)	<0.001	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.79 (1.39-2.31)	2.76 (1.97-3.87)	<0.001	0.072
	SPRINT†	1.00	1.31 (0.92-1.86)	2.18 (1.41-3.38)	<0.001	
	ACCORD†	1.00	2.37 (1.64-3.43)	3.36 (1.99-5.70)	<0.001	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.61 (1.24-2.08)	2.04 (1.44-2.88)	<0.001	0.033
	SPRINT†	1.00	1.12 (0.79-1.60)	1.59 (1.02-2.48)	0.042	
	ACCORD†	1.00	2.19 (1.51-3.18)	2.45 (1.43-4.20)	<0.001	
Heart failure						
No. events (%)	SPRINT	12 (0.7)	76 (1.2)	24 (2.6)	<0.001	
	ACCORD	14 (1.7)	108 (3.1)	17 (7.4)	<0.001	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.79 (1.18-2.69)	4.28 (2.61-7.01)	<0.001	0.785
	SPRINT†	1.00	1.67 (0.91-3.07)	3.68 (1.84-7.36)	<0.001	
	ACCORD†	1.00	1.88 (1.08-3.29)	5.09 (2.51-10.34)	<0.001	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.40 (0.93-2.12)	2.50 (1.50-4.16)	<0.001	0.859
	SPRINT†	1.00	1.29 (0.70-2.38)	2.19 (1.08-4.42)	0.019	
	ACCORD†	1.00	1.50 (0.85-2.63)	2.89 (1.40-5.97)	0.005	
Stroke						
No. events (%)	SPRINT	12 (0.7)	62 (1.0)	15 (1.6)	0.045	
	ACCORD	8 (1.0)	61 (1.7)	10 (4.3)	0.003	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.56 (0.97-2.50)	3.13 (1.73-5.66)	<0.001	0.391
	SPRINT†	1.00	1.36 (0.73-2.51)	2.29 (1.07-4.89)	0.035	
	ACCORD†	1.00	1.86 (0.89-3.89)	5.14 (2.03-13.03)	0.001	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.30 (0.81-2.10)	2.05 (1.11-3.79)	0.024	0.413
	SPRINT†	1.00	1.13 (0.60-2.10)	1.50 (0.69-3.27)	0.303	
	ACCORD†	1.00	1.57 (0.75-3.29)	3.35 (1.29-8.69)	0.017	
All-cause death						
No. events (%)	SPRINT	25 (1.5)	199 (3.1)	51 (5.4)	<0.001	
	ACCORD	34 (4.1)	189 (5.4)	14 (6.1)	0.120	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.66 (1.26-2.18)	2.69 (1.89-3.84)	<0.001	0.116
	SPRINT†	1.00	2.09 (1.38-3.17)	3.71 (2.30-5.99)	<0.001	
	ACCORD†	1.00	1.34 (0.93-1.94)	1.64 (0.88-3.06)	0.067	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.40 (1.06-1.84)	1.86 (1.29-2.68)	<0.001	0.159
	SPRINT†	1.00	1.70 (1.12-2.59)	2.50 (1.53-4.07)	<0.001	
	ACCORD†	1.00	1.17 (0.81-1.69)	1.16 (0.61-2.18)	0.486	

CI denotes confidence interval.

*Modeling of the pooled participants from SPRINT and ACCORD, with stratified baseline hazard functions by trial.

†Modeling separately of the participants from SPRINT or ACCORD.

‡Adjusted for age, race, sex, Framingham Risk Score, baseline systolic and diastolic blood pressure, use of antihypertensive medication before randomization, smoking status, aspirin use, estimated glomerular filtration rate, history of clinical/subclinical cardiovascular disease, total cholesterol, high-density lipoprotein, triglycerides, glucose, urine albumin/creatinine ratio, body-mass index, statin use, treatment assignment, number of antihypertensive medications used, visit adherence, and estimated achieved 1-year systolic blood pressure.

Table S4. Post 1-year outcomes associated with estimated systolic blood pressure (SBP) achieved at 1 year, for participants without missing SBP measurements during the first year.

Variable	Participants	Tertile of estimated achieved SBP			P value for trend	P value for trial heterogeneity of hazard ratios
		<122 mmHg	122-134 mmHg	>134 mmHg		
SPRINT primary outcome						
No. events (%)	SPRINT	81 (3.1)	108 (4.6)	122 (4.7)	0.005	
	ACCORD	74 (6.7)	131 (9.7)	132 (12.0)	<0.001	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.45 (1.19-1.78)	1.61 (1.32-1.96)	<0.001	0.681
	SPRINT†	1.00	1.52 (1.14-2.02)	1.54 (1.16-2.04)	0.003	
	ACCORD†	1.00	1.41 (1.06-1.88)	1.68 (1.26-2.23)	<0.001	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.32 (1.07-1.63)	1.53 (1.23-1.90)	<0.001	0.966
	SPRINT†	1.00	1.34 (1.00-1.79)	1.50 (1.12-2.01)	0.007	
	ACCORD†	1.00	1.31 (0.98-1.76)	1.55 (1.15-2.10)	0.004	
ACCORD primary outcome						
No. events (%)	SPRINT	55 (2.1)	77 (3.3)	85 (3.3)	0.014	
	ACCORD	64 (5.8)	102 (7.6)	103 (9.4)	0.001	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.39 (1.10-1.75)	1.52 (1.21-1.92)	<0.001	0.552
	SPRINT†	1.00	1.59 (1.12-2.24)	1.57 (1.12-2.21)	0.011	
	ACCORD†	1.00	1.29 (0.94-1.77)	1.45 (1.06-1.98)	0.015	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.26 (0.99-1.60)	1.42 (1.10-1.82)	0.007	0.725
	SPRINT†	1.00	1.40 (0.99-1.99)	1.51 (1.06-2.15)	0.025	
	ACCORD†	1.00	1.16 (0.84-1.59)	1.34 (0.96-1.86)	0.085	
Heart failure						
No. events (%)	SPRINT	18 (0.7)	35 (1.5)	39 (1.5)	0.014	
	ACCORD	20 (1.8)	39 (2.9)	44 (4.0)	0.001	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.84 (1.24-2.73)	2.16 (1.47-3.18)	<0.001	0.572
	SPRINT†	1.00	2.22 (1.26-3.92)	2.23 (1.28-3.90)	0.007	
	ACCORD†	1.00	1.56 (0.91-2.68)	2.09 (1.23-3.56)	0.006	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.62 (1.08-2.43)	2.10 (1.39-3.17)	<0.001	0.812
	SPRINT†	1.00	1.86 (1.04-3.31)	2.29 (1.28-4.08)	0.006	
	ACCORD†	1.00	1.43 (0.83-2.48)	1.92 (1.10-3.36)	0.020	
Stroke						
No. events (%)	SPRINT	18 (0.7)	29 (1.2)	25 (1.0)	0.324	
	ACCORD	8 (0.7)	25 (1.9)	28 (2.5)	<0.001	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.98 (1.24-3.17)	1.97 (1.23-3.15)	0.007	0.208
	SPRINT†	1.00	1.82 (1.01-3.28)	1.41 (0.77-2.59)	0.294	
	ACCORD†	1.00	2.43 (1.10-5.40)	3.17 (1.44-6.97)	0.004	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.82 (1.13-2.96)	1.80 (1.09-2.98)	0.033	0.334
	SPRINT†	1.00	1.61 (0.88-2.93)	1.34 (0.71-2.52)	0.414	
	ACCORD†	1.00	2.34 (1.04-5.24)	2.79 (1.24-6.30)	0.017	
All-cause death						
No. events (%)	SPRINT	43 (1.7)	84 (3.6)	80 (3.1)	0.002	
	ACCORD	43 (3.9)	58 (4.3)	53 (4.8)	0.278	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.58 (1.21-2.07)	1.49 (1.13-1.96)	0.006	0.017
	SPRINT†	1.00	2.22 (1.54-3.20)	1.91 (1.32-2.77)	0.001	
	ACCORD†	1.00	1.02 (0.69-1.52)	1.07 (0.71-1.60)	0.756	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.38 (1.05-1.82)	1.33 (1.00-1.78)	0.078	0.028
	SPRINT†	1.00	1.88 (1.29-2.73)	1.75 (1.19-2.57)	0.009	
	ACCORD†	1.00	0.93 (0.62-1.39)	0.92 (0.60-1.42)	0.727	

CI denotes confidence interval.

*Modeling of the pooled participants from SPRINT and ACCORD, with stratified baseline hazard functions by trial.

†Modeling separately of the participants from SPRINT or ACCORD.

‡Adjusted for age, race, sex, Framingham risk score, baseline systolic and diastolic blood pressure, use of antihypertensive medication before randomization, smoking status, aspirin use, estimated glomerular filtration rate, history of clinical/subclinical cardiovascular disease, total cholesterol, high-density lipoprotein, triglycerides, glucose, urine albumin/creatinine ratio, body-mass index, statin use, number of antihypertensive medications used and visit-to-visit variability class.

Table S5. Post 1-year outcomes associated with visit-to-visit variability, for participants without missing SBP measurements during the first year.

Variable	Participants	Class of visit-to-visit variability			P value for trend	P value for trial heterogeneity of hazard ratios
		5.3 mmHg	10.3mmHg	17.0 mmHg		
SPRINT primary outcome						
No. events (%)	SPRINT	40 (3.3)	208 (3.8)	63 (6.6)	<0.001	
	ACCORD	18 (3.4)	273 (9.9)	46 (16.1)	<0.001	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.75 (1.33-2.30)	3.00 (2.18-4.12)	<0.001	0.006
	SPRINT†	1.00	1.17 (0.83-1.64)	2.03 (1.37-3.02)	<0.001	
	ACCORD†	1.00	3.02 (1.88-4.87)	5.23 (3.03-9.02)	<0.001	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.53 (1.16-2.01)	2.13 (1.53-2.96)	<0.001	0.002
	SPRINT†	1.00	0.97 (0.69-1.37)	1.38 (0.92-2.07)	0.072	
	ACCORD†	1.00	2.76 (1.71-4.46)	3.86 (2.22-6.72)	<0.001	
ACCORD primary outcome						
No. events (%)	SPRINT	26 (2.2)	147 (2.7)	44 (4.6)	0.001	
	ACCORD	16 (3.0)	222 (8.1)	31 (10.9)	<0.001	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.84 (1.33-2.53)	2.84 (1.95-4.14)	<0.001	0.064
	SPRINT†	1.00	1.27 (0.84-1.93)	2.17 (1.34-3.53)	0.001	
	ACCORD†	1.00	2.74 (1.65-4.55)	3.84 (2.10-7.03)	<0.001	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.64 (1.19-2.26)	2.06 (1.39-3.04)	<0.001	0.032
	SPRINT†	1.00	1.08 (0.71-1.64)	1.52 (0.92-2.48)	0.068	
	ACCORD†	1.00	2.55 (1.53-4.24)	2.86 (1.55-5.28)	<0.001	
Heart failure						
No. events (%)	SPRINT	10 (0.8)	58 (1.1)	24 (2.5)	<0.001	
	ACCORD	4 (0.8)	78 (2.8)	21 (7.4)	<0.001	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	2.03 (1.17-3.51)	5.06 (2.78-9.23)	<0.001	0.178
	SPRINT†	1.00	1.31 (0.67-2.56)	3.08 (1.48-6.45)	<0.001	
	ACCORD†	1.00	3.82 (1.40-10.42)	10.36 (3.56-30.18)	<0.001	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.40 (0.93-2.12)	2.50 (1.50-4.16)	<0.001	0.153
	SPRINT†	1.00	1.01 (0.51-1.98)	1.73 (0.82-3.66)	0.070	
	ACCORD†	1.00	3.08 (1.13-8.45)	6.19 (2.09-18.31)	<0.001	
Stroke						
No. events (%)	SPRINT	10 (0.8)	47 (0.9)	15 (1.6)	0.103	
	ACCORD	6 (1.1)	43 (1.6)	12 (4.2)	0.006	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.18 (0.69-2.01)	2.57 (1.38-4.77)	0.002	0.484
	SPRINT†	1.00	1.06 (0.53-2.09)	1.92 (0.86-4.28)	0.095	
	ACCORD†	1.00	1.40 (0.59-3.28)	3.93 (1.47-10.46)	0.004	
Adjusted Hazard Ratio (95% CI)‡	All*	1.00	1.03 (0.60-1.76)	1.78 (0.93-3.39)	0.057	0.399
	SPRINT†	1.00	0.90 (0.45-1.79)	1.28 (0.56-2.90)	0.493	
	ACCORD†	1.00	1.26 (0.53-2.97)	2.92 (1.07-7.97)	0.025	
All-cause death						
No. events (%)	SPRINT	16 (1.3)	148 (2.7)	43 (4.5)	<0.001	
	ACCORD	16 (3.0)	121 (4.4)	17 (6.0)	0.045	
Unadjusted Hazard Ratio (95% CI)	All*	1.00	1.78 (1.23-2.57)	2.78 (1.81-4.27)	<0.001	0.517
	SPRINT†	1.00	2.08 (1.24-3.49)	3.42 (1.93-6.08)	<0.001	
	ACCORD†	1.00	1.34 (0.93-1.94)	1.64 (0.88-3.06)	0.067	
Adjusted Hazard Ratio (95% CI)‡	All†*	1.00	1.56 (1.08-2.25)	2.01 (1.29-3.13)	0.002	0.633
	SPRINT†	1.00	1.78 (1.06-2.99)	2.40 (1.34-4.31)	0.003	
	ACCORD†	1.00	1.33 (0.79-2.25)	1.55 (0.77-3.12)	0.205	

CI denotes confidence interval.

*Modeling of the pooled participants from SPRINT and ACCORD, with stratified baseline hazard functions by trial.

†Modeling separately of the participants from SPRINT or ACCORD.

‡Adjusted for age, race, sex, Framingham Risk Score, baseline systolic and diastolic blood pressure, use of antihypertensive medication before randomization, smoking status, aspirin use, estimated glomerular filtration rate, history of clinical/subclinical cardiovascular disease, total cholesterol, high-density lipoprotein, triglycerides, glucose, urine albumin/creatinine ratio, body-mass index, statin use, treatment assignment, number of antihypertensive medications used, and estimated achieved 1-year SBP.

Figure S1. Hazard ratios of post 1-year outcomes associated with estimated SBP achieved at 1 year for SPRINT and ACCORD, using restricted cubic splines.

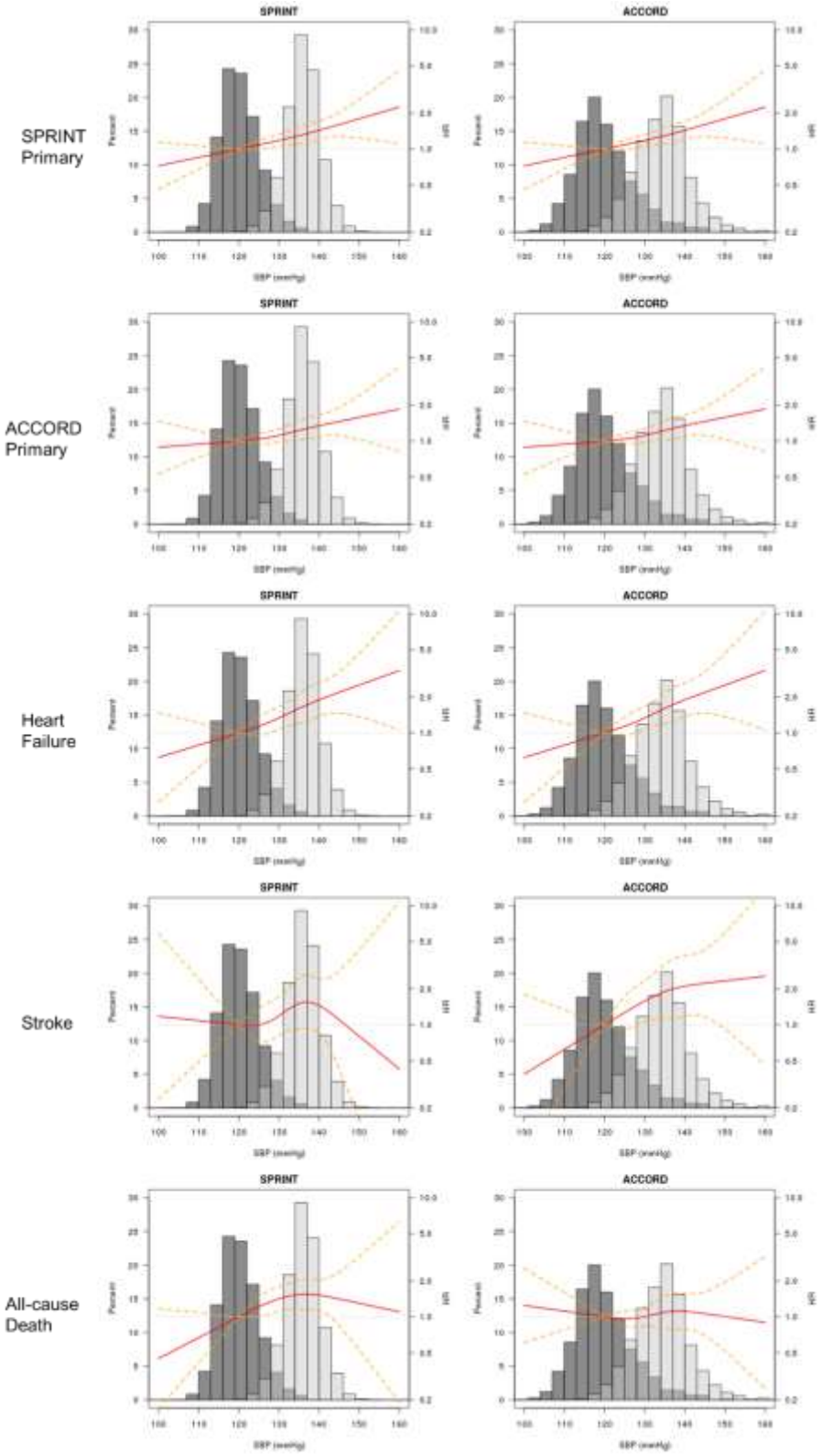
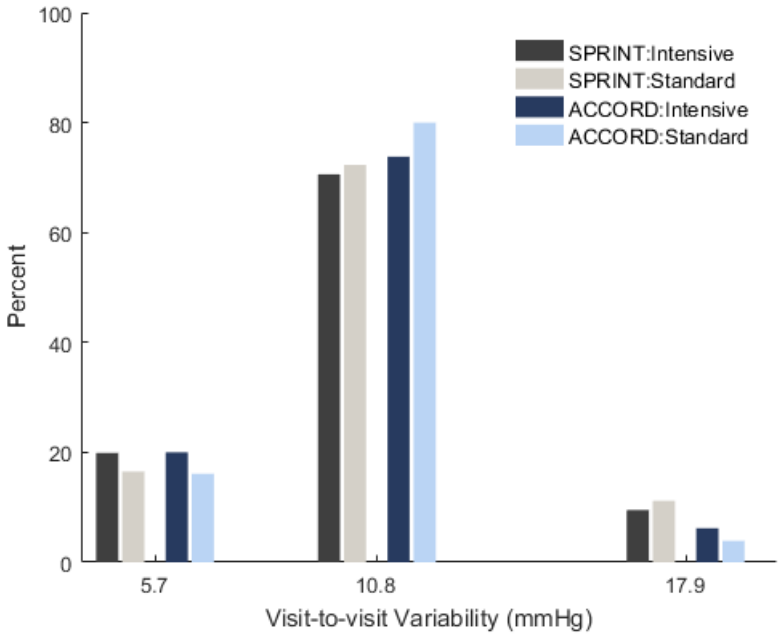
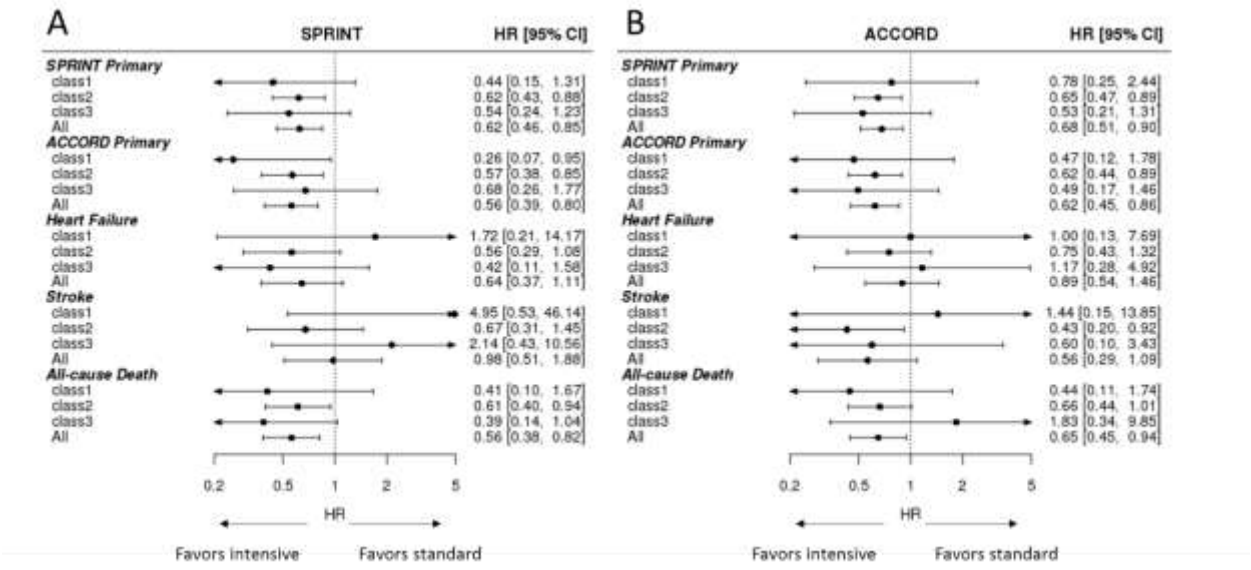


**Figure S2. Distribution of visit-to-visit variability classes for participants from the intensive and standard treatment groups of SPRINT and ACCORD. **



Bars represent percentages of participants assigned to 3 classes of visit-to-visit variability.

Figure S3. Hazard ratios of post 1-year outcomes associated with intensive versus standard treatment for classes of visit-to-visit variability in (A) SPRINT and (B) ACCORD.*



* HR denotes the hazard ratio and CI the confidence interval.
Hazard ratios were adjusted for age, race, sex, Framingham Risk Score, baseline systolic and diastolic blood pressure, use of antihypertensive medication before randomization, smoking status, aspirin use, estimated glomerular filtration rate, history of clinical/subclinical cardiovascular disease, total cholesterol, high-density lipoprotein, triglycerides, glucose, urine albumin/creatinine ratio, body-mass index, statin use, number of antihypertensive medications used, visit adherence, and estimated achieved 1-year SBP. All interactions were not significant for visit-to-visit variability class and each outcome except for heart failure in SPRINT (class 2 vs class 1 [p=0.062], and class 3 vs class 1 [p=0.088]).