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Effects of Intensive Systolic Blood Pressure Control on Kidney and Cardiovascular Outcomes in Persons Without Kidney Disease:

A Secondary Analysis of a Randomized Trial

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SPRINT Research Group*

Abstract

Background: The public health significance of the reported higher incidence of chronic kidney disease (CKD) with intensive systolic blood pressure (SBP) lowering is unclear.

Objective: To examine the effects of intensive SBP lowering on kidney and cardiovascular outcomes and contrast its apparent beneficial and adverse effects.

Design: Subgroup analyses of SPRINT (Systolic Blood Pressure Intervention Trial). (ClinicalTrials.gov: NCT01206062)

Setting: Adults with high blood pressure and elevated cardiovascular risk.

Participants: 6662 participants with a baseline estimated glomerular filtration rate (eGFR) of at least 60 mL/min/1.73 m^2.

Intervention: Random assignment to an intensive or standard SBP goal (120 or 140 mm Hg, respectively).

Measurements: Differences in mean eGFR during follow-up (estimated with a linear mixed-effects model), prespecified incident CKD (defined as a >30% decrease in eGFR to a value <60 mL/min/1.73 m^2), and a composite of all-cause death or cardiovascular event, with surveillance every 3 months.

Results: The difference in adjusted mean eGFR between the intensive and standard groups was −3.32 mL/min/1.73 m^2 (95% CI, −3.90 to −2.74 mL/min/1.73 m^2) at 6 months, was −4.50 mL/min/1.73 m^2 (CI, −5.16 to −3.85 mL/min/1.73 m^2) at 18 months, and remained relatively stable thereafter. An incident CKD event occurred in 3.7% of participants in the intensive group and 1.0% in the standard group at 3-year follow-up, with a hazard ratio of 3.54 (CI, 2.50 to 5.02). The corresponding percentages for the composite of death or cardiovascular event were 4.9% and 7.1% at 3-year follow-up, with a hazard ratio of 0.71 (CI, 0.59 to 0.86).

Limitation: Long-term data were lacking.

Conclusion: Intensive SBP lowering increased risk for incident CKD events, but this was outweighed by cardiovascular and all-cause mortality benefits.

Primary Funding Source: National Institutes of Health.

About 1.3 billion adults worldwide are believed to have hypertension, defined as systolic blood pressure (SBP) of at least 140 mm Hg, diastolic blood pressure (DBP) of at least 90 mm Hg, or the need for blood pressure medication (1). High blood pressure is one of the most important risk factors for cardiovascular disease (CVD) events (2–5), end-stage

renal disease (ESRD) (3), and all-cause death (3). Nearly two thirds of U.S. adults aged 60 years or older have hypertension (6), and the population of persons aged 65 years or older is projected to reach 83.7 million by 2050, almost double the estimate of 43.1 million in 2012 (7). Therefore, the prevalence and public health burden of hypertension will probably continue to increase unless effective interventions are implemented.

Although SBP is generally considered a more important CVD risk factor than DBP in patients older than 50 years, the optimal goal for SBP during antihypertensive therapy has been controversial (2, 8). SPRINT (Systolic Blood Pressure Intervention Trial) examined the effects of intensive (target <120 mm Hg) versus standard (target <140 mm Hg) SBP control (9). The intervention was stopped early after a median follow-up of 3.26 years because intensive therapy resulted in a substantial reduction in the primary outcome—a composite of CVD events (hazard ratio [HR], 0.75 [95% CI, 0.64 to 0.89])—and in the secondary outcome of all-cause mortality (HR, 0.73 [CI, 0.60 to 0.90]). However, in persons without kidney disease at baseline, the intensive SBP group had a 3.5-fold higher hazard of incident chronic kidney disease (CKD), based on an a priori definition of a reduction in estimated glomerular filtration rate (eGFR) of at least 30% to a confirmed level less than 60 mL/min/1.73 m^2.

We performed detailed analyses of the SPRINT prespecified kidney outcomes of incident CKD (as defined earlier) and incident albuminuria (defined as a doubling of urinary albumin–creatinine ratio from a value <10 mg/g to a value >10 mg/g) in participants with a baseline eGFR of at least 60 mL/min/1.73 m^2. In addition, we evaluated the following post hoc hypotheses. First, the effect of intensive SBP control on incident CKD is due to an acute effect occurring in the first several months of follow-up, without subsequent effects on the long-term rate of kidney disease progression. If this is true, the difference in mean eGFR between treatment groups would be expected to increase during the early phase of follow-up but remain constant during the later phase of treatment. Second, elderly participants (aged ≥65 years at baseline) and those with baseline albuminuria are at higher risk for kidney function decline with intensive treatment. Finally, the higher risk for incident CKD in the intensive treatment group is outweighed by protective cardiovascular and all-cause mortality effects.

Methods

SPRINT was a randomized, controlled, open-label trial that compared the effects of intensive (target <120 mm Hg) versus standard (target <140 mm Hg) SBP control in 9361 participants at 102 clinical centers across the United States and Puerto Rico (9). Details of the SPRINT protocol have been published (10, 11). The study was approved by the institutional review boards at each participating study site.

This article describes a secondary analysis of prespecified secondary outcomes (incident CKD and incident albuminuria) performed in the prespecified subgroup of participants without CKD at baseline. Secondary post hoc analyses examined the acute effects of the intervention on eGFR, outcomes by subgroup, and the numbers needed to treat for benefit or harm.

Study Population

Participants were recruited between November 2010 and March 2013 and were required to meet all of the following inclusion criteria: age 50 years or older, SBP of 130 to 180 mm Hg, and increased risk for CVD (defined as ≥1 of the following: clinical or subclinical CVD other than stroke; 10-year risk for CVD ≥15%, based on the Framingham global risk indicator [12]; aged ≥75 years; or eGFR of 20 to <60 mL/min/1.73 m^2). Major exclusion criteria included presence of diabetes, prior stroke, advanced CKD (eGFR <20 mL/min/1.73 m^2), proteinuria greater than 1 g/d, polycystic kidney disease, congestive heart failure (symptoms or ejection fraction <35%), dementia, or residence in a nursing home. Further details of the SPRINT inclusion and exclusion criteria have been published elsewhere (9, 10). This article is restricted to the prespecified subgroup of 6662 SPRINT participants with baseline eGFR of at least 60 mL/min/1.73 m^2.

Intervention, Follow-up, and Measurements

Volunteers who met the eligibility criteria and agreed to participate were randomly assigned to either intensive or standard SBP control. Randomization was stratified by clinical site but not by baseline presence of CKD. Neither the clinical investigators nor the participants were blinded to the intervention. Details of the SPRINT intervention algorithm are provided elsewhere (9, 10). In brief, participants were seen monthly for the first 3 months and every 3 months thereafter at standardized visits by trained study staff following requirements specified in the protocol. An automated system (Model 907 [Omron Healthcare]) was used to measure blood pressure at an office visit while the participant was seated and after 5 minutes of quiet rest. The mean of 3 blood pressure readings, each taken 1 minute apart, was used to estimate blood pressure.

Medication doses were initially adjusted every month in the intensive treatment group to target an SBP less than 120 mm Hg, and doses were adjusted to target an SBP of 135 to 139 mm Hg in the standard treatment group. The dose was reduced in the standard group if SBP was less than 130 mm Hg at a single visit or less than 135 mm Hg at 2 consecutive visits. Although achievement of SBP goals was emphasized in both groups, the investigators were allowed to adjust medication doses on the basis of clinical judgment. Lifestyle modification was encouraged.

Serum specimens were obtained at each visit for the first 3 months and quarterly thereafter for estimation of serum creatinine concentrations at the central laboratory at the University of Minnesota using an enzymatic creatinine assay (Roche). Fasting visits occurred at baseline and at 12, 24, and 48 months. The 4-variable MDRD (Modification of Diet in Renal Disease) study equation was used to estimate GFR (13).

Urine albumin and creatinine concentrations were measured at baseline and at 6, 12, 24, and 48 months. Albumin was measured using an immunoturbidimetric assay (Roche) at the central laboratory, and creatinine was measured using an enzymatic method (Roche). Event ascertainment and safety assessments were performed per protocol.

A decision to discontinue the SPRINT blood pressure intervention was made on 20 August 2015 after interim analyses of the primary outcome exceeded the monitoring boundary on

2 consecutive occasions, accompanied by a statistically significant difference in all-cause mortality (9). Only events that occurred on or before 20 August 2015 are included in this analysis; however, some eGFR or albuminuria outcomes were confirmed by samples collected after that date. Data for this analysis were frozen on 31 January 2016. As a result, 13 “new” incident CKD events in the intensive group and 3 in the standard group are included in addition to those in the previous report. Further details on additional event outcomes are provided in Appendix 2 (available at Annals.org) (9).

SPRINT Outcomes

The primary outcome in SPRINT was a composite of nonfatal myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from CVD. Secondary outcomes included the components of the primary outcome, all-cause death, and a composite of the primary outcome or all-cause death. All outcome events were adjudicated by an outcomes committee that was blinded to the intervention.

Incident CKD, defined as a greater than 30% decrease in eGFR with a confirmed value less than 60 mL/min/1.73 m^2 (confirmed by the next available official SPRINT laboratory value), was a prespecified secondary renal outcome in participants without CKD at baseline (eGFR ≥60 mL/min/1.73 m^2). Incident albuminuria was prespecified as a doubling of urinary albumin–creatinine ratio from a value less than 10 mg/g to a value greater than 10 mg/g (confirmed by the next available official SPRINT laboratory value). Incident ESRD was defined as a need for long-term dialysis or kidney transplantation.

Statistical Analysis

All randomly assigned participants without CKD at baseline were included in the analyses, which were based on the intention-to-treat principle. The number of antihypertensive medications was determined as the number of distinct classes prescribed for each participant at each visit. Follow-up SBP was compared between treatment groups by using a mixed linear model with an unstructured variance–covariance matrix to control for within-subject correlation. A mixed-effect linear model with an unstructured variance–covariance matrix was used to estimate mean eGFR at follow-up by treatment group, with baseline eGFR included as a covariate. Seventy-two participants (31 in the intensive group and 41 in the standard group) without postrandomization serum creatinine measurements did not contribute to estimation of mean eGFR at follow-up or the analysis of incident CKD.

Separate Cox proportional hazards regression analyses with stratification by clinic were used to examine the effect of treatment group assignment on the primary renal outcome (defined as time from randomization to incident CKD, with a confirmed 30% decrease in eGFR from baseline) and on time to incident albuminuria and CVD and death outcomes. Follow-up was censored at the participant’s date of last creatinine measurement for incident CKD (or last urine sample for urinary albumin–creatinine ratio) and the date of the last assessment of study events for CVD outcomes. Information on vital status was supplemented with data from the National Death Index. Follow-up for all-cause mortality was censored at the end of calendar year 2014 for participants who were lost to follow-up.

Analyses of the cumulative incidence and absolute risks for renal and nonfatal CVD outcomes were performed using competing-risks models, in which non-CVD death was treated as a competing risk for the CVD outcomes and all-cause death was treated as a competing risk for incident CKD and incident albuminuria (14). The proportionality assumption for treatment effects was assessed by examining martingale residuals; no significant departures were found. Interactions between treatment effect and prespecified subgroups based on age, sex, race, and baseline albuminuria were assessed by likelihood ratio tests, with *P* value adjustment to account for the 4 comparisons (15). Tests of significance were performed using a 2-sided 5% level of significance. The numbers needed to treat for benefit or harm and the corresponding 95% CIs were calculated for CVD outcomes and incident CKD as the inverse of the absolute risk reduction (number needed to treat for benefit) or increase (number needed to treat for harm) (16), using estimates of event-free survival from cumulative incidence curves adjusted for competing risks (nonfatal outcomes) or stratified Kaplan–Meier survival estimates (fatal outcomes) at 3 years.

All analyses were performed using SAS, version 9.4 (SAS Institute). Additional details on the statistical methods are presented in Appendix 2.

Role of the Funding Source

The steering committee designed SPRINT, gathered the data (in collaboration with investigators at the clinics and other study units), and approved the decision to submit the manuscript for publication. The writing committee wrote the manuscript and vouches for the completeness and accuracy of the data and analysis. The coordinating center was responsible for analyzing the data. Scientists at the National Institutes of Health participated in the design of the study and, as a group, had 1 vote on the steering committee.

Results

Of the 9361 SPRINT participants, 6662 (71.6%) had an eGFR of at least 60 mL/min/1.73 m^2 at baseline and were included in the current analysis (Appendix Figure 1, available at Annals.org). Median follow-up was 39.6 months (range, 0 to 57.4 months) in the intensive group and 39.4 months (range, 0 to 57.4 months) in the standard group. Summary values of baseline demographic, clinical, and laboratory characteristics were similar in both groups (Table 1). A high Framingham risk score was the most common indicator (60.6%) of increased cardiovascular risk in both groups. The mean age of the study population was 66.3 years (SD, 9.0), 33.7% were women, and 32.2% were black. Mean eGFR was 81.2 mL/min/1.73 m^2 (SD, 15.5), mean SBP was 139.9 mm Hg (SD, 15.4), and mean DBP was 79.4 mm Hg (SD, 11.6).

The intervention achieved SBP separation between groups by 6 months, and this separation was stable throughout the remainder of follow-up (Appendix Figure 2, available at Annals.org). Systolic BP decreased in both treatment groups, with the reduction being most pronounced during the first 6 months and steeper in the intensive group than the standard group. The average between-group difference in SBP after 6 months was 15.0 mm Hg (CI, 14.7 to 15.4 mm Hg).

The number of participants who were lost to follow-up or withdrew consent was similar in the intensive and standard groups (5.7% vs. 5.5%; $P = 0.69$). Fasting resulted in a lower estimated eGFR. Fasting and nonfasting eGFRs are presented in Figure 1. The difference in adjusted mean eGFR between groups was −3.32 mL/min/1.73 m^2 (CI, −3.90 to −2.74 mL/min/1.73 m^2) at 6 months; increased to −4.50 mL/min/1.73 m^2 (CI, −5.16 to −3.85 mL/min/1.73 m^2) at 18 months; and was relatively stable for the remainder of follow-up, with differences of −4.83 mL/min/1.73 m^2 (CI, −5.51 to −4.14 mL/min/1.73 m^2) at month 30 and −4.71 mL/min/1.73 m^2 (CI, −5.61 to −3.80 mL/min/1.73 m^2) at month 42 (Figure 1; Appendix Figure 3, available at Annals.org).

Overall, 140 of 3326 participants (4.2%) in the intensive group and 40 of 3336 (1.1%) in the standard group had an incident CKD event, based on the a priori protocol definition of a decrease in eGFR of at least 30% and a confirmed value less than 60 mL/min/1.73 m^2 (Table 2). Compared with the standard group, the intensive group had a significantly higher rate of incident CKD (1.33 vs. 0.37 events per 100 person-years; HR, 3.54 [CI, 2.50 to 5.02]; $P < 0.001$). At 3 years, the cumulative incidence of CKD was an absolute 2.6% higher in the intensive group (Figure 2 [*panel A*] and Table 2). The number needed to treat for 3 years to produce 1 incident CKD event (that is, the number needed to treat for harm) was 38 (CI, 29 to 53).

The effect of the intensive treatment intervention on incident CKD was similar across baseline age, sex, race, and albuminuria subgroups (Appendix Figure 4, available at Annals.org). The intervention significantly reduced risk for the composite of a primary CVD event or all-cause death (absolute risk reduction, 2.2% [CI, 1.1% to 3.3%]; HR, 0.71 [CI, 0.59 to 0.86]), primary CVD event (absolute risk reduction, 1.8% [CI, 0.8% to 2.8%]; HR, 0.67 [CI, 0.54 to 0.84]), and all-cause death (absolute risk reduction, 0.9% [CI, 0.2% to 1.7%]; HR, 0.74 [CI, 0.55 to 0.98]) (Table 2 and Figure 2 [*panels B* to *D*]). The numbers needed to treat for 3 years to prevent 1 occurrence of the composite outcome, the primary cardiovascular outcome, and all-cause death were 46 (CI, 29 to 94), 57 (CI, 36 to 129), and 108 (CI, 59 to 541), respectively.

Appendix Figure 5 (available at Annals.org) shows the cumulative incidence of albuminuria. Assessment of albuminuria during follow-up was limited to 3585 participants (1763 in the intensive group and 1822 in the standard group) with a baseline urinary albumin–creatinine ratio less than 10 mg/g. In this subgroup, the incidence of albuminuria did not differ significantly between the intensive and standard groups (absolute risk reduction for the intensive group, 1.2% [CI, −0.5% to 2.8%]; HR, 0.82 [CI, 0.64 to 1.05]) (Table 2).

The final status of participants who had incident CKD is shown in Figure 3. At the final study visit, 36 (25.7%) of those with incident CKD in the intensive group and 4 (10%) in the standard group recovered renal function and were deemed to no longer have incident CKD. None of the participants with incident CKD in either group developed ESRD. One of the 40 participants (2.5%) with incident CKD in the standard group and 2 of the 140 participants (1.4%) in the intensive group died.

Sensitivity analyses of incident CKD based on a 40% or 50% reduction in eGFR from baseline, a fixed decrease in eGFR of 27 mL/min/1.73 m^2 from baseline (regardless of whether eGFR decreased to <60 mL/min/1.73 m^2), and use of the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation instead of the MDRD study equation are presented in Appendix Tables 1, 2, and 3 (available at Annals.org), respectively. In general, these results were consistent with those of the main analyses.

Discussion

In SPRINT participants without CKD at baseline, intensive SBP treatment resulted in an absolute 2.6% higher risk for incident CKD at 3 years of follow-up than standard SBP treatment, based on our a priori definition of a reduction in eGFR of at least 30% with a confirmed level less than 60 mL/min/1.73 m^2. On the other hand, the intensive treatment group had an absolute 2.2% lower risk for the composite of a primary CVD event or all-cause death at 3 years.

Because glomerular filtration is highly dependent on the hydrostatic pressure gradient across the glomerular basement membrane, intensive SBP lowering would be expected to result in a reduction in glomerular capillary pressure and a corresponding decrease in eGFR (17). Hence, the early reduction in eGFR associated with intensive SBP lowering (Figure 1) was expected and is consistent with decreases noted during intensive blood pressure lowering in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (18), the SPS3 (Secondary Prevention of Small Subcortical Strokes) (19) trial, AASK (African American Study of Kidney Disease and Hypertension) (20), and the MDRD study (21). In addition, similar decreases in eGFR have been observed with the use of angiotensin-converting enzyme inhibitors (22) or aldosterone-receptor blockers (23) and with dietary protein restriction (24). Despite the acute decrease in eGFR during treatment with angiotensin-converting enzyme inhibitors and aldosterone-receptor blockers, such therapy is known to slow the progression of kidney disease compared with placebo in adults with diabetes mellitus and a high risk for CVD or nephropathy (25, 26). The long-term consequences of the acute reduction in eGFR noted during intensive treatment in SPRINT are unclear. However, the mean difference in eGFR between treatment groups remained relatively stable after 18 months (Figure 1 [*panel B*] and Appendix Figure 3), and no one in either group developed ESRD during follow-up (Figure 3).

In contrast to analyses of the difference in mean eGFR between groups, which involved averages across the full cohort, the time-to-event analyses of incident CKD focused on patients with a substantial decrease in eGFR during follow-up. These analyses indicated that the intensive group had an absolute risk increase of 2.6% over 3 years and a 3.5-fold higher hazard of incident CKD compared with the standard group. These differences persisted if the 30% threshold for decrease in eGFR was increased to 40% (Appendix Table 1) and were not fully attenuated when we attempted to account for the initial presumed hemodynamic effect of the treatments by restricting the analysis to after the first 6 months of treatment (Appendix Tables 1 and 2). These differences were observed across subgroups based on age, sex, race, and albuminuria (Appendix Figure 4).

The clinical and public health significance of CKD is a reflection of increases in risk for cardiovascular events, all-cause death, and ESRD (27). In the current study, none of the participants with incident CKD progressed to ESRD during the relatively short follow-up (Figure 3). Furthermore, 25.7% of those with incident CKD in the intensive group recovered renal function and were classified as no longer having CKD at the final study assessment (Figure 3).

Although more intensive treatment increased the risk for incident CKD—which has been found in observational studies to be a risk factor for future cardiovascular events and all-cause death—it resulted in a substantial decrease in CVD and all-cause mortality during the median of 3.26 years of treatment in SPRINT. The number needed to treat for harm for an asymptomatic incident CKD event within 3 years was 38 (CI, 29 to 53), whereas the number needed to treat to prevent a composite of cardiovascular event or all-cause death was 46 (CI, 29 to 94). In other words, for each cardiovascular event or all-cause death prevented over 3 years, we noted 1.2 incident CKD events. We believe that an asymptomatic CKD event is benign compared with a cardiovascular event or death; therefore, the benefits of the intervention outweigh the risks, at least for the duration of the current study. However, we acknowledge that some patients and providers might consider incident CKD to be more important than a cardiovascular event or death.

When the SPRINT intervention is adopted in routine clinical practice, the incidence and, therefore, the prevalence of CKD might increase at the population level. Chronic kidney disease due to blood pressure lowering might not have the same clinical and public health significance as CKD due to progression of underlying intrinsic renal disease, but long-term follow-up of the SPRINT participants will be important to study this issue.

Although randomization of participants in the non-CKD subgroup was not stratified by eGFR, all participants were randomly allocated to intervention assignments. The subset of participants without CKD is a proper subgroup because it is based on information known at baseline. Furthermore, the probability of an important imbalance in a given covariate, measured or unmeasured, is very small in a sample this large (>70% of the entire SPRINT cohort of 9361 participants). Indeed, the baseline characteristics of the intensive and standard groups within the non-CKD stratum were similar. Therefore, we believe that the outcomes reported in this article are based on a randomized comparison. Limitations of this study include short follow-up, which limits inferences on long-term effects, such as progression to ESRD.

In summary, although an acute decrease in eGFR was observed in the intensive treatment group, the differences in mean eGFR remained relatively stable between groups. Intensive SBP lowering increased the risk for incident CKD events, but this was outweighed by the potential for cardiovascular and all-cause mortality benefits over the relatively short follow-up. None of the participants with incident CKD progressed to ESRD. The long-term consequences of incident CKD due to intensive SBP lowering need to be established.

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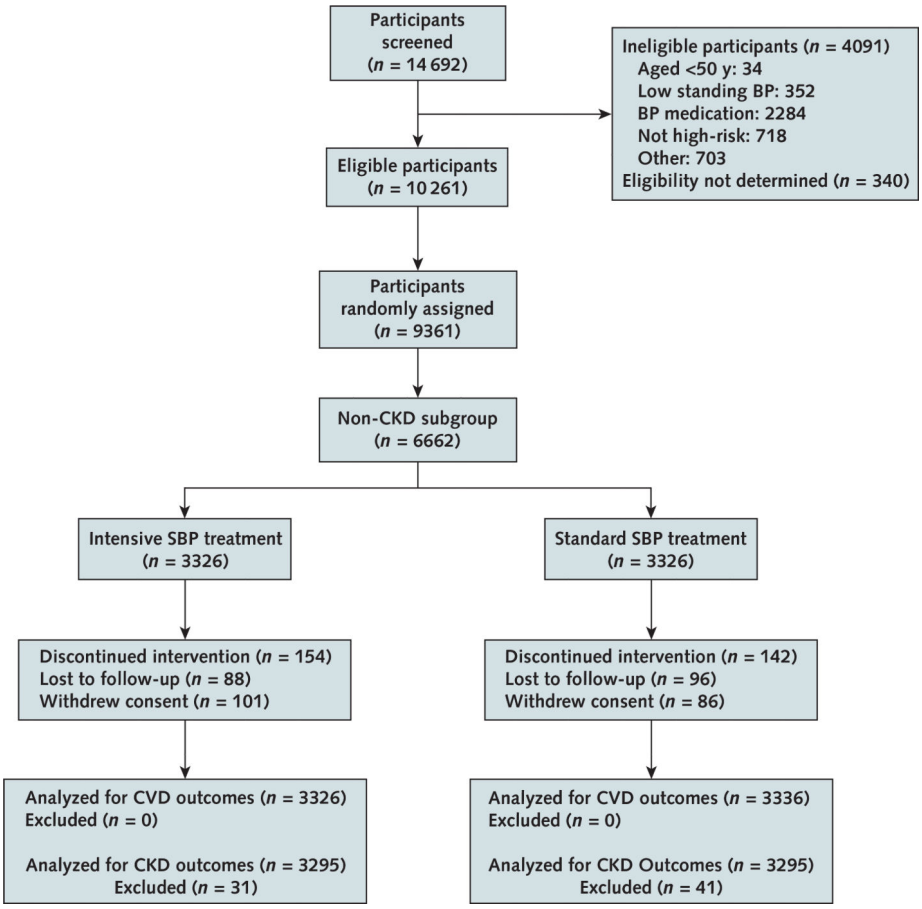
Appendix 2:: Additional Statistical Details

Sensitivity Analyses

Because time-to-event analyses of incident CKD based on a decrease in eGFR of 30% are believed to be sensitive to hemodynamic effects, we performed sensitivity analyses in which similar Cox regressions were applied for incident CKD with 40% and 50% decreases in eGFR from baseline, as well as for incident CKD with 30%, 40%, or 50% decreases in eGFR from the 6-month visit (Appendix Table 1). Furthermore, because relative changes from 6 months could be influenced by an acute effect leading to different eGFRs at 6 months, we also examined the time to a fixed decrease in eGFR of 27 mL/min/1.73 m^2 (representing a 30% decrease from a baseline eGFR of 90 mL/min/1.73 m^2) from 6 months, with and without requiring the threshold of 60 mL/min/1.73 m^2 (Appendix Table 2). Finally, analyses of incident CKD based on 30%, 40%, and 50% change in eGFR calculated using the CKD-EPI equation rather than the MDRD study equation were performed (Appendix Table 3).

Additional Event Outcomes

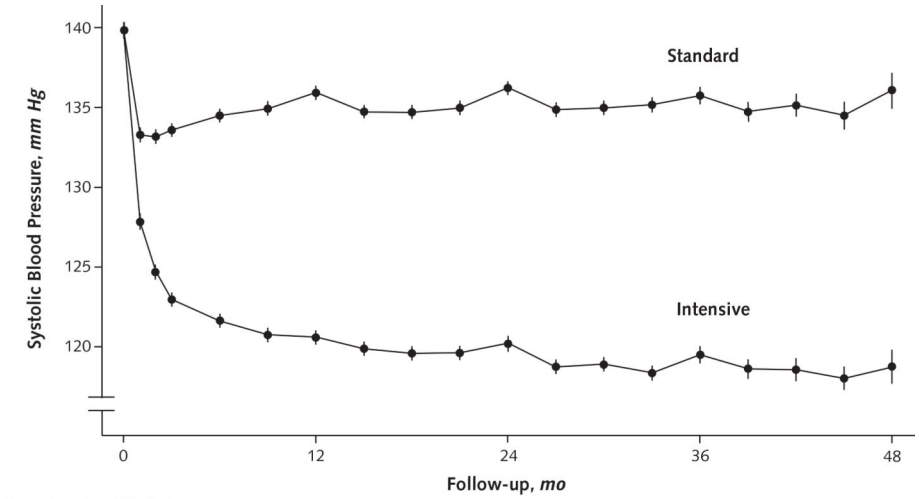
This article is limited to the 6662 randomly assigned participants with baseline eGFR of at least 60 mL/min/1.73 m^2 and excludes 53 without baseline serum creatinine measurements who were included in the “non-CKD” group in the primary results manuscript that was published previously (9). The primary CKD outcome in the non-CKD subgroup was a greater than 30% decrease in eGFR to a value less than 60 mL/min/1.73 m^2, with a consecutive confirmatory value at least 90 days later. The addition of potential confirmatory laboratory values subsequent to the cutoff date for follow-up events (20 August 2015) resulted in identification of 16 CKD events (13 in the intensive group and 3 in the standard group) in addition to those reported in the primary results manuscript. Likewise, continued review of serious adverse events and surveillance after the cutoff date resulted in identification of 10 primary CVD outcomes (1 in the intensive group and 9 in the standard group) and 1 more fatal event in the standard group that occurred before the cutoff date. All of these events were included in the current analysis.



Appendix Figure 1.

CONSORT flow diagram of study participants.

BP = blood pressure; CKD = chronic kidney disease; CONSORT = Consolidated Standards of Reporting Trials; CVD = cardiovascular disease; SBP = systolic blood pressure.

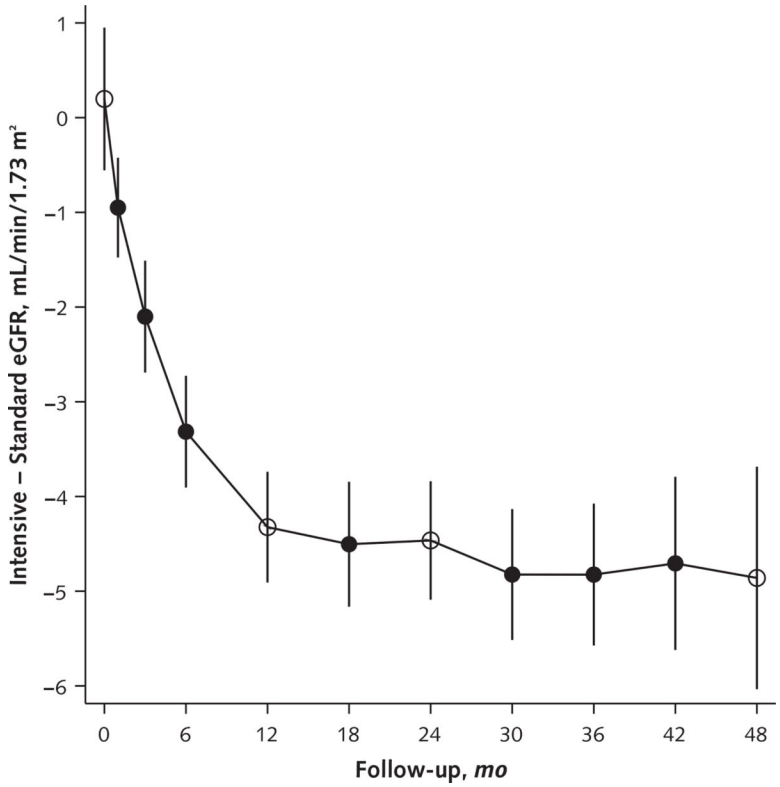


Participants with data, *n*									
Standard	3336	3108	3045	2954	2893	2748	2043	1196	525
Intensive	3326	3116	3025	2933	2880	2739	2078	1212	525
Mean number of medications									
Standard	1.7	1.7	1.7	1.7	1.7	1.8	1.7	1.8	1.8
Intensive	1.7	2.7	2.7	2.8	2.8	2.8	2.8	2.8	2.8

Appendix Figure 2.

Systolic blood pressure separation in the non-CKD population, by treatment group.

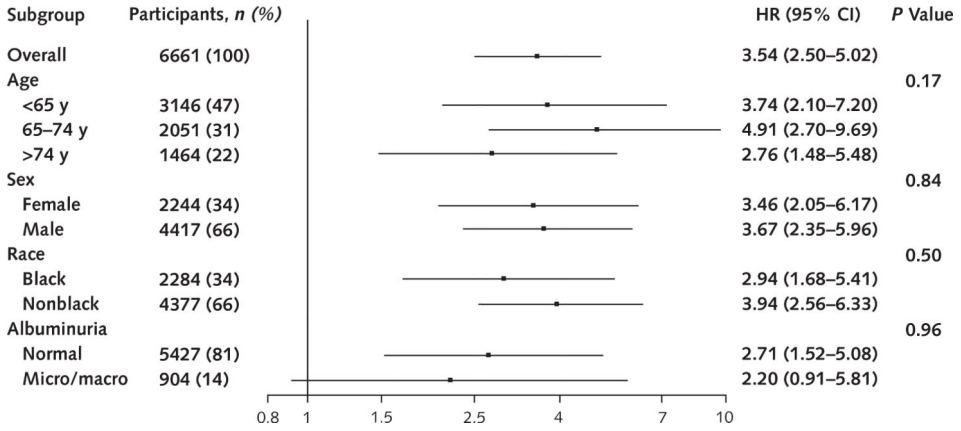
The mean number of medications was the average number of antihypertensive medication classes prescribed per participant. Closed circles depict raw means. Error bars indicate 95% CIs. CKD = chronic kidney disease.



Appendix Figure 3.

Difference in eGFR during follow-up in the non-CKD population.

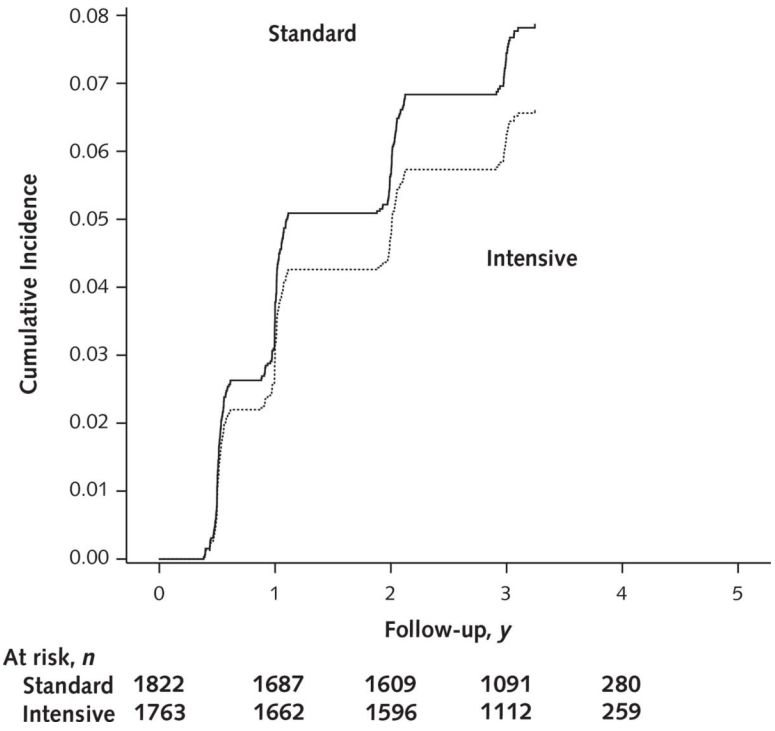
Adjusted means (intensive minus standard group) with 95% CIs (*error bars*) are shown. Open circles depict fasting visits; closed circles depict nonfasting visits. CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.



Appendix Figure 4.

Forest plot of HRs for incident CKD (>30% decrease from baseline) in the entire non-CKD population and in subgroups defined by age, sex, race, and albuminuria (urinary albumin–creatinine ratio <30 vs. ≥30 mg/g).

CKD = chronic kidney disease; HR = hazard ratio.



Appendix Figure 5.

Cumulative incidence of albuminuria in non-CKD subgroup.

CKD = chronic kidney disease.

Appendix Table 1.

Rates of Incident CKD, Defined as eGFR <60 mL/min/1.73 m^2 and Calculated by the MDRD Study Equation, With a Confirmed 30%, 40%, or 50% Decrease in eGFR From Baseline or Month 6

Decrease in eGFR	Intensive Group		Standard Group		Hazard Ratio (95% CI)	*P* Value
	Events per 100 Person-Years, *n*	Events/Total Years of Follow-up, *n/N*	Events per 100 Person-Years, *n*	Events/Total Years of Follow-up, *n/N*		
From baseline *						
>30%	1.32	140/10 584	0.37	40/10 751	3.55 (2.52–5.11)	<0.001
>40%	0.43	46/10 748	0.12	13/10 794	3.51 (1.95–6.77)	<0.001
>50%	0.10	11/10 812	0.05	5/10 803	2.11 (0.76–6.71)	0.15
From 6 mo †						
>30%	0.57	58/10 195	0.23	24/10 284	2.50(1.57–4.11)	<0.001
>40%	0.19	19/10 265	0.11	11/10 304	1.70(0.82–3.69)	0.16
>50%	0.04	4/10 282	0.02	2/10 315	1.97 (0.38–14.23)	0.40

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.

* *n* = 3332 for the intensive group and 3345 for the standard group.

† *n* = 3097 for the intensive group and 3106 for the standard group.

Appendix Table 2.

Rates of Incident CKD, Defined as eGFR <60 mL/min/1.73 m^2 and Calculated by the MDRD Study Equation, With a Fixed Decrease in eGFR of 27 mL/min/1.73 m^2 From Month 6

Variable	Intensive Group		Standard Group		Hazard Ratio (95% CI)	*P* Value
	Events per 100 Person-Years, *n*	Events/Total Years of Follow-up, *n/N*	Events per 100 Person-Years, *n*	Events/Total Years of Follow-up, *n/N*		
Fixed 27-unit decrease in eGFR to <60 mL/min/1.73 m^2	0.28	29/10 248	0.14	14/10 298	2.05 (1.10–4.00)	0.023
Fixed 27-unit decrease in eGFR to any eGFR	0.73	74/10 174	0.53	54/10 240	1.43 (1.01–2.05)	0.044

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.

Appendix Table 3.

Rates of Incident CKD, Defined as eGFR <60 mL/min/1.73 m^2 and Calculated by the CKD-EPI Equation, With a Confirmed 30%, 40%, or 50% Decrease in eGFR From Baseline or Month 6

Decrease in eGFR	Intensive Group		Standard Group		Hazard Ratio (95% CI)	*P* Value
	Events per 100 Person-Years, *n*	Events/Total Years of Follow-up, *n/N*	Events per 100 Person-Years, *n*	Events/Total Years of Follow-up, *n/N*		
From baseline *						
>30%	1.56	164/10 584	0.47	50/10 751	3.34 (2.45–4.63)	<0.001
>40%	0.53	57/10 748	0.15	16/10 794	3.67 (2.16–6.62)	<0.001
>50%	0.13	14/10 812	0.05	5/10 803	2.75(1.05–8.53)	0.039
From 6 mo †						
>30%	0.65	66/10 195	0.30	31/10 284	2.22 (1.46–3.46)	<0.001
>40%	0.21	22/10 265	0.12	12/10 304	1.86 (0.93–3.88)	0.079
>50%	0.04	4/10 282	0.02	2/10 315	1.94(0.38–14.00)	0.40

CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate.

* *n* = 3332 for the intensive group and 3345 for the standard group.

† *n* = 3097 for the intensive group and 3106 for the standard group.

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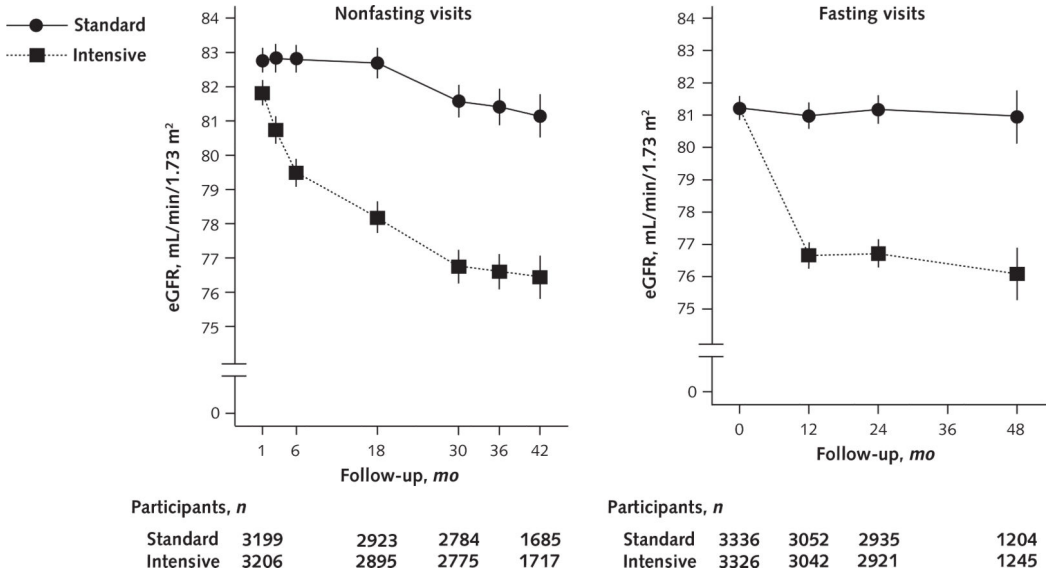

Figure 1.

Predicted mean eGFRs and 95% CIs (*error bars*) from a linear model accounting for baseline eGFR in the non-CKD population.

Results from nonfasting (*left*) and fasting (*right*) visits, including the raw (unadjusted) baseline mean. CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

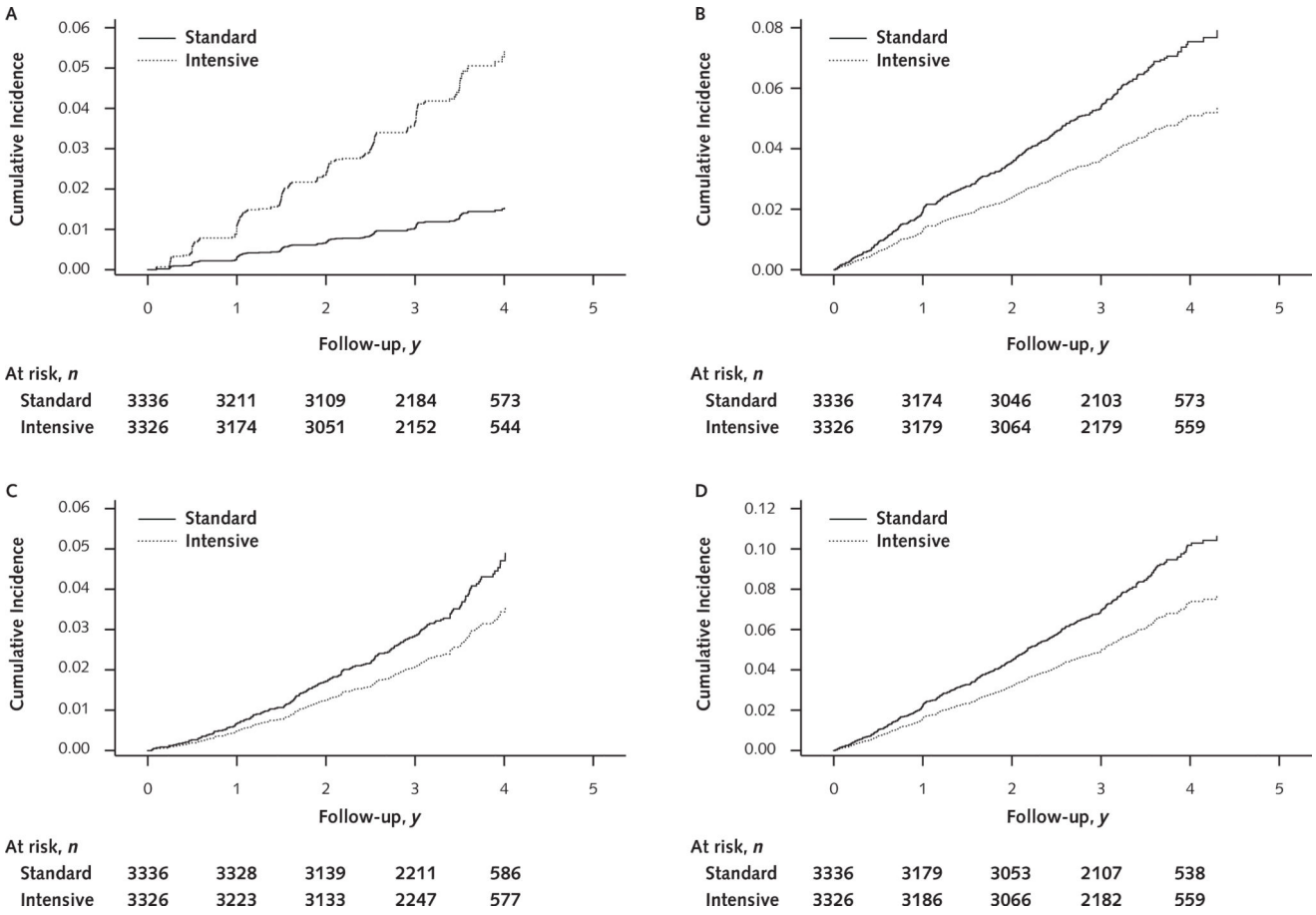

Figure 2.

Cumulative incidence plots for incident CKD (*A*), primary CVD outcome (*B*), all-cause death (*C*), and the composite of primary CVD outcome or all-cause death (*D*) in the non-CKD population, by treatment group.

CKD = chronic kidney disease; CVD = cardiovascular disease.

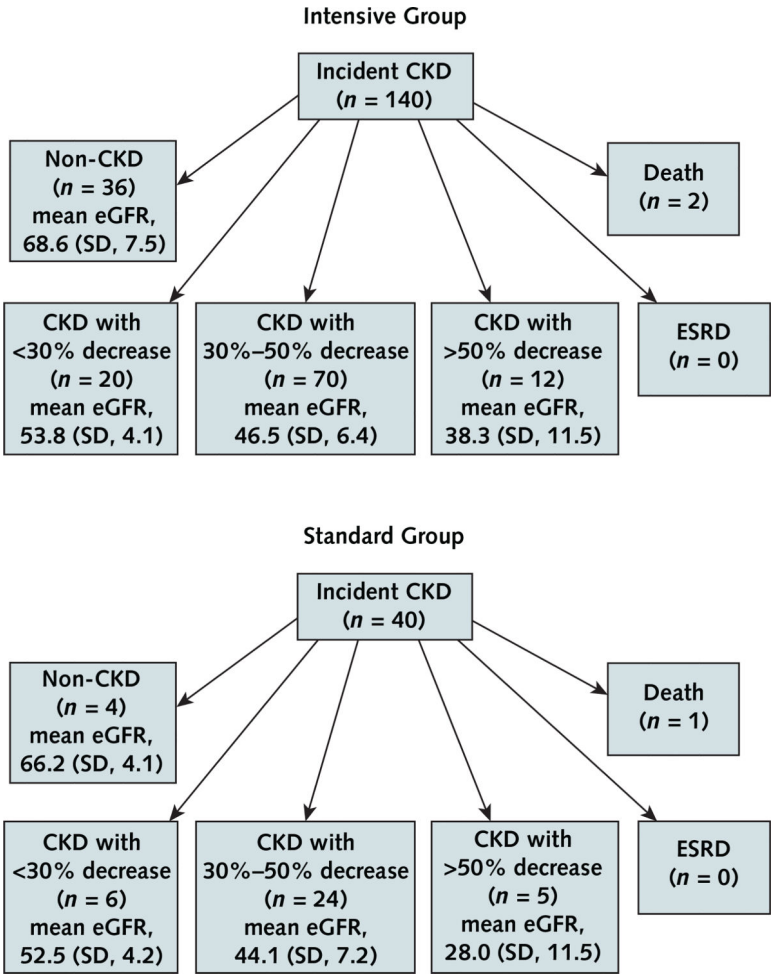

Figure 3.

Final status of participants with incident CKD.

Final disposition (categorized as non-CKD, CKD with varying decreases in eGFR, ESRD, or death) of persons who met the criteria for incident CKD during follow-up in the intensive (*top*) and standard (*bottom*) groups. The mean (SD) end-of-study eGFR is provided for each category. The 180 incident CKD events occurred a median of 21.0 mo (range, 1.2 to 47.9 mo) after randomization. The final eGFR assessments for patients with incident CKD occurred 42.4 mo (range, 11.4 to 58.9 mo) after randomization. CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease.

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Table 1.

Baseline Characteristics of SPRINT Participants Without CKD, by Treatment Group*

Characteristic	Intensive Group		Standard Group		Total	
	Participants, *n*	Value	Participants, *n*	Value	Participants, *n*	Value
Criteria for increased cardiovascular risk, *n (%)*						
Age ≥75 y	3326	726 (21.8)	3336	732 (21.9)	6662	1458 (21.9)
Clinical cardiovascular disease	3326	473 (14.2)	3336	460 (13.8)	6662	933 (14.0)
Subclinical cardiovascular disease	3326	258 (7.8)	3336	270 (8.1)	6662	528 (7.9)
Framingham riskscore ≥15%	3321	2004 (60.4)	3331	2020 (60.8)	6652	4024 (60.6)
Clinical characteristics						
Mean age (SD), *y*	3326	66.3 (9.0)	3336	66.3 (9.0)	6662	66.3 (9.0)
Female, *n (%)*	3326	1131 (34.0)	3336	1113 (33.4)	6662	2244 (33.7)
Race/ethnicity, *n (%)*	3326	–	3336	–	6662	–
Non-Hispanic black	–	1045 (31.4)	–	1101 (33.0)	–	2146 (32.2)
Hispanic	–	405 (12.2)	–	380 (11.4)	–	785 (11.8)
Non-Hispanic white	–	1804 (54.2)	–	1794 (53.8)	–	3598 (54.0)
Other race	–	72 (2.2)	–	61 (1.8)	–	133 (2.0)
Mean blood pressure (SD), *mm Hg*	3324	–	3335	–	6659	–
Systolic	–	139.9 (15.6)	–	139.8 (15.1)	–	139.9 (15.4)
Diastolic	–	79.5 (11.5)	–	79.3 (11.7)	–	79.4 (11.6)
Mean serum creatinine level (SD)	3326	–	3336	–	6662	–
μmol/L	–	82 (15)	–	83 (16)	–	82 (15)
mg/dL	–	0.93 (0.17)	–	0.94 (0.18)	–	0.93 (0.17)
Mean eGFR (SD), *mL/min/1.73 m²*	3326	81.3 (15.5)	3336	81.2 (15.5)	6662	81.2 (15.5)
Median urinary albumin-creatinine ratio (IQR), *mg/g*	3167	8.8 (5.5–17.2)	3165	8.5 (5.4–16.8)	6332	8.6 (5.5–17.1)
Mean fasting total cholesterol level (SD)	3326	–	3336	–	6662	–
mmol/L	–	4.97 (1.08)	–	4.97 (1.06)	–	4.97 (1.07)
mg/dL	–	191.7 (41.6)	–	192.0 (40.8)	–	191.8 (41.2)
Mean fasting HDL cholesterol level (SD)	3326	–	3336	–	6662	–
mmol/L	–	1.37 (0.37)	–	1.37 (0.38)	–	1.37 (0.37)
mg/dL	–	53.0 (14.2)	–	52.9 (14.5)	–	53.0 (14.4)

Characteristic	Intensive Group		Standard Group		Total	
	Participants, *n*	Value	Participants, *n*	Value	Participants, *n*	Value
Mean fasting triglyceride level (SD)	3326	–	3336	–	6662	–
mmol/L	–	1.41 (1.04)	–	1.41 (1.10)	–	1.41 (1.07)
mg/dL	–	124.8 (91.6)	–	124.6 (97.2)	–	124.7 (94.4)
Mean fasting plasma glucose level (SD)	3326	–	3336	–	6662	–
mmol/L	–	5.50 (0.76)	–	5.49 (0.76)	–	5.50 (0.76)
mg/dL	–	99.1 (13.7)	–	99.0 (13.7)	–	99.1 (13.7)
Statin use, *n (%)*	3308	1318 (39.8)	3312	1364 (41.2)	6620	2682 (40.5)
Aspirin use, *n (%)*	3316	1646 (49.6)	3330	1609 (48.3)	6646	3255 (49.0)
Angiotensin-converting enzyme inhibitor/aldosterone-receptor blocker use, *n (%)*	3326	1299 (39.1)	3336	1248 (37.4)	6662	2547 (38.2)
Smoking status, *n (%)*	3321	–	3331	–	6652	–
Never	–	1436 (43.2)	–	1461 (43.9)	–	2897 (43.5)
Former	–	1354 (40.8)	–	1385 (41.6)	–	2739 (41.1)
Current	–	531 (16.0)	–	485 (14.6)	–	1016 (15.3)
Mean Framingham risk score (SD)	3321	23.9 (11.7)	3331	23.9 (11.6)	6652	23.9 (11.7)
Mean body mass index (SD), kg/m^2	3305	30.1 (5.8)	3313	30.0 (5.7)	6618	30.0 (5.8)
Mean antihypertensive agents (SD), *n*	3326	1.74 (1.03)	3336	1.72 (1.04)	6662	1.73 (1.03)
Not using antihypertensive agents, *n (%)*	3326	370 (11.1)	3336	387 (11.6)	6662	757 (11.4)

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; IQR = interquartile range; SPRINT = Systolic Blood Pressure Intervention Trial.

*Percentages may not sum to 100 due to rounding.

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Table 2.

Effects of the SPRINT Intervention on Incident CKD, Cardiovascular Outcomes, and All-CAUSE Mortality in Participants Without CKD

Variable	Intensive Group			Standard Group			Hazard Ratio per 100 Person-Years (95% CI)*	Absolute Risk Reduction at 3 Years (95% CI), %†
	Participants, *n*	Events per 100 Person-Years, *n*	Events/Total Years of Follow-up, *n/N*	Participants, *n*	Events per 100 Person-Years, *n*	Events/Total Years of Follow-up, *n/N*		
Incident CKD	3326	1.33	140/10 564	3335	0.37	40/10 715	3.54 (2.50 to 5.02)	−2.6 (−3.4 to −1.9)
SPRINT primary outcome‡ or all-cause death	3326	1.78	189/10 631	3336	2.51	264/10 530	0.71 (0.59 to 0.86)	2.2 (1.1 to 3.3)
SPRINT primary outcome‡	3326	1.28	136/10 615	3326	1.92	202/10 509	0.67 (0.54 to 0.84)	1.8 (0.8 to 2.8)
All-cause death	3326	0.77	83/10 831	3336	1.05	114/10 814	0.74 (0.55 to 0.98)	0.9 (0.2 to 1.7)
Incident albuminuria	1763	1.98	109/5497	1822	2.39	133/5575	0.82 (0.64 to 1.05)	1.2 (−0.5 to 2.8)

CKD = chronic kidney disease; SPRINT = Systolic Blood Pressure Intervention Trial.

*Calculated from Cox proportional hazards regression models.

†The difference in the survival estimate (i.e., 1 minus the cumulative incidence) at 3-y follow-up in the intensive group minus that in the standard group, calculated from a proportional hazards regression model. Models for incident CKD, incident albuminuria, and the SPRINT primary outcome were adjusted for competing risk for death not caused by cardiovascular disease. Negative values indicate increase in absolute risk.

‡First occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or cardiovascular death. Surveillance for cardiovascular outcomes and death was performed every 3 mo.