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

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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 1**). 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. The cumulative time-varying effect of intensive versus standard treatment indicated lower risk for all-cause mortality during the trial phase and was attenuated during the cohort phase (**Figure 1**).

# 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

The views expressed in this paper are those of the authors and do not represent the official position of the National Institutes of Health (NIH), the National Heart, Lung, and Blood Institute, the Department of Veterans Affairs, or the U.S. Government, or the SPRINT Research Group. This paper was not reviewed by the SPRINT Publications and Presentations Committee. The authors also wish to acknowledge computing support provided the Veterans Affairs Informatics and Computing Infrastructure (VINCI).

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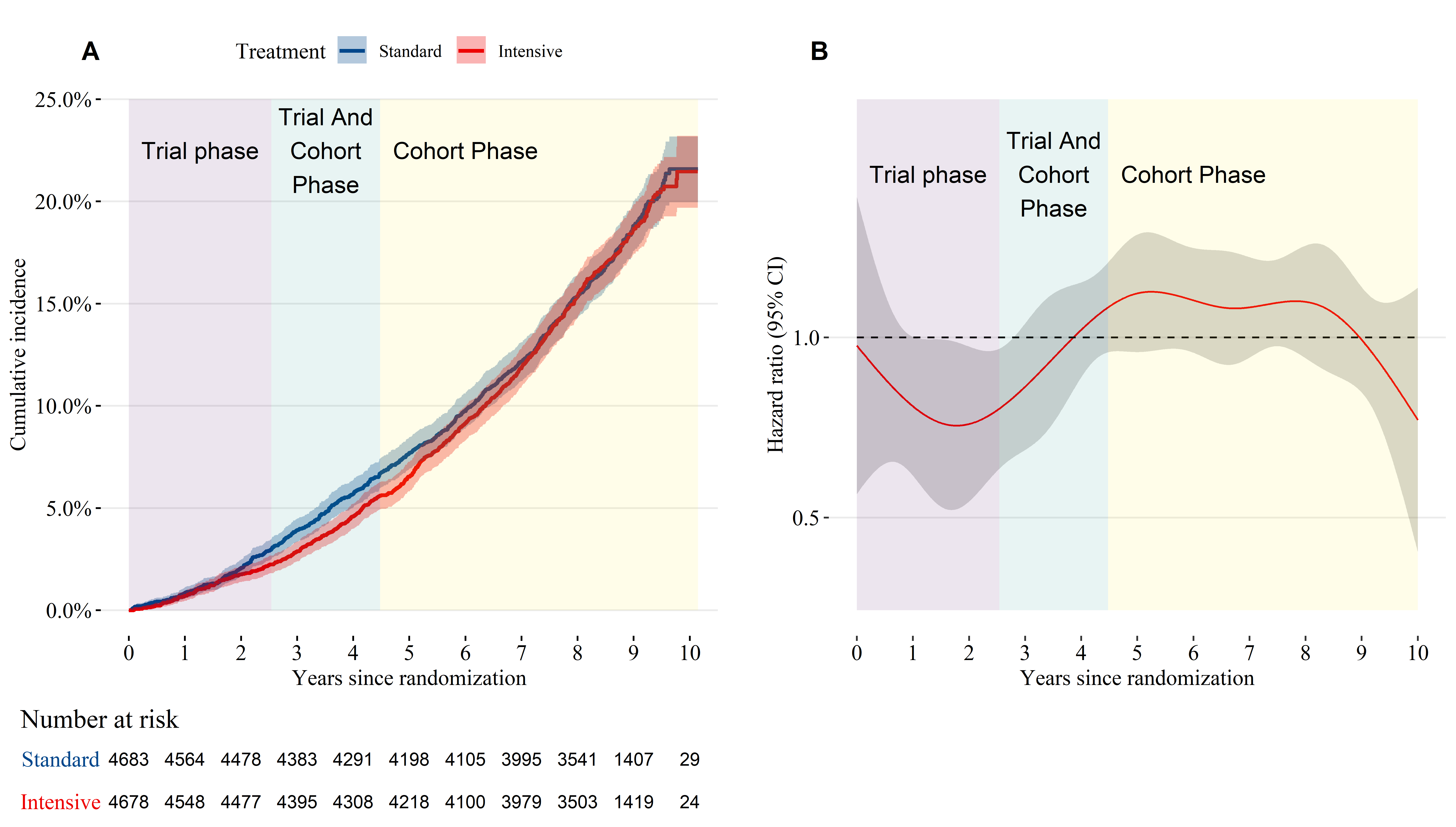
**Table 1**: All-cause mortality by treatment group and subgroup

|  | **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, years* | | | | | | | | | | |
| <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. aChronic Kidney Disease defined as an estimated glomerular filtration rate <60 ml/min/1.73 m2 based on the 2021 CKD-EPI creatinine equation. | | | | | | | | | | |

**Table 2**: 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, years* | | | | | | | | |
| <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) |

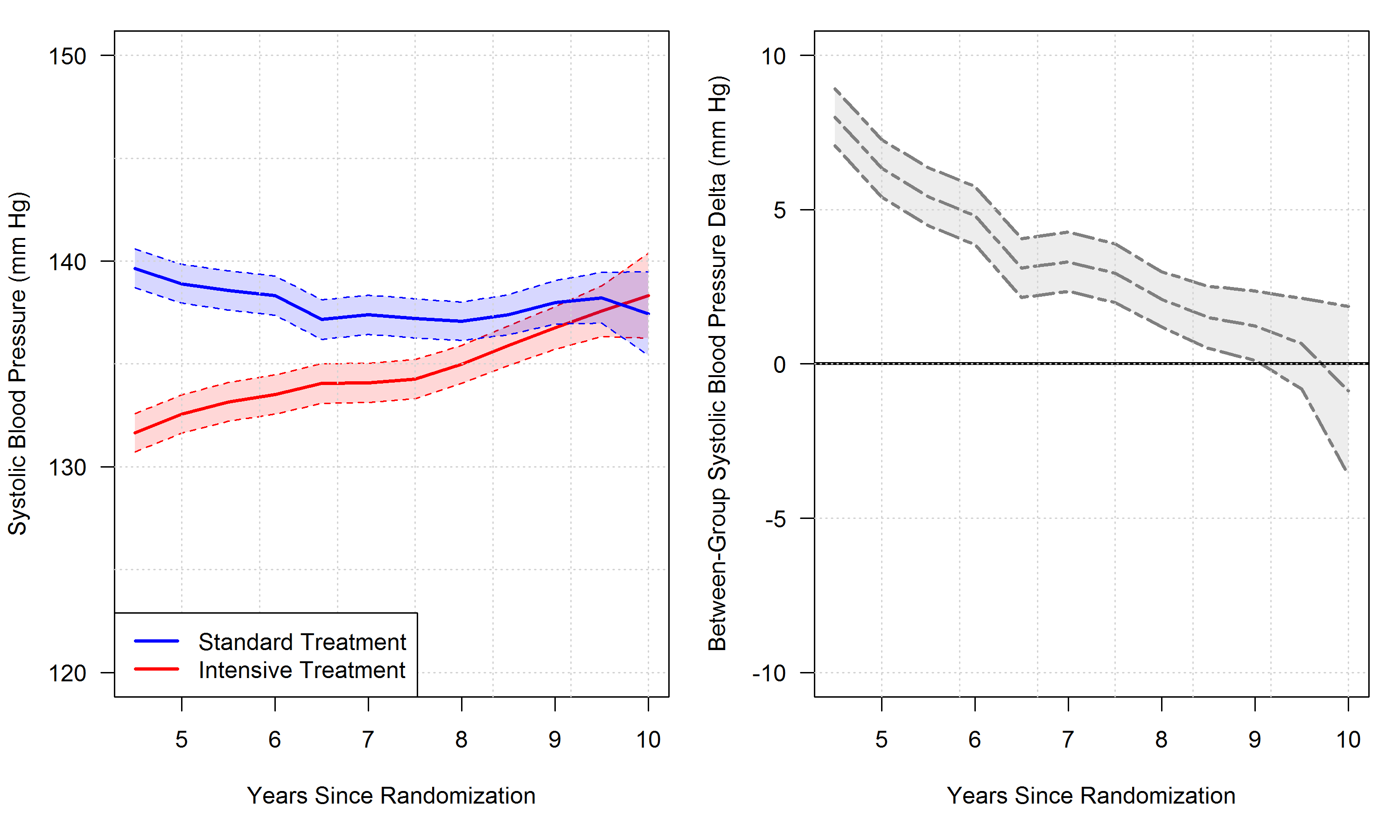
**Figure 1**: (A) Cumulative incidence of all-cause mortality by treatment group. (B) Time-dependent effect of randomization to intensive treatment for all-cause mortality.



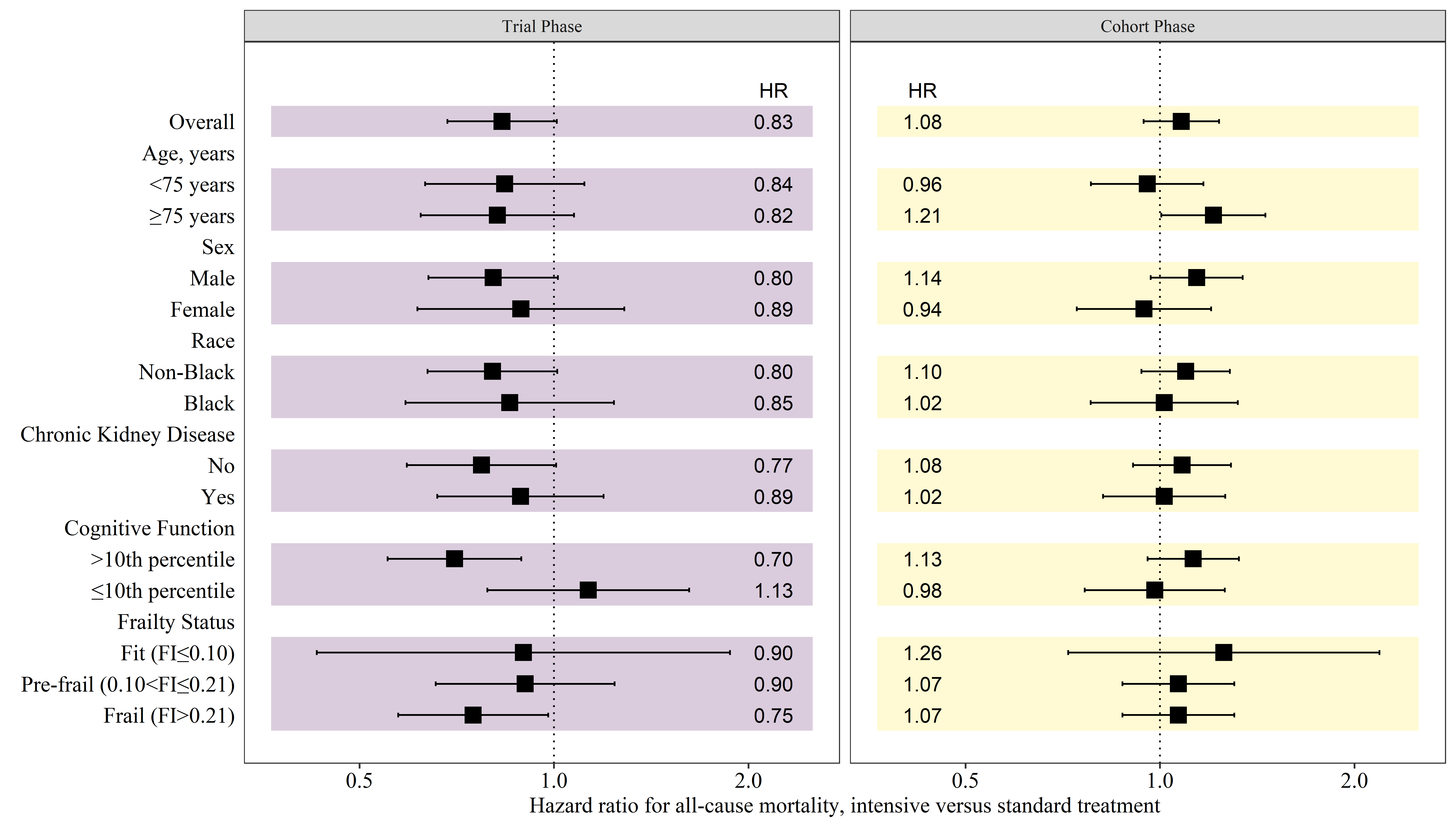
**Figure 2**: (A) Cumulative incidence of cardiovascular and non-cardiovascular mortality by treatment group. (B) Time-dependent effect of randomization to intensive treatment for cardiovascular mortality.



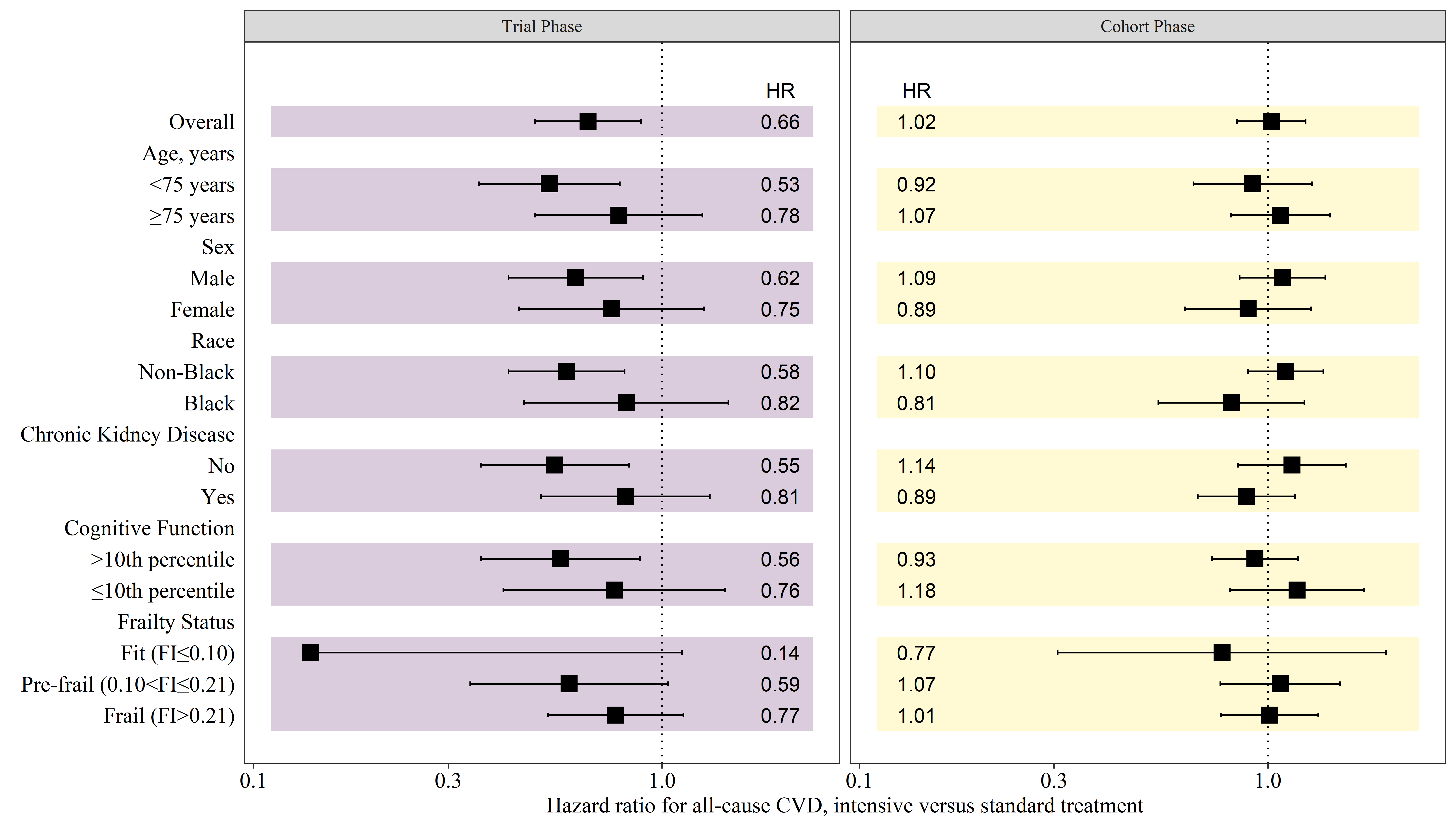
**Figure 3**: Mean systolic blood pressure over time by treatment group. Shaded areas indicate a 95% confidence interval for the mean.



**Figure 4**: All-cause mortality hazard ratio for participants randomized to intensive versus standard treatment.



**Figure 5**: Cardiovascular mortality hazard ratio for participants randomized to intensive versus standard treatment.



# SUPPLEMENT

To be decided.

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