Supplementary Online Content

The SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2018.21442

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

eAppendix. Multiple Imputation to Assess the Influence of Missing Outcome Data

General Approach

We used the non-parametric risk-set imputation approach of Hsu and Taylor[1] to investigate the influence of incomplete ascertainment of cognitive outcomes, i.e. participants that did not complete any cognitive testing during follow-up or those with incomplete follow-up. Briefly, this approach works by fitting two Cox proportional hazards regression models, separately by treatment group, one for the observed event times and the other for the observed censoring times. Let $\boldsymbol{X} = \{X_1, X_2, \dots, X_p\}$ be a set of auxiliary variables, which we assume to be time-independent. If we let $\boldsymbol{\beta_E} = \{\beta_{1E}, \beta_{2E}, \dots, \beta_{pE}\}$ and $\boldsymbol{\beta_C} = \{\beta_{1C}, \beta_{2C}, \dots, \beta_{pC}\}$ be the estimated log hazard ratios from the event and censoring models respectively, then define risk-scores from each model as the linear combinations, $\boldsymbol{RS_E} = \boldsymbol{X\beta_E}$ and $\boldsymbol{RS_C} = \boldsymbol{X\beta_C}$. After standardizing the risk-scores by subtracting the mean and dividing by the standard deviation, the scaled risk scores are then used to define a pair-wise distance between participants *j* and *k* as

$$d(j,k) = \sqrt{w\{\boldsymbol{RS_E}(j) - \boldsymbol{RS_E}(k)\}^2 + (1-w)\{\boldsymbol{RS_C}(j) - \boldsymbol{RS_C}(k)\}^2},$$

where *w* is a weight used to account for dependent censoring. The imputing risk set is then a group of *NN* participants with longer follow-up times than subject *j* and the smallest pair-wise distances (or simply the number of participants still at risk if it is less than *NN*). Observations are then imputed by drawing an event time from the Kaplan-Meier estimate of participants in the imputing risk set.[2]

Outcomes for multiple imputation

While the risk-set approach has the advantage of being non-parametric, we note that it is not appropriate for our protocol definition of mild cognitive impairment (MCI), which required an adjudicated classification of MCI at two consecutive assessments. For example, in order to impute longer follow-up for a participant that missed the extended follow-up visit (and had not

been classified as having MCI by the close-out visit), there needs to be participants in the risk-set with follow-up and observed events beyond the point in time of when this participant was censored. No participants experience MCI beyond the close-out visits given the two-time point definition, and so there are no events with which to inform such an imputation. Because of this, we have only conducted imputation analyses for the outcomes of probable dementia and the outcome of time to first MCI (used in sensitivity analyses, see **eTABLE 5**).

Details of Multiple Imputation Procedure

For all scenarios, we used 10 imputed datasets. We varied both the censoring weight (w = 0.2, 0.5, or 0.8) and the size of the imputing risk-set (*NN*=5, 10, 15, or 20). Outcomes were not imputed for participants that either experienced the event of interest, or those with complete follow-up through the extended follow-up visits. For participants that were censored prior to the extended follow-up visit, we set the maximum observation time as the time between 7/22/2018 and their date of randomization. The lone exception to this was if a participant died during follow-up, then their maximum observation time was the time between their date of death and randomization.

We used the following baseline auxiliary variables to define the risk-sets: age, sex, race/ethnicity (White, Black, Hispanic, or Other), education (less than high school education, high school graduate, additional training beyond high school but no college degree, college graduate or higher), smoking status (never, former, or current smoker), polypharmacy (<5 medications, 5 to <10 medications, 10 or more medications), history of cardiovascular disease (CVD, Yes vs No), estimated glomerular filtration rate (eGFR), log urine albumin to creatinine ratio, serum bicarbonate, HDL cholesterol, body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), use of aspirin, use of statins, Montreal Cognitive Assessment (MoCA) score, Digit Symbol Coding score, physical and mental component summary scores

from the VR-12, and a PHQ-9 score ≥ 10 (yes vs no). There was a small degree of sporadic missing data amongst the baseline auxiliary variables, so we first imputed those variables based on a fully conditional specification as shown in the table below. The base set of predictors for those imputations included the following set of variables with no missing data: age, sex, race/ethnicity, education, history of CVD, smoking status, SBP, DBP, polypharmacy, use of statins, and use of aspirin.

Auxiliary Variable	**No. Missing (%)**	**Imputation Model**	**Predictors**
Body Mass Index (BMI)	76 (0.8)	Linear	Base Set
HDL Cholesterol (HDL)	38 (0.4)	Linear	Base Set + BMI
Serum Bicarbonate (CO2)	27 (0.3)	Linear	Base Set + BMI + HDL
eGFR	53 (0.6)	Linear	Base Set + BMI + HDL + CO2
Log Urine Albumin to Creatinine Ratio (log UACR)	449 (4.8)	Linear	Base Set + BMI + HDL + CO2+ eGFR
MoCA Score (MoCA)	65 (0.7)	Linear	Base Set + BMI + HDL + CO2 + eGFR + log UACR
Digit Symbol Coding Score (DSC)	87 (0.9)	Linear	Base Set + BMI + HDL + CO2 + eGFR + log UACR + MoCA
VR-12 Physical Component Summary Score (VR-12 PCS)	42 (0.5)	Linear	Base Set+BMI+HDL+CO2+eGFR+log UACR+MoCA+DSC
VR-12 Mental Component Summary Score (VR-12 MCS)	48 (0.5)	Linear	Base Set + BMI + HDL + CO2 + eGFR + log UACR + MoCA + DSC + VR-12 PCS
PHQ-9 Score ≥ 10	47 (0.5)	Logistic	Base Set + BMI + HDL + CO2 + eGFR + log UACR + MoCA + DSC + VR-12 PCS + VR-12 MCS

The multiple imputation procedure was implemented using *proc mi* and *proc mianalyze* in SAS v9.4 (SAS, Cary, NC), and the *InformativeCensoring* package for the R Statistical Computing Environment.[3]

REFERENCES

1. Hsu C-H, Taylor JMG. Nonparametric comparison of two survival functions with dependent censoring via nonparametric multiple imputation. *Stat Med*. 2009;28(3):462-475. doi:10.1002/sim.3480.
2. Hsu C-H, Taylor JMG, Murray S, Commenges D. Survival analysis using auxiliary variables via non-parametric multiple imputation. *Stat Med*. 2006;25(20):3503-3517. doi:10.1002/sim.2452.
3. Raau D, Burkoff N, Bartlett J, et al. InformativeCensoring: Multiple Imputation for Informative Censoring. R Package version 0.3.4. https://cran.r-project.org/package=InformativeCensoring. Published 2016.

eTable 1. Components of the SPRINT Cognitive Battery

	Components of In-Person Cognitive Screening Battery	Components of In-Person Cognitive Extended Battery	Components of Telephone Cognitive Battery
Global Functioning	Montreal Cognitive Assessment		Modified Telephone Interview for Cognitive Status
Executive Function	Digit Symbol Coding Test		
Speed of Processing		Trail Making Test Parts A and B	Oral Trail Making Test Parts A and B
Learning and Memory	Logical Memory I	Hopkins Verbal Learning Test-Revised	
Visual-Spatial Memory		Modified Rey-Osterreith Complex Figure	
Working Memory and Attention		Digit Span Forward and Backward	
Verbal Fluency		Category Fluency-Animals	Category Fluency-Animals
Language and Naming		Boston Naming Test	

eTable 2. Comparison of Participants Included in Analyses of Probable Dementia Versus Those Excluded

	Included in Analyses For Probable Dementia N=8,563	**Excluded from Analyses For Probable Dementia** N=798	p value
Randomized to intensive treatment, No. (%)	4,278 (50.0)	400 (50.1)	0.96
Age, mean (SD), years	67.9 (9.3)	67.8 (10.6)	0.63
Age 75 years or older, No. (%)	2,391 (27.9)	245 (30.7)	0.10
Female sex, No. (%)	3,009 (35.1)	323 (40.5)	0.003
Race/Ethnicity, No. (%)			<0.001
White	5,013 (58.5)	386 (48.4)	
Black	2,509 (29.3)	293 (36.7)	
Hispanic	886 (10.3)	98 (12.3)	
Other	155 (1.8)	21 (2.6)	
Seated blood pressure, mean (SD), mm Hg			
Systolic	139.6 (15.5)	140.9 (16.5)	0.02
Diastolic	78.1 (11.8)	78.7 (13.0)	0.18
Orthostatic hypotension, No. (%)	615 (7.2)	70 (9.0)	0.08
History of cardiovascular disease, No. (%)	1,705 (19.9)	172 (21.6)	0.29
Serum creatinine, median (IQR), mg/dl	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.3)	0.04
Estimated GFR, mean (SD), mL/min/1.73 m^2	71.9 (20.4)	70.7 (22.6)	0.14
Estimated GFR<60 ml/min/1.73 m^2, No. (%)	2,385 (28.0)	260 (33.4)	0.002
Urinary albumin to creatinine ratio, median (IQR), mg/g	9.5 (5.6 to 21.0)	10.3 (5.5 to 30.6)	0.04
Total cholesterol, mean (SD), mg/dl	190.0 (41.1)	191.0 (41.8)	0.55
HDL cholesterol, mean (SD), mg/dl	52.8 (14.3)	53.9 (15.8)	0.04
Triglycerides, median (IQR), mg/dl	107.0 (77.0 to 150.0)	104.0 (76.0 to 142.5)	0.16
Glucose, mean (SD), mg/dl	98.9 (13.5)	98.1 (14.1)	0.15
Statin use, No. (%)	3,750 (44.1)	304 (39.2)	0.01
Aspirin use, No. (%)	4,395 (51.4)	361 (46.2)	0.006
10-y Framingham cardiovascular disease risk, median (IQR), %	22.2 (15.3 to 31.9)	22.3 (15.0 to 32.5)	>0.99
Body mass index, mean (SD), kg/m^2	29.9 (5.8)	29.6 (6.0)	0.28

	Included in Analyses For Probable Dementia N=8,563	Excluded from Analyses For Probable Dementia N=798	p value
No. of antihypertensive agents at baseline, mean (SD)	1.9 (1.0)	1.9 (1.0)	0.59
Montreal Cognitive Assessment, median (IQR)[a]	24.0 (21.0 to 26.0)	22.0 (19.0 to 25.0)	<0.001
Logical Memory Delayed Recall, median (IQR)[b]	8.0 (6.0 to 11.0)	7.0 (5.0 to 10.0)	<0.001
Digit Symbol Coding, median (IQR)[c]	51.0 (42.0 to 61.0)	47.0 (36.0 to 57.0)	<0.001
Frailty index, mean (SD)[d]	0.17 (0.08)	0.20 (0.09)	<0.001
Frailty status, No. (%)			<0.001
Fit, frailty index ≤0.10	1,671 (19.6)	76 (19.8)	
Less fit, frailty index >0.10 and ≤0.21	4,623 (54.2)	376 (48.7)	
Frail, frailty index >0.21	2,240 (26.2)	320 (41.5)	
Gait speed, median (IQR), m/s[e]	0.92 (0.77 to 1.06)	0.83 (0.67 to 0.99)	<0.001
Gait speed<0.8 m/s, No. (%)	669 (29.0)	96 (41.9)	<0.001
VR-12 PCS, mean (SD)[f]	44.9 (10.2)	42.1 (10.9)	<0.001
VR-12 MCS, mean (SD)[f]	53.3 (9.4)	51.5 (10.6)	<0.001
PHQ-9 score, median (IQR)[g]	2.0 (0.0 to 4.0)	2.0 (0.0 to 6.0)	<0.001
PHQ-9 score≥10, No. (%)	627 (7.3)	102 (13.2)	<0.001

Abbreviations: GFR, glomerular filtration rate; HDL, high-density lipoprotein; IQR Interquartile range; MCS, Mental Component Summary, PCS Physical Component Summary; PHQ-9, Patient Health Questionnaire 9-item depression scale; SD standard deviation; VR-12 Veterans RAND 12-item health survey

SI conversion factors: To convert HDL and total cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; and glucose to mmol/L, multiply by 0.0555.

Scores range from 0 to 30,[a] 0 to 14,[b] and 0 to 135[c] with higher scores on each test denoting better cognitive function.
[d]Scores range from 0 to 1, with higher values indicating greater frailty.
[e]Only measured in participants 75 years or older at baseline
[f]Scores on the PCS and MCS of the VR-12 are standardized with a mean of 50 and a standard deviation of 10. Scores range from 0 to 100, with higher scores denoting better physical health and mental health, respectively.
[g]Scores on the PHQ-9 range from 0 to 27, with higher scores indicating greater severity of depressive symptoms and with scores of 10 or higher suggesting moderate-to-severe depressive symptoms.

eTable 3. Occurrence of Indeterminate Adjudications by Treatment Group

	Intensive Treatment (No.=4,309) No. Patients (%)	**Standard Treatment** (No.=4,317) No. Patients (%)	p value
Cannot classify at last cognitive assessment	114 (2.6)	122 (2.8)	0.65
Cannot classify for at least one cognitive assessment	142 (3.3)	140 (3.2)	0.94
Cannot classify for all cognitive assessments	31 (0.7)	32 (0.7)	>0.99

Denominators includes participants included in analyses of cognitive outcomes (see Figure 1) and participants with adjudication of cannot classify at all follow-up visits, i.e. 4,278 + 31 = 4,309 (intensive treatment) and 4,285 + 32 = 4,317 (standard treatment).

During follow-up, 4,527 cognitive assessments were adjudicated, with the two assigned adjudicators disagreeing on the broad classification (no impairment, mild cognitive impairment, probable dementia, or cannot classify) for 1,270 (28.0%), thereby necessitating committee review.

eTable 4. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group With Follow-up Through Study Closeout Visits (Excluding Data From Extended Follow-up Visits)

	Intensive Treatment		Standard Treatment			
Outcome	No.	Cases / 1000 Person-Years	No.	Cases / 1000 Person-Years	Hazard Ratio (95% CI)[a]	P value
Probable Dementia	129	8.4	140	9.1	0.93 (0.73 – 1.18)	0.54
Mild Cognitive Impairment	239	16.2	284	19.4	0.83 (0.70 – 0.99)	0.04
Composite of Mild Cognitive Impairment or Probable Dementia	345	23.0	382	25.8	0.90 (0.78 – 1.04)	0.16

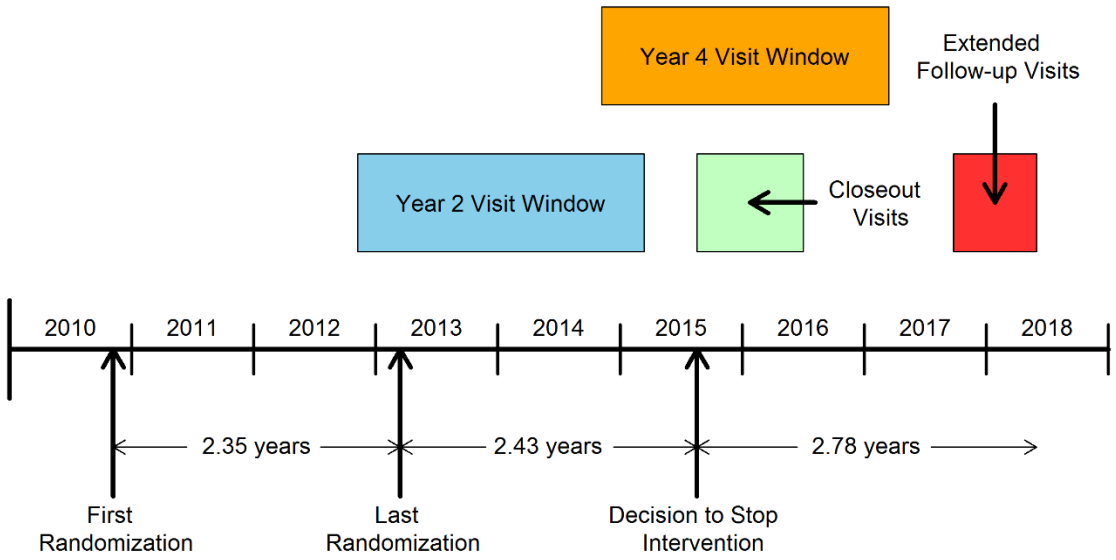
CI denotes Confidence Interval.
[a]Intensive treatment group versus standard treatment group based on Cox proportional hazards regression.
[b]Person-years of observation: for the intensive treatment group, 15 383; for the standard treatment group, 15 301
[c]Person-years of observation: for the intensive treatment group, 14 791; for the standard treatment group, 14 617
[d]Person-years of observation: for the intensive treatment group, 14 986; for the standard treatment group, 14 823

eTable 5. Sensitivity Analyses for Missing Data Using Risk-Set Multiple Imputation

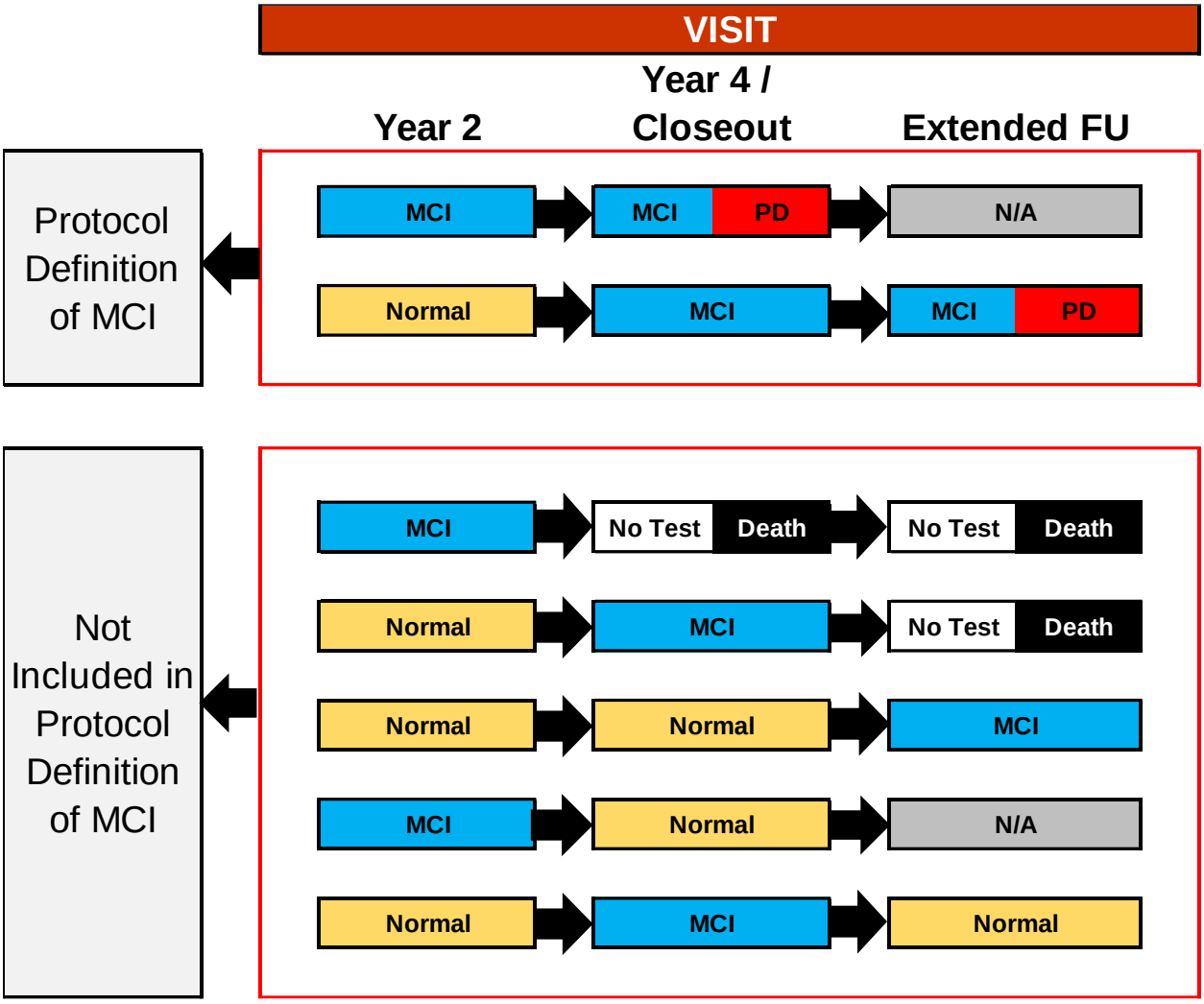
Outcome	NN	w	Cases per 1000 Person-Years INT	STD	Hazard Ratio (95% CI)	P Value
Probable Dementia : Observed	-	-	7.2	8.6	0.83 (0.67 - 1.04)	0.10
Probable Dementia : Imputed	5	0.2	8.7	10.4	0.84 (0.68 - 1.03)	0.10
		0.5	8.6	10.3	0.83 (0.67 - 1.04)	0.11
		0.8	8.5	10.2	0.83 (0.64 - 1.08)	0.16
	10	0.2	9.0	10.4	0.86 (0.71 - 1.05)	0.14
		0.5	8.6	10.3	0.83 (0.69 - 1.02)	0.07
		0.8	8.7	10.2	0.85 (0.67 - 1.07)	0.16
	15	0.2	8.8	10.5	0.84 (0.69 - 1.02)	0.08
		0.5	8.9	10.6	0.84 (0.66 - 1.07)	0.15
		0.8	8.7	10.4	0.83 (0.65 - 1.07)	0.15
	20	0.2	8.9	10.5	0.85 (0.69 - 1.03)	0.10
		0.5	8.8	10.2	0.86 (0.70 - 1.06)	0.15
		0.8	8.8	10.5	0.84 (0.69 - 1.03)	0.10
Outcome	**NN**	**w**	**Cases per 1000 Person-Years INT**	**STD**	**Hazard Ratio (95% CI)**	**P Value**
Time to First MCI : Observed	-	-	44.9	49.8	0.90 (0.82, 0.98)	0.02
Time to First MCI : Imputed	5	0.2	49.1	53.0	0.93 (0.85, 1.01)	0.07
		0.5	49.1	53.1	0.92 (0.84, 1.01)	0.07
		0.8	48.8	53.1	0.92 (0.83, 1.01)	0.07
	10	0.2	50.2	53.2	0.94 (0.86, 1.03)	0.17
		0.5	49.3	53.4	0.92 (0.84, 1.00)	0.05
		0.8	49.5	53.1	0.93 (0.85, 1.02)	0.12
	15	0.2	50.1	54.2	0.92 (0.84, 1.01)	0.08
		0.5	50.2	53.9	0.93 (0.84, 1.02)	0.12
		0.8	50.2	53.5	0.93 (0.85, 1.02)	0.15
	20	0.2	50.4	53.8	0.93 (0.85, 1.02)	0.13
		0.5	50.1	53.7	0.93 (0.84, 1.03)	0.14
		0.8	50.5	54.0	0.93 (0.85, 1.02)	0.14

INT denotes intensive treatment group and STD standard treatment group.

eFigure 1. Timeline for Follow-up Cognitive Assessments in SPRINT



eFigure 2. Schematic Depicting Possible Combinations of Adjudication Decisions Including Mild Cognitive Impairment (MCI)

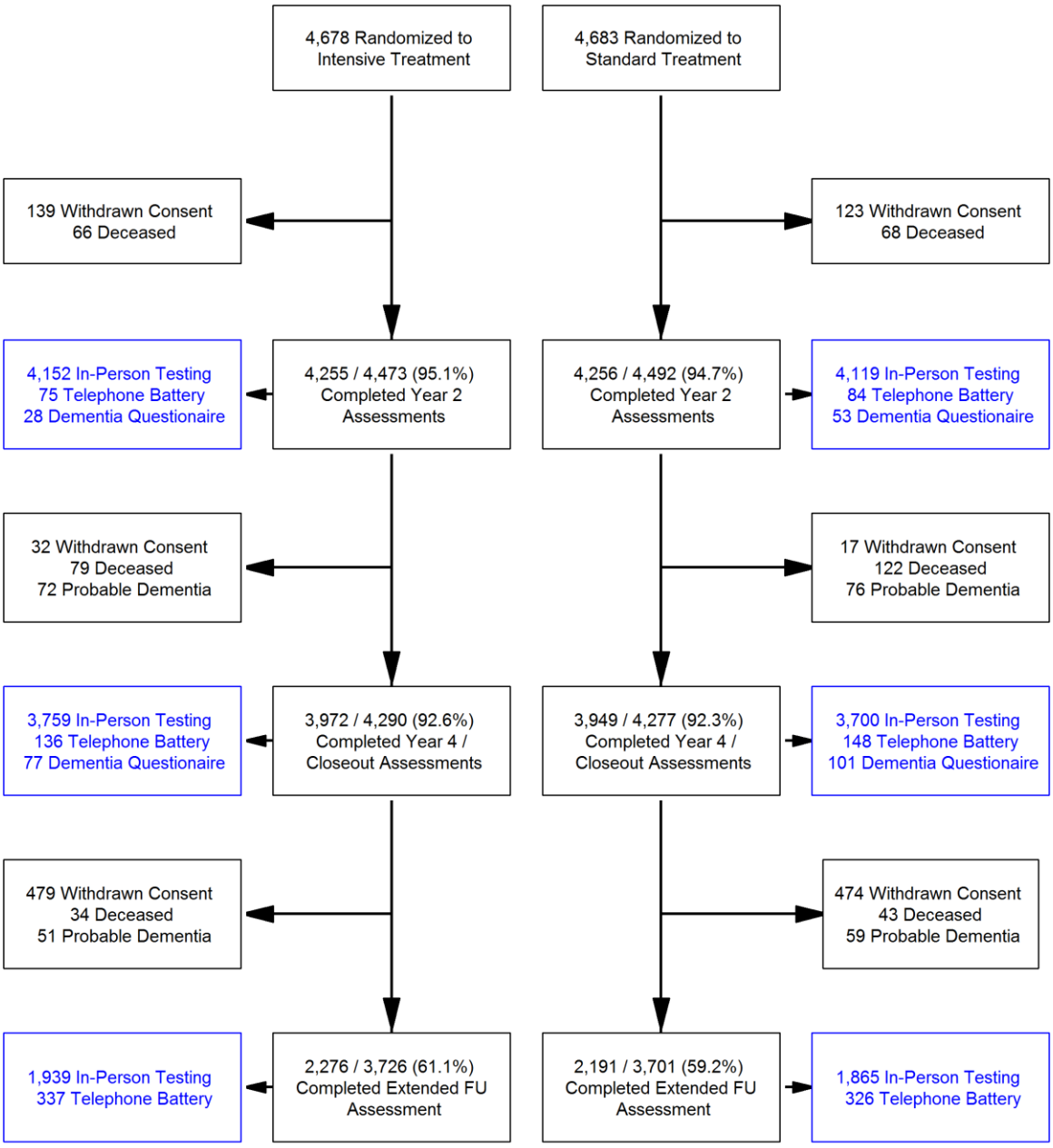


PD denotes Probable Dementia, Normal indicates no cognitive impairment, and N/A indicates that outcome definition of MCI is not dependent upon cognitive status at that particular visit. Note that all scenarios shown above are included in the definition for the outcome of time to first MCI, used in the sensitivity analyses shown in eTable 5.

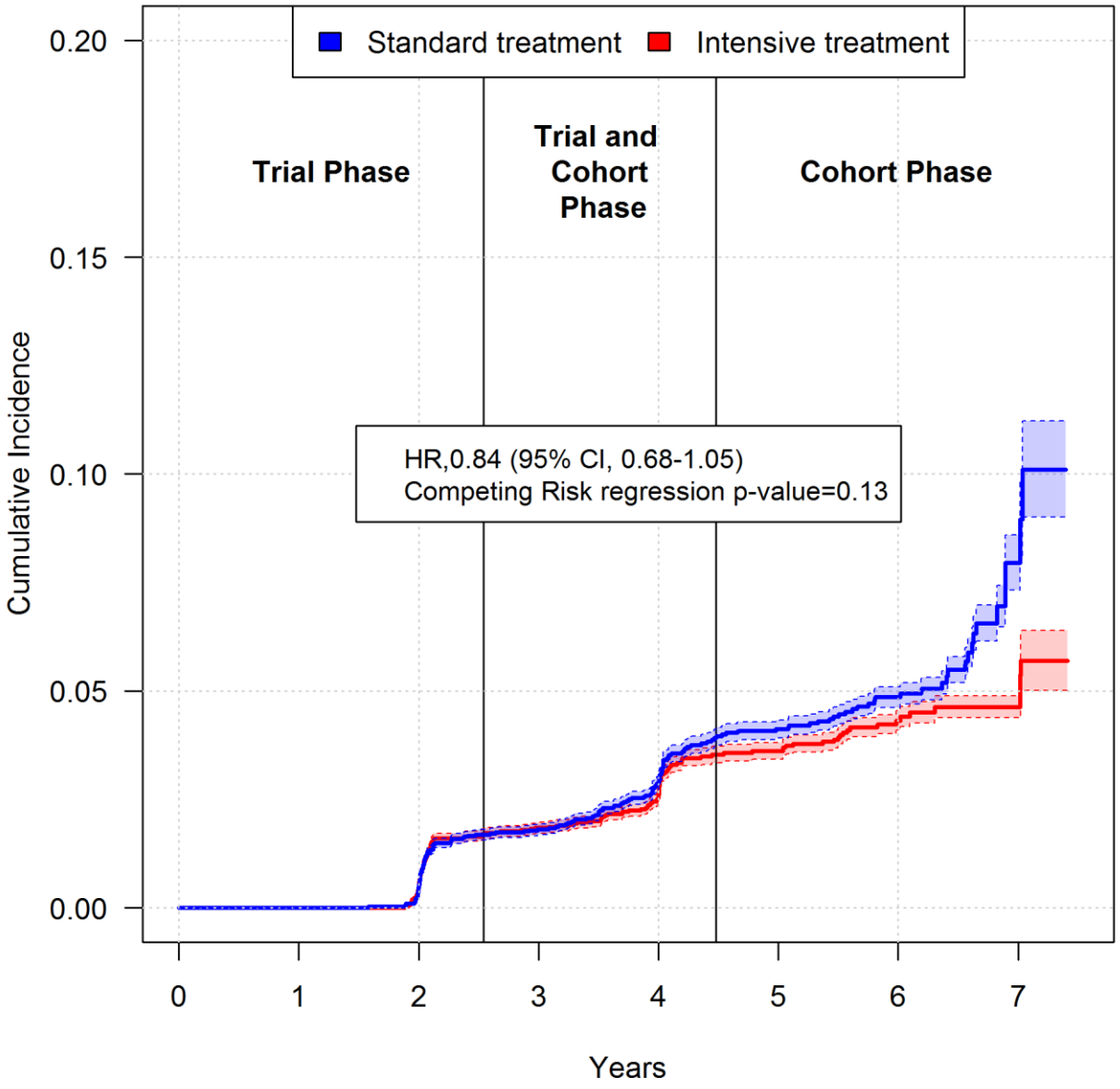
eFigure 3. Systolic Blood Pressure in the Two Treatment Groups Over the Course of Follow-up

The systolic blood pressure (SBP) target was <120 mmHg in the Intensive Treatment group, and <140 mmHg in the Standard Treatment group. Trial phase includes follow-up through the decision to stop the SPRINT intervention on 8/20/2015, while cohort phase denotes visits that occurred after that date. Points indicate means with error bars denoting 95% Confidence Intervals.

eFigure 4. Completion of Cognitive Assessments by Treatment Group During Follow-up



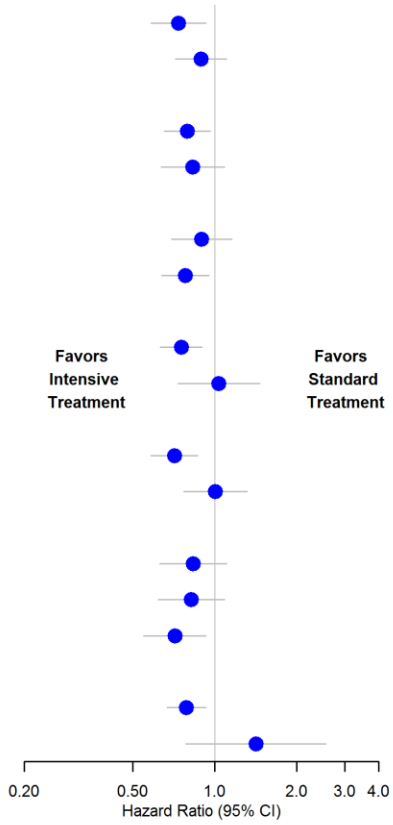
eFigure 5. Probable Dementia by Treatment Group Accounting for the Competing Risk of Death



HR denotes hazard ratio. Shaded regions indicate 95% point-wise confidence intervals.

eFigure 6. Treatment Differences for Mild Cognitive Impairment by Subgroups

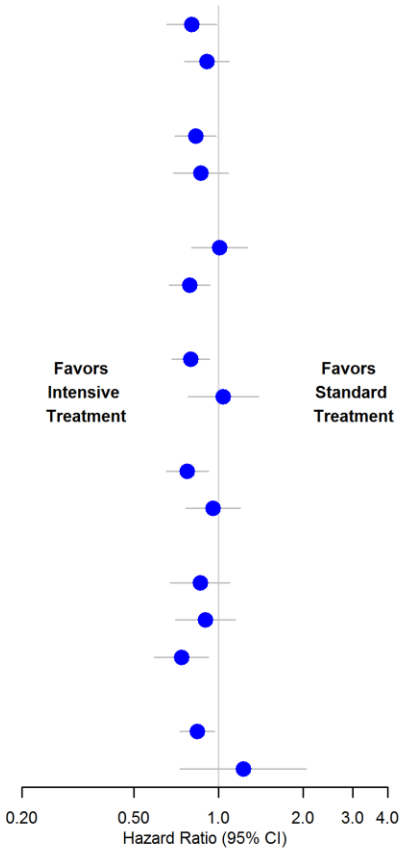
	Intensive Treatment No./Cases per 1000 Person-Years	Standard Treatment No./Cases per 1000 Person-Years	Hazard Ratio (95% CI)	Interaction P value
Age				**0.22**
<75 years	125 / 8.4	172 / 11.8	0.74 (0.58 - 0.93)	
75 years or older	162 / 33.5	181 / 38.8	0.89 (0.72 - 1.11)	
Sex				**0.78**
Male	185 / 14.6	235 / 18.7	0.79 (0.65 - 0.96)	
Female	102 / 14.6	118 / 17.5	0.83 (0.64 - 1.08)	
Race				**0.47**
Black	111 / 19.1	130 / 22.1	0.90 (0.69 - 1.16)	
Non-Black	176 / 12.7	223 / 16.6	0.78 (0.64 - 0.95)	
History of CVD				**0.12**
No	217 / 13.6	286 / 18.4	0.75 (0.63 - 0.90)	
Yes	70 / 18.7	67 / 18.1	1.03 (0.73 - 1.46)	
Chronic Kidney Disease				**0.04**
No	170 / 11.8	244 / 17.1	0.71 (0.58 - 0.86)	
Yes	117 / 22.1	109 / 21.7	1.00 (0.77 - 1.31)	
Systolic BP tertiles				**0.72**
132 mm Hg or less	94 / 13.8	106 / 16.4	0.83 (0.63 - 1.10)	
>132 and <145 mm Hg	94 / 14.7	112 / 17.2	0.82 (0.62 - 1.09)	
145 mm Hg or more	99 / 15.3	135 / 21.5	0.71 (0.55 - 0.93)	
Orthostatic hypotension				**0.30**
No	259 / 14.2	327 / 18.2	0.79 (0.67 - 0.93)	
Yes	28 / 19.5	26 / 19.4	1.41 (0.78 - 2.56)	



Abbreviations: CVD, Cardiovascular Disease; BP Blood Pressure. Chronic Kidney Disease defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2 based on the MDRD study equation. Systolic BP tertiles were based on BP measured at the randomization visit.

eFigure 7. Treatment Differences for the Composite Outcome of Mild Cognitive Impairment or Probable Dementia by Subgroups

	Intensive Treatment No./Cases per 1000 Person-Years	Standard Treatment No./Cases per 1000 Person-Years	Hazard Ratio (95% CI)	Interaction P value
Age				**0.35**
<75 years	168 / 11.3	210 / 14.3	0.80 (0.65 - 0.98)	
75 years or older	234 / 47.1	259 / 53.7	0.91 (0.76 - 1.09)	
Sex				**0.74**
Male	254 / 19.8	304 / 24.0	0.83 (0.70 - 0.98)	
Female	148 / 21.0	165 / 24.2	0.87 (0.69 - 1.08)	
Race				**0.11**
Black	148 / 25.3	152 / 25.7	1.01 (0.80 - 1.27)	
Non-Black	254 / 18.1	317 / 23.3	0.79 (0.67 - 0.93)	
History of CVD				**0.12**
No	301 / 18.7	374 / 23.7	0.80 (0.68 - 0.93)	
Yes	101 / 26.6	95 / 25.4	1.04 (0.78 - 1.39)	
Chronic Kidney Disease				**0.12**
No	237 / 16.4	307 / 21.4	0.77 (0.65 - 0.92)	
Yes	165 / 30.6	162 / 31.6	0.96 (0.77 - 1.20)	
Systolic BP tertiles				**0.50**
132 mm Hg or less	129 / 18.8	139 / 21.3	0.86 (0.67 - 1.10)	
>132 and <145 mm Hg	129 / 20.0	142 / 21.6	0.90 (0.70 - 1.15)	
145 mm Hg or more	144 / 22.0	188 / 29.5	0.74 (0.59 - 0.92)	
Orthostatic hypotension				**0.77**
No	366 / 19.9	429 / 23.7	0.84 (0.73 - 0.97)	
Yes	36 / 24.9	40 / 29.2	1.22 (0.73 - 2.05)	



Abbreviations: CVD, Cardiovascular Disease; BP Blood Pressure. Chronic Kidney Disease defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2 based on the MDRD study equation. Systolic BP tertiles were based on BP measured at the randomization visit.