Longer term All-Cause and Cardiovascular Mortality with Intensive Blood Pressure Control: A Secondary Analysis of SPRINT

Byron C. Jaeger, PhD,1 Adam P. Bress, PharmD, MS,2,3 Alfred K. Cheung, MD,4,5 William C. Cushman, MD,6 Paul E. Drawz, MD,7 Lawrence J. Fine, MD,8 Karen C. Johnson, MD,6 Cora E. Lewis, MD,9 Suzanne Oparil, MD,10 Michael V. Rocco, MD,11 Mark A. Supiano, MD,12 Paul K. Whelton, MD,13 Joshua D. Bundy, PhD,13 Jeff D. Williamson, MD, MHS,14 Jackson T. Wright, Jr, MD, PhD,15 David M. Reboussin, PhD,1 and Nicholas M. Pajewski, PhD,1

1Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC. 2Informatics, Decision-Enhancement, and Analytic Sciences (IDEAS) Center, Veterans Affairs, Salt Lake City Health Care System, Salt Lake City, UT. 3Department of Population Health Sciences, University of Utah School of Medicine, Salt Lake City, UT. 4Renal Section, Veterans Affairs Salt Lake City Healthcare System, UT. 5Division of Nephrology and Hypertension, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake Cite, UT. 6Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis. 7Division of Renal Diseases & Hypertension, University of Minnesota, MN. 8Clinical Applications and Prevention Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD. 9Department of Epidemiology, University of Alabama at Birmingham. 10Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham. 11Section on Nephrology, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC. 12Division of Geriatrics, University of Utah School of Medicine, Salt Lake City. 13Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA. 14Section on Gerontology and Geriatric Medicine, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC. 15Division of Nephrology and Hypertension, University Hospitals Cleveland Medical Center, Case Western Reserve University, OH  

**Correspondence to:**  
Nicholas M. Pajewski, PhD  
Department of Biostatistics and Data Science  
Division of Public Health Sciences  
Wake Forest School of Medicine  
Medical Center Boulevard  
Winston-Salem, NC 27154  
(336) 713-1396  
[npajewsk@wakehealth.edu](mailto:npajewsk@wakehealth.edu)

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# ABSTRACT

**IMPORTANCE**. Both the Systolic Blood Pressure Intervention Trial (SPRINT) and the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial have shown benefits of intensive blood pressure control on cardiovascular morbidity and mortality. However, as both trials were ended after slightly more than 3 years of follow-up, the effect of intensive treatment on longer term mortality is unknown.

**OBJECTIVE**. To evaluate the legacy effect of intensive hypertension treatment on longer term all-cause and cardiovascular mortality.

**DESIGN, SETTING, AND PARTICIPANTS**. SPRINT, a randomized clinical trial of 9361 patients aged 50 years or older with hypertension and increased cardiovascular risk, but without diabetes or history of stroke. Randomization began on November 8, 2010, the trial intervention was stopped early on August 20, 2015, and trial follow-up visits occurred through July 2016.

**INTERVENTIONS**. Randomization to a systolic blood pressure goal of either less than 120 mm Hg (intensive treatment, n=4678) versus less than 140 mm Hg (standard treatment, N=4683).

**MAIN OUTCOMES AND MEASURES**. Cardiovascular and all-cause mortality assessed via the US National Death Index, beginning in 2016 through December 31st, 2020. Outpatient blood pressures measured in routine clinical practice were examined in a subset of trial participants (N=3644).

**RESULTS**. Among 9361 randomized participants (mean age, 67.9 years; 3332 women [35.6%]), the median intervention period was 3.34 years. Over a median follow-up of 8.76 years, intensive treatment was beneficial for both cardiovascular (Hazard Ratio [HR] = 0.66, 95% CI 0.49 to 0.89) and all-cause mortality (HR = 0.83, 95% CI 0.68 to 1.01) through close-out visits for the trial (follow-up through July 2016). However, there was no indication of benefit during post-trial follow-up for either cardiovascular (HR = 1.02, 95% CI 0.84 to 1.24) or all-cause mortality (HR = 1.08, 95% CI 0.94 to 1.23). Results were similar for subgroups based on baseline age, cognitive function, and frailty status. Analyses of outpatient blood pressures indicated a steady decline in the mean between group difference following the trial, largely driven by increases in mean systolic blood pressure in participnts randomized to intensive treatment, increasing from a mean of X at 4.5 years of follow-up to Y at 9 years of follow-up.

there were 248 and 818 cardiovascular and all-cause deaths with intensive treatment respectively, and 273 cardiovascular / 826 all-cause deaths for standard treatment.

**CONCLUSIONS AND RELEVANCE**. The observed benefit of intensive treatment on cardiovascular and all-cause mortality was largely attenuated during post-trial observational follow-up. Given increasing blood pressures in participants randomized to intensive treatment following the trial, these results highlight the importance of consistent long-term management of hypertension.

# INTRODUCTION

both the The Systolic Blood Pressure Intervention Trial (SPRINT) and the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial have shown the benefits of intensive blood pressure control on cardiovascular morbidity and mortality.1,2 However, both trials were stopped early after a median follow-up of 3 years.

**Reminder: bring in the recent BPTTC meta-analyses into the introduction**3.

Here we examined the longer term effect of randomization to intensive treatment on through linkage to the National Death Index (NDI).

# METHODS

**Trial Design**: The trial design and methods have been published previously.4 Briefly, we conducted a multicenter randomized clinical trial that compared two strategies for managing systolic BP (SBP) in older adults with hypertension who were at increased risk of cardiovascular disease (CVD). Participants were aged 50 years or older and had an SBP between 130 and 180 mm Hg at the screening visit, depending on the number of anti-hypertensive agents prescribed. Participants were considered to have an increased cardiovascular risk if they had clinical or subclinical cardiovascular disease, chronic kidney disease (defined by an estimated glomerular filtration rate of <60 mL/min/1.73 m2), or a Framingham Risk Score of 15% or greater or if they were aged 75 years or older. Individuals residing in a nursing home, persons with a diagnosis of dementia (based on medical record review), and those treated with medications primarily used for dementia therapy were excluded, as were persons with prevalent diabetes mellitus, history of stroke, proteinuria > 1 gram per day, or polycystic kidney disease. Individuals at 102 sites in the United States and Puerto Rico were randomized (1:1) to a SBP goal of less than 120 mm Hg (intensive treatment group, n = 4678) or a goal of less than 140 mm Hg (standard treatment group, n = 4683), using random permuted blocks with the randomization stratified by clinic site. The algorithms and formulary for the trial are listed in the published study protocol ( **citations needed**? ). Trial enrollment began in November 2010 and ended in March 2013, with active follow-up through July 1, 2016. The study was approved by the institutional review board at each participating site, and each participant provided written informed consent. The study is registered at ClinicalTrials.gov (NCT01206062).

**Baseline Study Measurements**: Sociodemographic data were collected at baseline, with race or ethnicity information collected via self-report. The estimated glomerular filtration rate (eGFR) was calculated by the race-free 2021 CKD-EPI creatinine equation.5 Cognitive function was assessed using Montreal Cognitive Assessment (MoCA).6 Lower cognitive function was defined as scoring 18 or lower (less than high school education) or 20 or lower (high school education or higher) on the MoCA. This roughly corresponds to the estimated normative 10th percentile in the Irish Longitudinal Study of Aging.7 We defined frailty status at baseline using a previously developed Frailty Index (FI) based upon the model of deficit accumulation.8 Briefly, the FI comprises a total of 36 items, and is calculated as the sum of the score for each deficit divided by the total number of nonmissing items. We categorized frailty status as fit (FI ≤ 0.10), less fit (0.10 < FI ≤ 0.21), or frail (FI > 0.21).

**National Death Index Linkage**: Outcomes of interest included all-cause and CVD mortality. Methods of ascertainment and adjudication through the course of trial follow-up have been previously described. Subsequently, mortality was ascertained through a US National Death Index (NDI) search. Possible matches were identified according to NDI guidelines. To be considered a confirmed death, we required 4 or more of 5 matches among Social Security number, name, date of birth, city, and state in the NDI. NDI follow-up began in 2016 and ended on the date of death or date of the NDI search (2020). Deaths ascertained in 2020 were based on the preliminary data release. CVD mortality for NDI-based follow-up used the NDI Plus System, which automatically identifies underlying causes of death from death certificates, including conversion to ICD-10 codes. we defined CVD mortality as any death containing the ICD-10 codes of I00 to I99.

**EHR Ancillary Study**: We examined the trajectory of systolic blood pressure (SBP) following the conclusion of the trial using outpatient SBPs extracted from the electronic health record (EHR). Methods for the linkage of participants to their medical record number and the extraction of vital sign data have been previously described.9 Because encounter type information was inconsistently available (i.e. outpatient, inpatient, observation, etc.), we defined a BP measurement as outpatient if there were was not a BP measurement on the preceding or following day, and if there were 2 or less BP measurements on a particular day. We averaged outpatient EHR BP readings when there were 2 on the same day.

***Statistical Analysis***: The effect of randomization to intensive treatment was estimated as a function of time using two approaches. The first approach split the follow-up of study participants into non-overlapping trial and cohort phases, then estimated the effect of randomization to intensive treatment in each phase.10 The second approach estimated a continuous time-dependent effect.11,12 All analyses accounted for correlation within study sites,13 and analyses of cardiovascular mortality accounted for the competing risk of non-cardiovascular mortality.14 The mean between-group differences in SBP following the conclusion of trial follow-up (after July 2016) were estimated using linear mixed models. Models included random effects for participant and clinic site. Our primary models included an interaction between treatment group and time since randomization, which was flexibly modeled using B-splines.

All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC) and R version 4.1.2 (R Project for Statistical Computing [<http://www.r-project.org>]) with multiple auxiliary R packages.15–20 All hypothesis tests were 2-sided, and P values less than 0.05 were considered statistically significant. No adjustments for multiple comparisons were made.

# RESULTS

In both treatment groups, median follow-up time was 8.76 years. A total of 818 and 826 all-cause mortality events occurred among participants randomized to intensive and standard treatment, respectively (**Table 2**). The hazard ratio (HR) for all-cause mortality among participants randomized to intensive versus standard treatment was 0.83 (95% confidence interval [CI] 0.68, 1.01) during the trial phase and 1.08 (95% CI 0.94, 1.23) during the cohort phase. In subgroups based on age, sex, race, CKD, cognitive function, and frailty, there was no evidence that intensive treatment during the trial phase had benefit for all-cause mortality during the cohort phase (**eFigure 1**). The continuous time-dependent effect of intensive versus standard treatment indicated a benefit for all-cause mortality from 1.03 to 2.80 years from randomization, and was attenuated throughout the remainder of the cohort phase (**Figure 1**).

A total of 248 and 273 CVD mortality events occurred among participants randomized to intensive and standard treatment, respectively (**Table 3**). The HR for CVD mortality among participants randomized to intensive versus standard treatment was 0.66 (95% CI 0.49, 0.89) during the trial phase and 1.02 (95% CI 0.84, 1.24) during the cohort phase. Adults randomized to intensive treatment who were <75 years of age, men, non-black, without CKD, or with cognitive function >10th percentile had lower CVD mortality risk during the trial phase compared to their counterparts randomized to standard treatment, but there was no evidence that intensive treatment during the trial phase had benefit for CVD mortality during the cohort phase (**eFigure 2**). The time-dependent effect of intensive versus standard treatment indicated a benefit for CVD mortality from 2.30 to 5.62 years from randomization, and was attenuated throughout the remainder of the cohort period (**Figure 2**).

The estimated mean SBP among participants randomized to intensive treatment was <placeholder (95% CI)> at 5 years and <placeholder (95% CI)> at 10 years post-randomization (**Figure 3**). For participants randomized to standard treatment, mean SBP was estimated to be <placeholder (95% CI)> at 5 years and <placeholder (95% CI)> at 10 years post-randomization.

# DISCUSSION

A striking aspect of our results is the quickly weakening level of BP control for participants randomized to intensive treatment. While an attenuation of the between-group BP delta subsequent to the trial was certainly expected, one hypothesis was that such an attenuation would be driven by participants randomized to standard treatment pursuing a lower BP goal, given the results of SPRINT and subsequent changes to hypertension guidelines. However, this is clearly not what occurred. While we do not have access to prescription records to know how participant medication regimes may have changed after the trial, these results likely show some contribution of clinician therapeutic inertia, which has been identified as a significant barrier to improving population level control of hypertension. Combined with evidence showing recent decreases in the population of prevalence of controlled hypertension in the US,21 our results highlight the sobering reality facing the hypertension community. Sustainability is a clear limiting factor, especially with trying to implement lower BP goals and interventions earlier in adulthood.

This study has several limitations. First, while we restricted analyses to high quality NDI matches, some small degree of misclassification in linking participants to the NDI is likely. Second, while several studies have shown reasonable performance of using NDI diagnosis codes for defining CVD mortality, it is clearly not as robust as the adjudication process used in the primary follow-up for the trial. Third, information about BP control after the trial was limited to routine outpatient BPs extracted from the EHR, which are well known to poorly reflect the standardized BP measurement process used during the trial.9

# ACKNOWLEDGMENTS

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**Table 1**: Characteristics of study participants overall and stratified by inclusion in the electronic health record ancillary study.

| **Characteristic** | **Overall N = 9,361** | **Included in ancillary EHR study** | | **p-valuea** |
| --- | --- | --- | --- | --- |
| **No N = 4,756** | **Yes N = 4,605** |
| Age, years |  |  |  | 0.4 |
| Mean (SD) | 68 (9) | 68 (9) | 68 (9) |  |
| Median (IQR) | 67 (61, 76) | 67 (61, 76) | 67 (61, 75) |  |
| Age ≥75 years | 28 | 28 | 28 | 0.5 |
| Female | 36 | 36 | 35 | 0.4 |
| Black | 31 | 31 | 32 | 0.3 |
| Chronic Kidney Diseaseb | 25 | 25 | 25 | 0.5 |
| MoCA ≤10th percentile | 27 | 27 | 27 | 0.6 |
| Frailty Status |  |  |  | 0.8 |
| Fit (FI≤0.10) | 16 | 16 | 16 |  |
| Pre-frail (0.10<FI≤0.21) | 51 | 52 | 51 |  |
| Frail (FI>0.21) | 33 | 33 | 33 |  |
| Table values are percentages unless otherwise specified | | | | |
| aP-values computed using Wilcoxon rank sum test for age in years, chi-square test for age ≥75 years, and chi-square test for all other variables | | | | |
| bChronic Kidney Disease was defined by an estimated glomerular filtration rate <60 ml/min/1.73 m2 based on the 2021 CKD-EPI creatinine equation. | | | | |
| EHR represents electronic health records, FI frailty index, IQR interquartile range, MoCA Montreal cognitive assessment and SD standard deviation | | | | |

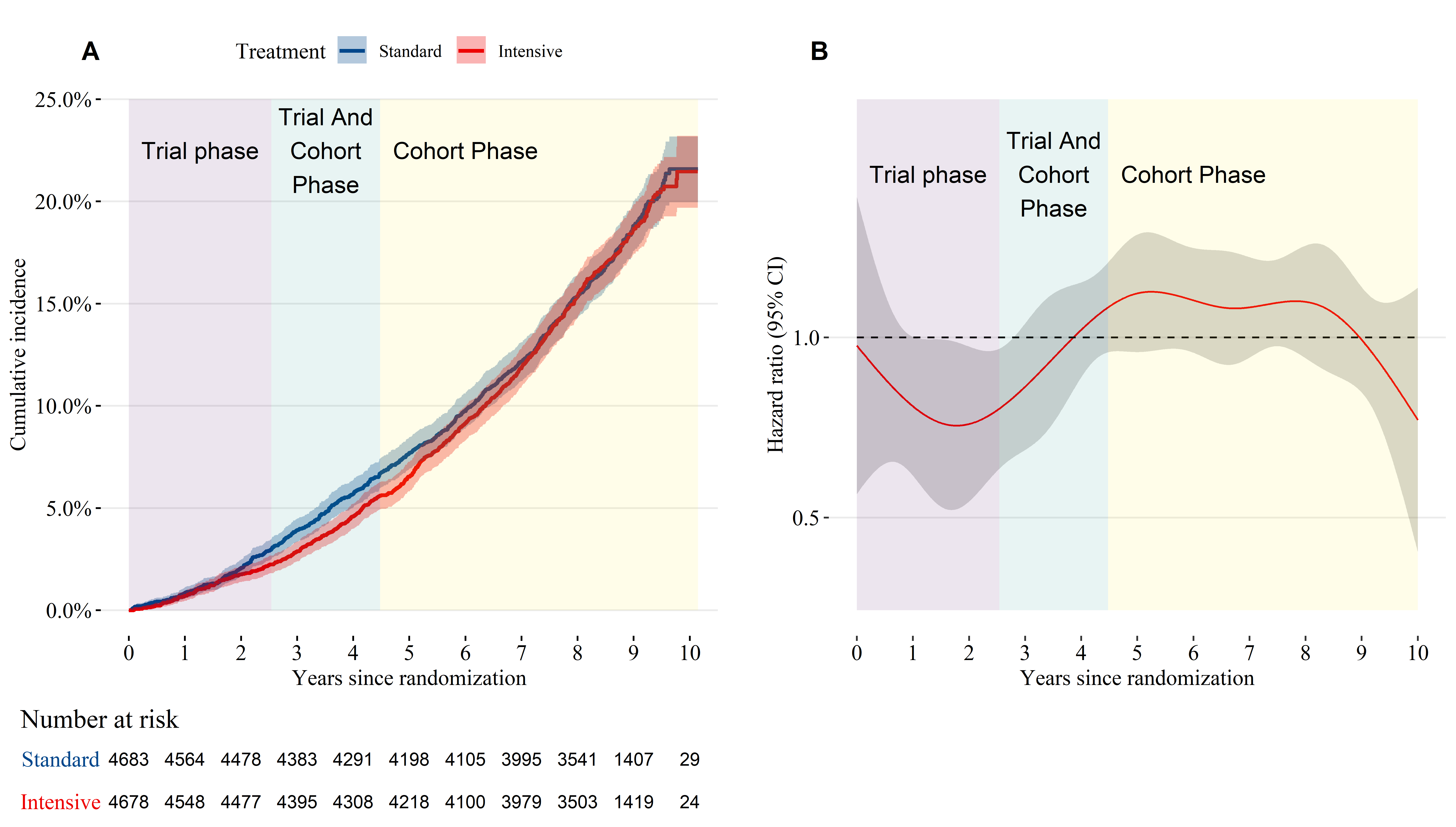
**Table 2**: All-cause mortality by treatment group and subgroup

|  | **Trial Follow-up Through Close-out Visits** | | | | | **Post-trial Follow-up** | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **N Events / N Total** | | **Incidence (95% CI)** | | **Hazard Ratio (95% CI)** | **N Events / N Total** | | **Incidence (95% CI)** | | **Hazard Ratio (95% CI)** |
| **Standard** | **Intensive** | **Standard** | **Intensive** | **Standard** | **Intensive** | **Standard** | **Intensive** |
| Overall | 290 / 4,683 | 241 / 4,678 | 15.1 (13.4, 16.9) | 12.5 (11.0, 14.2) | 0.83 (0.68, 1.01) | 536 / 4,260 | 577 / 4,274 | 29.6 (27.1, 32.1) | 31.9 (29.3, 34.5) | 1.08 (0.94, 1.23) |
| *Age group* | | | | | | | | | | |
| <75 years | 137 / 3,364 | 115 / 3,361 | 9.73 (8.19, 11.5) | 8.18 (6.78, 9.77) | 0.84 (0.63, 1.11) | 257 / 3,129 | 246 / 3,123 | 18.9 (16.7, 21.3) | 18.1 (15.9, 20.5) | 0.96 (0.78, 1.17) |
| ≥75 years | 153 / 1,319 | 126 / 1,317 | 29.8 (25.3, 34.7) | 24.3 (20.3, 28.8) | 0.82 (0.62, 1.07) | 279 / 1,131 | 331 / 1,151 | 61.6 (54.7, 69.1) | 73.3 (65.7, 81.5) | 1.21 (1.00, 1.46) |
| *Sex* | | | | | | | | | | |
| Male | 212 / 3,035 | 170 / 2,994 | 17.2 (15.0, 19.6) | 13.8 (11.9, 16.0) | 0.80 (0.64, 1.01) | 353 / 2,743 | 400 / 2,745 | 30.3 (27.3, 33.6) | 34.6 (31.3, 38.1) | 1.14 (0.97, 1.34) |
| Female | 78 / 1,648 | 71 / 1,684 | 11.4 (9.02, 14.1) | 10.2 (8.01, 12.8) | 0.89 (0.61, 1.28) | 183 / 1,517 | 177 / 1,529 | 28.2 (24.3, 32.5) | 27.0 (23.2, 31.2) | 0.94 (0.74, 1.20) |
| *Race* | | | | | | | | | | |
| Non-Black | 209 / 3,190 | 173 / 3,224 | 16.0 (13.9, 18.2) | 13.0 (11.2, 15.0) | 0.80 (0.64, 1.01) | 386 / 2,897 | 426 / 2,953 | 31.4 (28.4, 34.6) | 34.2 (31.1, 37.6) | 1.10 (0.94, 1.28) |
| Black | 81 / 1,493 | 68 / 1,454 | 13.2 (10.5, 16.3) | 11.5 (8.95, 14.4) | 0.85 (0.59, 1.24) | 150 / 1,363 | 151 / 1,321 | 25.7 (21.8, 30.0) | 26.7 (22.6, 31.1) | 1.02 (0.78, 1.32) |
| *Chronic Kidney Disease* | | | | | | | | | | |
| No | 163 / 3,491 | 126 / 3,485 | 11.3 (9.67, 13.1) | 8.74 (7.30, 10.4) | 0.77 (0.59, 1.01) | 316 / 3,232 | 349 / 3,250 | 22.7 (20.3, 25.2) | 25.0 (22.5, 27.7) | 1.08 (0.91, 1.29) |
| Yes | 125 / 1,161 | 112 / 1,170 | 26.5 (22.1, 31.4) | 23.6 (19.5, 28.2) | 0.89 (0.66, 1.19) | 220 / 1,007 | 227 / 1,012 | 53.8 (47.0, 61.2) | 55.5 (48.6, 63.1) | 1.02 (0.82, 1.26) |
| *Cognitive Function* | | | | | | | | | | |
| >10th percentile | 212 / 3,397 | 152 / 3,389 | 15.1 (13.1, 17.2) | 10.8 (9.14, 12.6) | 0.70 (0.55, 0.89) | 357 / 3,101 | 408 / 3,125 | 26.9 (24.2, 29.8) | 30.7 (27.8, 33.8) | 1.13 (0.96, 1.33) |
| ≤10th percentile | 77 / 1,253 | 83 / 1,257 | 15.3 (12.1, 19.0) | 16.5 (13.2, 20.3) | 1.13 (0.79, 1.62) | 176 / 1,135 | 165 / 1,131 | 36.8 (31.7, 42.6) | 34.7 (29.6, 40.2) | 0.98 (0.76, 1.26) |
| *Frailty Status* | | | | | | | | | | |
| Fit (FI ≤ 0.10) | 21 / 729 | 18 / 751 | 6.90 (4.35, 10.3) | 5.68 (3.45, 8.73) | 0.90 (0.43, 1.87) | 34 / 685 | 42 / 715 | 11.3 (7.88, 15.5) | 13.4 (9.71, 17.8) | 1.26 (0.72, 2.19) |
| Pre-frail (0.10 < FI ≤ 0.21) | 107 / 2,406 | 93 / 2,359 | 10.7 (8.79, 12.8) | 9.52 (7.71, 11.6) | 0.90 (0.66, 1.24) | 251 / 2,244 | 261 / 2,193 | 26.1 (23.0, 29.5) | 27.8 (24.5, 31.3) | 1.07 (0.87, 1.30) |
| Frail (FI > 0.21) | 161 / 1,523 | 127 / 1,538 | 26.4 (22.5, 30.7) | 20.4 (17.1, 24.2) | 0.75 (0.57, 0.98) | 251 / 1,317 | 274 / 1,349 | 46.2 (40.7, 52.2) | 49.9 (44.2, 56.0) | 1.07 (0.87, 1.30) |
| Abbreviations: CI, confidence interval; FI, frailty index. | | | | | | | | | | |

**Table 3**: Cardiovascular and non-cardiovascular mortality by treatment group and subgroup

|  | **Trial Follow-up Through Close-out Visits** | | | | **Post-trial Follow-up** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **N CVD / non-CVD / Total** | | **Hazard Ratio (95% CI)** | | **N CVD / non-CVD / Total** | | **Hazard Ratio (95% CI)** | |
| **Standard** | **Intensive** | **CVD** | **Non-CVD** | **Standard** | **Intensive** | **CVD** | **Non-CVD** |
| Overall | 92 / 198 / 4,683 | 65 / 176 / 4,678 | 0.66 (0.49, 0.89) | 0.89 (0.71, 1.10) | 181 / 355 / 4,260 | 183 / 394 / 4,274 | 1.02 (0.84, 1.24) | 1.13 (0.97, 1.31) |
| *Age group* | | | | | | | | |
| <75 years | 45 / 92 / 3,364 | 27 / 88 / 3,361 | 0.53 (0.36, 0.79) | 0.95 (0.68, 1.32) | 81 / 176 / 3,129 | 73 / 173 / 3,123 | 0.92 (0.66, 1.28) | 1.01 (0.84, 1.22) |
| ≥75 years | 47 / 106 / 1,319 | 38 / 88 / 1,317 | 0.78 (0.49, 1.26) | 0.81 (0.61, 1.09) | 100 / 179 / 1,131 | 110 / 221 / 1,151 | 1.07 (0.81, 1.42) | 1.23 (0.99, 1.53) |
| *Sex* | | | | | | | | |
| Male | 68 / 144 / 3,035 | 47 / 123 / 2,994 | 0.62 (0.42, 0.90) | 0.85 (0.67, 1.08) | 119 / 234 / 2,743 | 125 / 275 / 2,745 | 1.09 (0.85, 1.38) | 1.20 (1.00, 1.44) |
| Female | 24 / 54 / 1,648 | 18 / 53 / 1,684 | 0.75 (0.45, 1.27) | 0.97 (0.64, 1.48) | 62 / 121 / 1,517 | 58 / 119 / 1,529 | 0.89 (0.63, 1.28) | 0.98 (0.71, 1.34) |
| *Race* | | | | | | | | |
| Non-Black | 67 / 142 / 3,190 | 44 / 129 / 3,224 | 0.58 (0.42, 0.81) | 0.87 (0.68, 1.12) | 126 / 260 / 2,897 | 135 / 291 / 2,953 | 1.10 (0.89, 1.37) | 1.13 (0.94, 1.36) |
| Black | 25 / 56 / 1,493 | 21 / 47 / 1,454 | 0.82 (0.46, 1.45) | 0.93 (0.64, 1.37) | 55 / 95 / 1,363 | 48 / 103 / 1,321 | 0.81 (0.54, 1.23) | 1.10 (0.84, 1.44) |
| *Chronic Kidney Disease* | | | | | | | | |
| No | 50 / 113 / 3,491 | 29 / 97 / 3,485 | 0.55 (0.36, 0.83) | 0.87 (0.65, 1.14) | 90 / 226 / 3,232 | 101 / 248 / 3,250 | 1.14 (0.84, 1.55) | 1.09 (0.90, 1.33) |
| Yes | 41 / 84 / 1,161 | 36 / 76 / 1,170 | 0.81 (0.51, 1.31) | 0.88 (0.62, 1.24) | 91 / 129 / 1,007 | 82 / 145 / 1,012 | 0.89 (0.67, 1.16) | 1.18 (0.93, 1.49) |
| *Cognitive Function* | | | | | | | | |
| >10th percentile | 62 / 150 / 3,397 | 40 / 112 / 3,389 | 0.56 (0.36, 0.88) | 0.74 (0.58, 0.96) | 128 / 229 / 3,101 | 122 / 286 / 3,125 | 0.93 (0.73, 1.19) | 1.25 (1.03, 1.53) |
| ≤10th percentile | 29 / 48 / 1,253 | 23 / 60 / 1,257 | 0.76 (0.41, 1.43) | 1.22 (0.83, 1.78) | 52 / 124 / 1,135 | 58 / 107 / 1,131 | 1.18 (0.81, 1.72) | 0.90 (0.72, 1.12) |
| *Frailty Status* | | | | | | | | |
| Fit (FI ≤ 0.10) | 7 / 14 / 729 | 1 / 17 / 751 | 0.14 (0.02, 1.12) | 1.22 (0.59, 2.53) | 8 / 26 / 685 | 7 / 35 / 715 | 0.77 (0.31, 1.95) | 1.26 (0.78, 2.04) |
| Pre-frail (0.10 < FI ≤ 0.21) | 34 / 73 / 2,406 | 23 / 70 / 2,359 | 0.59 (0.34, 1.03) | 1.00 (0.73, 1.37) | 75 / 176 / 2,244 | 81 / 180 / 2,193 | 1.07 (0.77, 1.50) | 1.04 (0.85, 1.27) |
| Frail (FI > 0.21) | 51 / 110 / 1,523 | 41 / 86 / 1,538 | 0.77 (0.53, 1.13) | 0.75 (0.56, 1.00) | 98 / 153 / 1,317 | 95 / 179 / 1,349 | 1.01 (0.77, 1.33) | 1.20 (0.96, 1.50) |

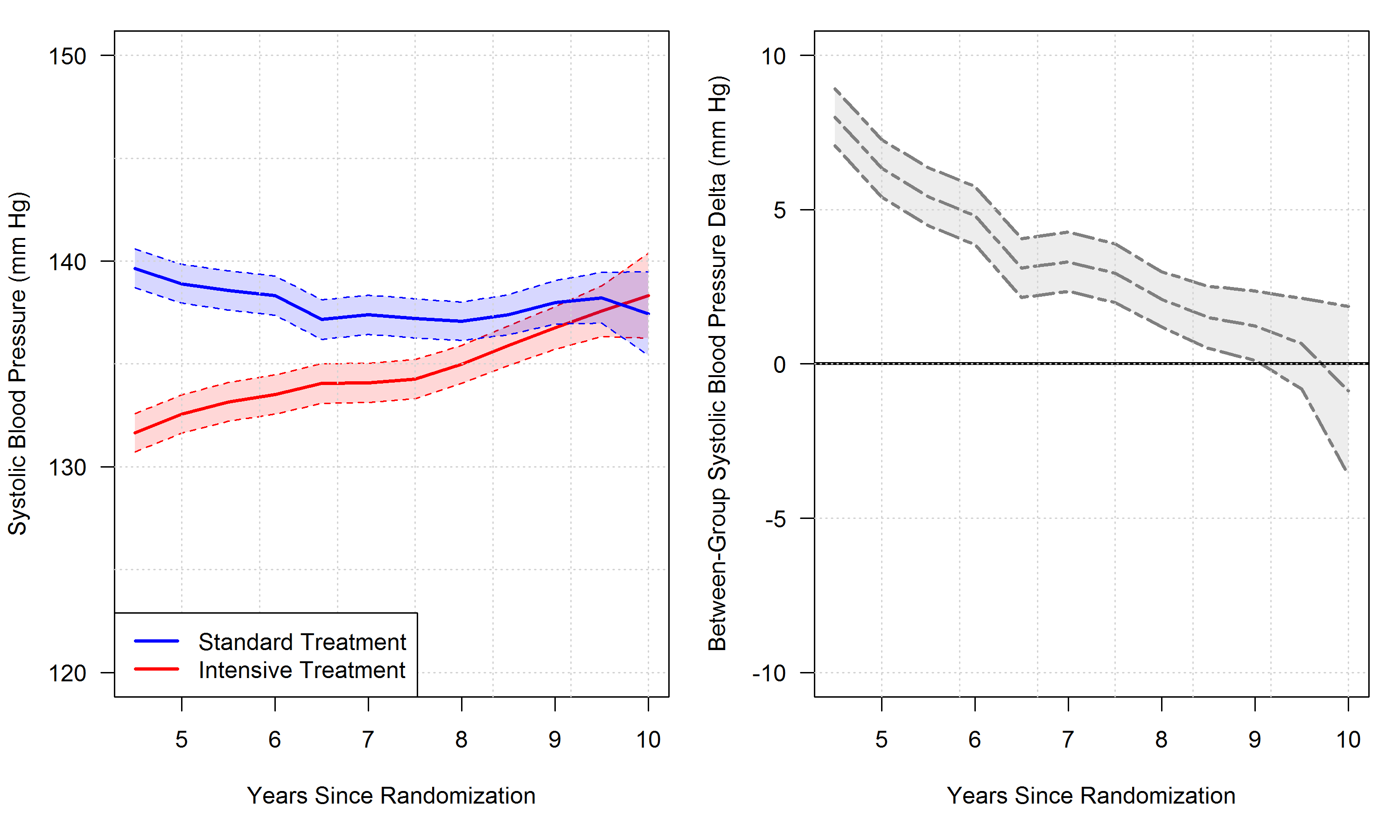
**Figure 1**: (A) Cumulative incidence of all-cause mortality by treatment group. (B) Time-dependent effect of randomization to intensive treatment for all-cause mortality.



**Figure 2**: (A) Cumulative incidence of cardiovascular and non-cardiovascular mortality by treatment group. (B) Time-dependent effect of randomization to intensive treatment for cardiovascular mortality.



**Figure 3**: Mean systolic blood pressure over time by treatment group. Shaded areas indicate a 95% confidence interval for the mean.



Online supplement only

Longer term All-Cause and Cardiovascular Mortality with Intensive Blood Pressure Control: A Secondary Analysis of SPRINT

Byron C. Jaeger, PhD1 Paul E. Drawz, MD2 Paul K. Whelton, MD3 Mark A. Supiano, MD4 Adam P. Bress, PharmD, MS5,6 Jeff D. Williamson, MD, MHS7 David M. Reboussin, PhD1, and Nicholas M. Pajewski, PhD1

1Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC

2Division of Renal Diseases & Hypertension, University of Minnesota, Minneapolis.

3Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA.

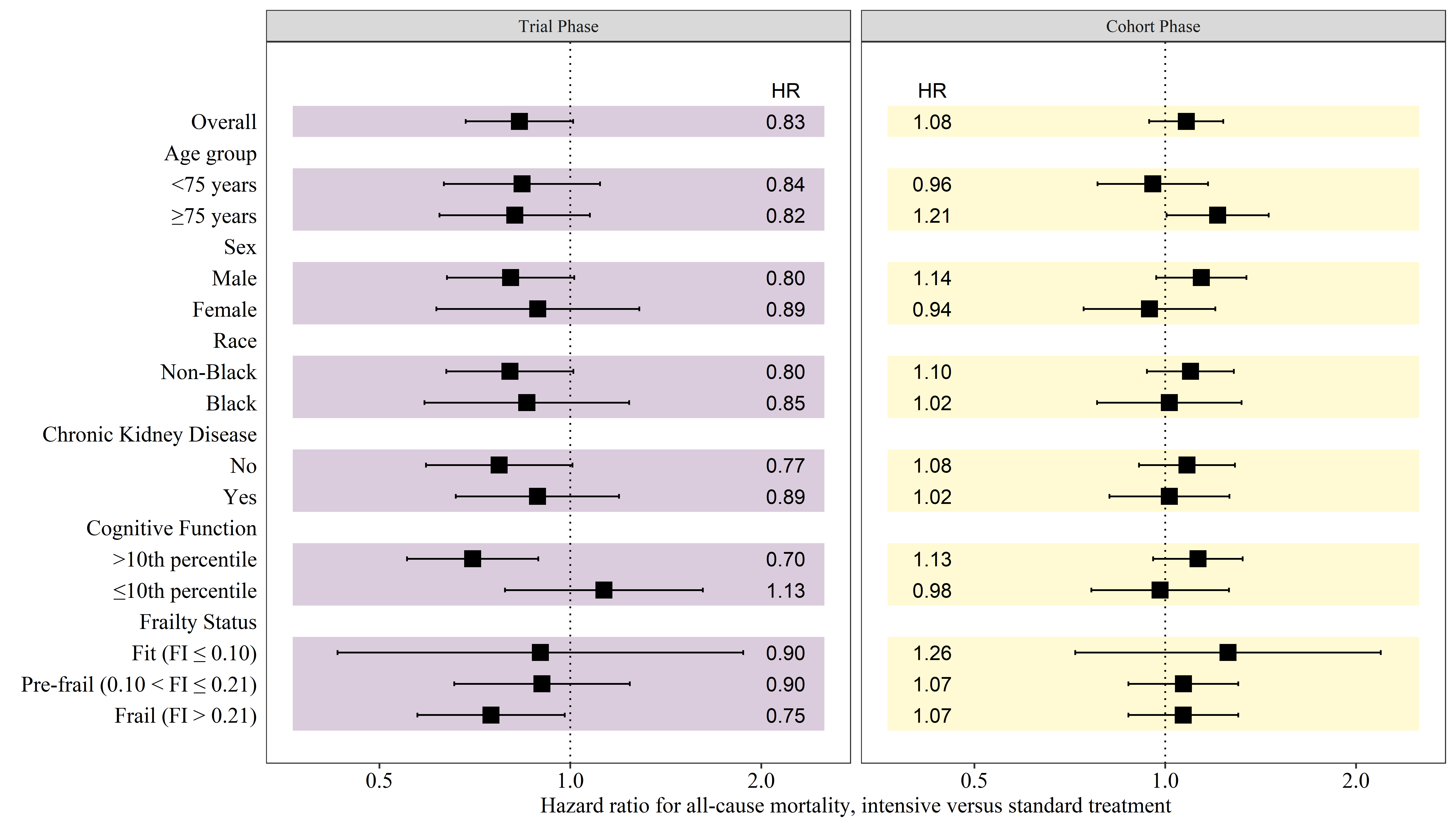
4Division of Geriatrics, University of Utah School of Medicine, Salt Lake City.

5 Informatics, Decision-Enhancement, and Analytic Sciences (IDEAS) Center, Veterans Affairs, Salt Lake City Health Care System, Salt Lake City, UT

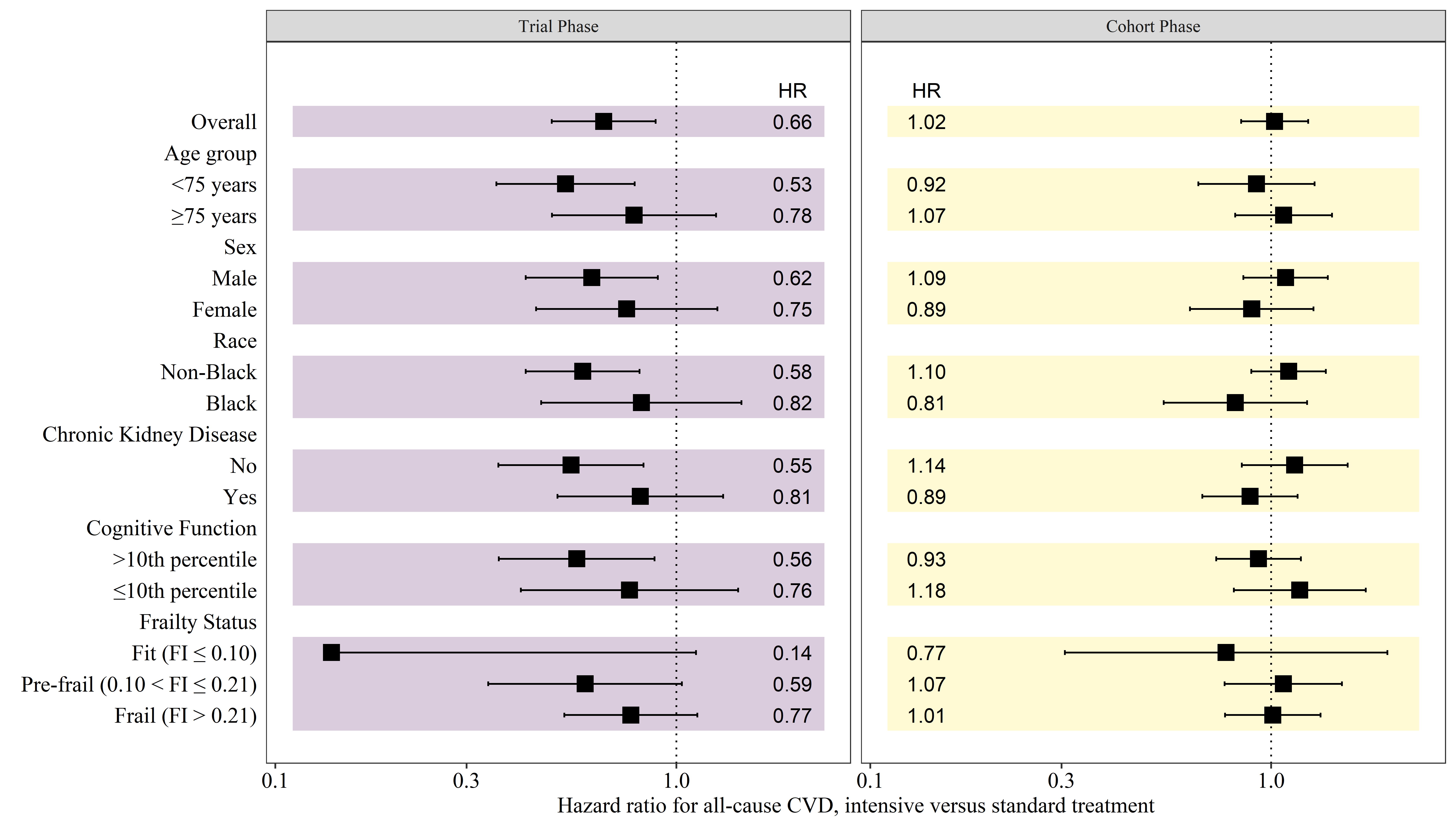
6 Department of Population Health Sciences, University of Utah School of Medicine, Salt Lake City, UT

7Section on Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, NC.

**eFigure 1**: All-cause mortality hazard ratio for participants randomized to intensive versus standard treatment.



**eFigure 2**: Cardiovascular mortality hazard ratio for participants randomized to intensive versus standard treatment.



# REFERENCES

1 Group SR. A randomized trial of intensive versus standard blood-pressure control. *New England Journal of Medicine* 2015; **373**: 2103–16.

2 Zhang W, Zhang S, Deng Y, *et al.* Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension. *New England Journal of Medicine* 2021; published online Aug. DOI:[10.1056/NEJMoa2111437](https://doi.org/10.1056/NEJMoa2111437).

3 Rahimi K, Bidel Z, Nazarzadeh M, *et al.* Age-stratified and blood-pressure-stratified effects of blood-pressure-lowering pharmacotherapy for the prevention of cardiovascular disease and death: An individual participant-level data meta-analysis. *The Lancet* 2021; **398**: 1053–64.

4 Ambrosius WT, Sink KM, Foy CG, *et al.* The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: The Systolic Blood Pressure Intervention Trial (SPRINT). *Clinical Trials* 2014; **11**: 532–46.

5 Inker LA, Eneanya ND, Coresh J, *et al.* New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. *New England Journal of Medicine* 2021; **385**: 1737–49.

6 Nasreddine ZS, Phillips NA, Bédirian V, *et al.* The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *Journal of the American Geriatrics Society* 2005; **53**: 695–9.

7 Kenny RA, Coen RF, Frewen J, Donoghue OA, Cronin H, Savva GM. Normative values of cognitive and physical function in older adults: Findings from the Irish Longitudinal Study on Ageing. *Journal of the American Geriatrics Society* 2013; **61 Suppl 2**: S279–290.

8 Pajewski NM, Williamson JD, Applegate WB, *et al.* Characterizing Frailty Status in the Systolic Blood Pressure Intervention Trial. *The Journals of Gerontology Series A, Biological Sciences and Medical Sciences* 2016; **71**: 649–55.

9 Drawz PE, Agarwal A, Dwyer JP, *et al.* Concordance Between Blood Pressure in the Systolic Blood Pressure Intervention Trial and in Routine Clinical Practice. *JAMA internal medicine* 2020; **180**: 1655–63.

10 Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. *Annals of Translational Medicine* 2018; **6**: 121.

11 Martinussen T, Scheike TH. Dynamic regression models for survival data. Springer Science & Business Media, 2007.

12 Therneau T, Crowson C, Atkinson E. Using time dependent covariates and time dependent coefficients in the cox model. *Survival Vignettes* 2017; **2**: 3.

13 Lin DY, Wei L-J. The robust inference for the Cox proportional hazards model. *Journal of the American statistical Association* 1989; **84**: 1074–8.

14 Scheike TH, Zhang M-J. Flexible competing risks regression modeling and goodness-of-fit. *Lifetime Data Analysis* 2008; **14**: 464–83.

15 R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2020 <https://www.R-project.org/>.

16 Jaeger B. Table.glue: Make and apply customized rounding specifications for tables. <https://github.com/bcjaeger/table.glue>.

17 Wickham H, Averick M, Bryan J, *et al.* Welcome to the tidyverse. *Journal of Open Source Software* 2019; **4**: 1686.

18 Therneau TM. A package for survival analysis in R. 2021 <https://CRAN.R-project.org/package=survival>.

19 Scheike TH, Zhang M-J. Analyzing competing risk data using the R timereg package. *Journal of Statistical Software* 2011; **38**: 1–5.

20 Landau WM. The targets R package: A dynamic make-like function-oriented pipeline toolkit for reproducibility and high-performance computing. *Journal of Open Source Software* 2021; **6**: 2959.

21 Muntner P, Hardy ST, Fine LJ, *et al.* Trends in Blood Pressure Control Among US Adults With Hypertension, 1999-2000 to 2017-2018. *JAMA* 2020; **324**: 1190–200.