**Supplementary File**

Table S1. Exclusion criteria of SPRINT cohort.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Full SPRINT data | Exclusion: CKD diagnosed before trial entry | Exclusion: baseline systolic blood pressure <130 or >180mmHg | Exclusion: not prescribed antihypertensive drugs at trial entry | Exclusion: not reached systolic blood pressure target in six months | Exclusion: missing values in potential confounders |
| Number excluded | NA | 2,684 | 1,699 | 134 | 693 | 40 |
| Sample size | 9,361 | 6,677 | 4,978 | 4,844 | 4,205 | 4,165 |
| Intensive treatment\* (%) | 4,678 (50%) | 3,332 (50%) | 2,463 (49%) | 2,451 (51%) | 1,898 (45%) | 1,880 (45%) |
| Event death (%) | 365 (4%) | 197 (3%) | 155 (3%) | 149 (3%) | 123 (3%) | 121 (3%) |
| Unadjusted HR mortality† | 0.74 (0.60-0.90) | 0.74 (0.56-0.99) | 0.68 (0.49-0.94) | 0.70 (0.50-0.96) | 0.69 (0.48-1.00) | 0.71 (0.49-1.03) |
| Event CKD (%) | NA | 164 (2%) | 131 (3%) | 131 (3%) | 106 (3%) | 105 (3%) |
| Unadjusted HR CKD† | NA | 3.49 (2.42-5.03) | 3.21 (2.15-4.78) | 3.07 (2.06-4.57) | 2.83 (1.87-4.28) | 2.79 (1.84-4.22) |

\*Standard and intensive treatment of lowering systolic blood pressure to <140 and <120 mmHg, respectively.
†The hazard ratio (HR) of all-cause mortality or chronic kidney disease (CKD) associated with intensive treatment compared to standard treatment.

Table S2. Description and coding of covariates.

|  |  |  |  |
| --- | --- | --- | --- |
| Covariate | SPRINT | THIN | Coding\* |
| Baseline | Trial entry in November 2010 – March 2013 | Date of a hypertensive systolic blood pressure reading of 141-180 mmHg in November 2010 – March 2013 (cohort with same study period as SPRINT) or in January 2005 – December 2013 (cohort with extended study period) | Date (only available in THIN) |
| Clinical site | Randomisation site | General practice | ID  |
| Systolic blood pressure target | Systolic blood pressure target of <140 mmHg for standard treatment and of <120 mmHg for intensive treatment | A systolic blood pressure reading of ≤140 mmHg (standard treatment) or ≤120 mmHg (intensive treatment) within six months after baseline | <140 mmHg (standard)/ <120 mmHg (intensive)(≤ for THIN) |
| Systolic blood pressure baseline | Systolic blood pressure reading in mmHg at baseline (130-180 mmHg). Blood pressure was measured by an automated device while unattended by a health care professional after the patient rested for five minutes alone in a room. | Hypertensive systolic blood pressure reading in mmHg at baseline (140-180 mmHg), Blood pressure was measured by a sphygmomanometer used by a healthcare professional with no rest period for the patient (i.e. office blood pressure). | Continuous, centred at 140 mmHg |
| Number of antihypertensive drug prescriptions at baseline | The number of antihypertensive drugs prescribed at baseline | The number of antihypertensive drugs prescribed in the month prior to the baseline. | 0/1/2/3+ |
| Change in number of antihypertensive drugs at entry | Change in the number of antihypertensive drugs prescribed at randomisation visit compared to baseline | Change in the number of antihypertensive drugs prescribed in the month prior to when the systolic blood pressure target was reached compared to the month prior to the baseline | More/same or less |
| Aspirin | Aspirin prescription at baseline | Aspirin prescription in the month prior to the baseline | No/yes |
| Statin | Statin prescription at baseline | Aspirin prescription in the month prior to the baseline | No/yes |
| Cardiovascular disease | History of clinical cardiovascular disease at baseline | History of cardiovascular disease at baseline | No/yes |
| Sex | Sex | Sex | Male/female |
| Age | Age at baseline | Age at baseline | Continuous, centred at age 65 |
| Ethnicity | Ethnicity | NA | Non-black/black |
| Deprivation | NA | Townsend deprivation quintiles | 1 (most)/2/3/4/5 (least) |
| Smoking status | Smoking status at baseline | Smoking status within six months to baseline | No/ex/yes |
| Body mass index | Body mass index at baseline(weight in kg)/(height in m)² | Body mass index within six months to baseline (weight in kg)/(height in m)² | under/normal weight: <25, overweight: 25-29obese: ≥30  |
| Death | Death from any cause | Death from any cause | No/yes |
| Time to death | Elapsed time for death from any cause | Elapsed time for death from any cause | Number of days |
| Chronic kidney disease | ≥30% reduction in eGFR to <60 ml/min/1.73m2 | Chronic kidney disease stages 3-5 with eGFR <60 ml/min/1.73m2  | No/yes |
| Time to chronic kidney disease | Elapsed time for ≥30% reduction in eGFR to <60 ml/min/1.73m2 | Elapsed time for chronic kidney disease stages 3-5 with eGFR <60 ml/min/1.73m2 | Number of days |

\*First category was the reference category.

Table S3: Characteristics of SPRINT cohort and THIN cohort with extended study period.

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | SPRINT | THIN |
|  |  | Standard treatment\*  | Intensive treatment†  | Standard treatment\* | Intensive treatment†  |
| Enrolment years of study period‡ (mean) | 2010-13 (NA) | 2010-13 (NA) | 2005-13 (2007) | 2005-2013 (2008) |
| Number of participants | 2,285 | 1,880 | 34,927 | 19,756 |
| Total person-years follow-up (mean) | 7,439 (3.3) | 6,173 (3.3) | 270,937 (7.8) | 142,939 (7.2) |
| Deaths during follow-up | 76 (3%) | 45 (2%) | 3,792 (11%) | 2,519 (13%) |
| Chronic kidney disease during follow-up | 32 (1%) | 73 (4%) | 5,039 (14%) | 3,139 (16%) |
| Systolic blood pressure at baseline | Mean (sd) | 145.0 (11.2) | 144.3 (10.9) | 158.7 (9.9) | 155.8 (9.7) |
| Number of antihypertensive drugs at baseline | 1 | 756 (33%) | 602 (32%) | 7,680 (22%) | 5,095 (26%) |
|  | 2 | 791 (35%) | 626 (33%) | 5,336 (15%) | 4,044 (20%) |
|  | 3+ | 519 (23%) | 418 (22%) | 3,743 (11%) | 3,128 (16%) |
| Change in number of antihypertensive drugs at entry  | More | 577 (25%) | 908 (48%) | 25,160 (72%) | 12,695 (64%) |
|  | Less | 156 (7%) | 59 (3%) | 4,738 (14%) | 3,447 (17%) |
| Aspirin | Yes | 1,097 (48%) | 929 (49%) | 4,851 (14%) | 4,165 (21%) |
| Statin | Yes | 905 (40%) | 759 (40%) | 6,916 (20%) | 6,087 (31%) |
| Cardiovascular disease | Yes | 324 (14%) | 292 (16%) | 1,216 (3%) | 1,099 (6%) |
| Sex | Male | 1,501 (66%) | 1,212 (64%) | 17,909 (51%) | 9,122 (46%) |
| Age | Mean (sd) | 66.5 (9.0) | 66.5 (9.1) | 64.6 (9.2) | 65.1 (9.7) |
| Ethnicity | Black | 806 (35%) | 610 (32%) | NA | NA |
| Deprivation quintile | 2 | NA | NA | 8,192 (23%) | 4,439 (22%) |
|  | 3 | NA | NA | 7,809 (22%) | 4,329 (22%) |
|  | 4 | NA | NA | 6,596 (19%) | 3,878 (20%) |
|  | 5 Least | NA | NA | 4,386 (13%) | 2,706 (14%) |
| Smoking status | Ex | 928 (41%) | 762 (41%) | 11,915 (34%) | 7,188 (36%) |
|  | Yes | 326 (14%) | 286 (15%) | 6,272 (18%) | 3,431 (17%) |

\*Standard treatment of lowering systolic blood pressure to <140 mmHg.
†Intensive treatment of lowering systolic blood pressure to <120 mmHg.
‡Enrolment date of SPRINT patients was unknown.

Table S4. Adjusted effects of antihypertensive treatment associated with the hazard of all-cause mortality.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | SPRINTHR (95%CI) | THIN\_spr\*no propensity score matchingHR (95%CI) | THIN\_spr\*propensity score matchingHR (95%CI) | THIN\_ext†no propensity score matchingHR (95%CI) | THIN\_ext\_ps†propensity score matchingHR (95%CI) |
| Treatment arm‡ | Intensive <1 yr fu | 0.63 (0.43-0.92) | 2.40 (1.35-4.24) | 2.34 (1.27-4.31) | 1.35 (1.11-1.65) | 1.33 (1.07-1.65) |
|  | Intensive ≥1 yr fu | NA | 1.51 (1.14-2.02) | 1.52 (1.13-2.06) | 1.20 (1.14-1.27) | 1.21 (1.14-1.29) |
| Prior no. blood pressure regulating drugs | 2+ | 1.35 (0.88-2.05) | 1.33 (0.96-1.84) | 1.32 (0.95-1.83) | 1.19 (1.11-1.26) | 1.19 (1.11-1.27) |
| Change no. blood pressure regulating drugs | More | 1.54 (1.01-2.34) | 1.01 (0.74-1.38) | 1.01 (0.74-1.38) | 0.93 (0.88-0.99) | 0.93 (0.87-1.00) |
| Aspirin | Yes | 1.27 (0.86-1.87) | 1.05 (0.74-1.50) | 1.04 (0.73-1.49) | 1.01 (0.94-1.08) | 0.98 (0.92-1.06) |
| Statin | Yes | 0.79 (0.53-1.17) | 0.80 (0.58-1.10) | 0.80 (0.58-1.10) | 0.88 (0.83-0.94) | 0.89 (0.83-0.95) |
| Cardiovascular disease | Yes | 1.72 (1.10-2.67) | 1.51 (1.06-2.15) | 1.56 (1.09-2.22) | 1.41 (1.31-1.51) | 1.42 (1.31-1.53) |
| Sex | Female | 0.61 (0.40-0.94) | 0.68 (0.53-0.88) | 0.70 (0.53-0.90) | 0.77 (0.73-0.81) | 0.78 (0.73-0.83) |
| Age§ | Years  | 1.08 (1.05-1.10) | 1.10 (1.09-1.12) | 1.10 (1.09-1.12) | 1.11 (1.11-1.11) | 1.11 (1.11-1.12) |
| Ethnicity | Black | 1.20 (0.80-1.81) | NA | NA | NA | NA |
| Deprivation quintile | 2nd  | NA | 0.92 (0.63-1.34) | 0.91 (0.62-1.34) | 1.05 (0.97-1.14) | 1.04 (0.95-1.15) |
|  | 3rd  | NA | 1.05 (0.73-1.51) | 0.99 (0.68-1.45) | 1.11 (1.02-1.21) | 1.11 (1.01-1.21) |
|  | 4th  | NA | 1.22 (0.85-1.77) | 1.22 (0.83-1.77) | 1.26 (1.16-1.37) | 1.21 (1.10-1.33) |
|  | 5th Least | NA | 1.17 (0.78-1.76) | 1.18 (0.78-1.79) | 1.42 (1.30-1.56) | 1.39 (1.25-1.54) |
| Smoking status | Ex | 1.66 (1.08-2.55) | 1.65 (1.25-2.19) | 1.61 (1.21-2.15) | 1.41 (1.33-1.49) | 1.42 (1.32-1.51) |
|  | Yes | 3.55 (2.02-6.26) | 2.70 (1.94-3.75) | 2.33 (1.64-3.31) | 2.89 (2.70-3.10) | 2.84 (2.62-3.07) |

\*THIN cohort with the same study period as SPRINT of 2010-15. †THIN cohort with extended study period of 2005-17. ‡Intensive treatment of lowering systolic blood pressure to <120 mmHg compared to standard treatment to <140 mmHg. In SPRINT, there was no time-dependent effect of treatment arm during follow-up (fu). §Baseline age centred at 65 years.

Model performance: The model based on the THIN cohort with extended dates performed the best, with 59% of survival differentials explained, 79% concordance between the hazard of mortality and survival time, and <1% overestimation of the coefficients. The model based on the THIN cohort with the same SPRINT dates explained 58% of survival differentials, had 77% concordance between the hazard of mortality and survival time, and overestimated the coefficients by 4%. The model based on the SPRINT cohort explained 39% of survival differentials, had 72% concordance between the hazard of mortality and survival time, and overestimated the coefficients by 6%.

Table S5. Adjusted effects of antihypertension treatment associated with the hazard of chronic kidney disease.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | SPRINTHR (95%CI) | THIN\_spr\*no propensity score matchingHR (95%CI) | THIN\_spr\*propensity score matchingHR (95%CI) | THIN\_ext†no propensity score matchingHR (95%CI) | THIN\_ext\_ps†propensity score matchingHR (95%CI) |
| Treatment arm & prior no. blood pressure regulating drugs‡ | Standard 1 drug |  |  |  | 1.37 (1.27-1.49) | 1.33 (1.20-1.48) |
|  | Standard 2 drugs | 1.19 (0.57-2.46) | 1.09 (0.67-1.75) | 1.09 (0.67-1.77) | 1.86 (1.71-2.02) | 1.91 (1.72-2.13) |
|  | Standard 3+ drugs |  |  |  | 2.51 (2.28-2.75) | 2.55 (2.27-2.86) |
|  | Intensive 0 drug | 2.57 (1.35-4.90) | 1.35 (1.05-1.73) | 1.33 (1.02-1.73) | 1.15 (1.05-1.25) | 1.14 (1.03-1.27) |
|  | Intensive 1 drug |  |  |  | 1.44 (1.32-1.58) | 1.45 (1.30-1.61) |
|  | Intensive 2 drugs | 3.38 (1.81-6.32) | 1.80 (1.28-2.53) | 1.80 (1.27-2.54) | 1.77 (1.61-1.95) | 1.79 (1.60-2.00) |
|  | Intensive 3+ drugs |  |  |  | 2.26 (2.04-2.50) | 2.28 (2.03-2.56) |
| Systolic blood pressure at baseline§ | mmHg  | 1.03 (1.02-1.05) | 1.00 (0.99-1.01) | 1.00 (0.99-1.01) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) |
| Change no. blood pressure regulating drugs | More | 1.49 (0.94-2.34) | 1.13 (0.85-1.50) | 1.13 (0.85-1.50) | 1.23 (1.16-1.30) | 1.24 (1.17-1.32) |
| Aspirin | Yes | 0.59 (0.38-0.90) | 0.78 (0.55-1.11) | 0.78 (0.55-1.10) | 1.06 (1.00-1.12) | 1.07 (1.00-1.14) |
| CVD | Yes | 1.51 (0.88-2.58) | 1.37 (0.98-1.94) | 1.37 (0.96-1.93) | 1.33 (1.25-1.41) | 1.34 (1.25-1.43) |
| Sex | Female | 1.08 (0.71-1.63) | 1.09 (0.88-1.35) | 0.99 (0.79-1.24) | 1.27 (1.22-1.33) | 1.30 (1.23-1.37) |
| Age§ | Years  | 1.04 (1.01-1.06) | 1.07 (1.06-1.09) | 1.07 (1.06-1.09) | 1.07 (1.07-1.07) | 1.07 (1.06-1.08) |
| Ethnicity | Black | 1.06 (0.67-1.67) | NA | NA | NA | NA |
| Deprivation quintile | 2nd  | NA | 1.28 (0.91-1.78) | 1.19 (0.85-1.68) | 1.04 (0.97-1.12) | 1.05 (0.97-1.14) |
|  | 3rd  | NA | 1.50 (1.08-2.07) | 1.38 (0.99-1.93) | 1.11 (1.03-1.19) | 1.10 (1.01-1.19) |
|  | 4th  | NA | 1.34 (0.95-1.90) | 1.26 (0.89-1.80) | 1.14 (1.06-1.23) | 1.13 (1.04-1.23) |
|  | 5th Least | NA | 1.29 (0.87-1.89) | 1.21 (0.81-1.79) | 1.19 (1.10-1.29) | 1.18 (1.08-1.29) |

\*THIN cohort with the same study period as SPRINT of 2010-15. †THIN cohort with extended study period of 2005-17. ‡Intensive treatment of lowering systolic blood pressure to <120 mmHg compared to standard treatment of <140 mmHg. In SPRINT and THIN\_spr, the interaction of treatment arm with prior number of blood pressure regulating drugs had the levels: standard treatment with 0/1 drug, standard treatment with 2+ drugs, intensive treatment with 0/1 drug, and intensive treatment with 2+ drugs. §Baseline systolic blood pressure was centred at 140 mmHg and baseline age at 65 years.

Model performance: With respect to goodness-of-fit, the model based on the SPRINT cohort performed the best, explaining 59% of survival differentials and with 80% concordance between the hazard of CKD and event-free survival time. These performance statistics for the model based on the THIN cohort with SPRINT dates were 49% and 80%, respectively, and for the model based on the THIN cohort with extended dates were 44% and 75%, respectively. With respect to external validation, however, the model based on the THIN cohort with extended dates performed the best, overestimating the coefficients by <1%. This was 7% and 11% for the models based on the THIN cohort with SPRINT dates and the SPRINT cohort, respectively.