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Optimal SBP targets in routine clinical care

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Objective: Compare outcomes of intensive treatment of SBP to less than 120 mmHg versus standard treatment to less than 140 mmHg in the US clinical Systolic Blood Pressure Intervention Trial (SPRINT) with similar hypertensive patients managed in routine primary care in the United Kingdom.

Methods: Hypertensive patients aged 50–90 without diabetes or chronic kidney disease (CKD) were selected in SPRINT and The Health Improvement Network (THIN) database. Patients were enrolled in 2010–2013 and followed-up to 2015 (SPRINT $N = 4112$; THIN $N = 8631$). Cox's proportional hazards regressions were fitted to estimate the hazard of all-cause mortality or CKD (main adverse effect) associated with intensive treatment, adjusted for sex, age, ethnicity, smoking, blood pressure, cardiovascular disease, aspirin, statin, number of antihypertensive drugs at baseline, change in number of antihypertensive drugs at trial entry, and clinical site.

Results: Almost half of the patients had intensive treatment (43–45%). In SPRINT, intensive treatment was associated with a decreased hazard of mortality of 0.63 (0.43–0.92), while in THIN with an increased hazard of 1.66 (1.28–2.15). In THIN, this effect was time-dependent. Intensive treatment was associated with an increased hazard of CKD of 2.67 (1.74–4.11) in SPRINT and 1.35 (1.08–1.70) in THIN. In THIN, this effect differed by the number of antihypertensive drugs prescribed at baseline.

Conclusion: It appears that intensive treatment of SBP may be harmful in the general population where all have access to routine healthcare as with the UK National Health Services, but could be beneficial in high-risk patients who are closely monitored.

Keywords: antihypertensive treatment, chronic kidney disease, clinical guidelines, hypertension, survival prospects

Abbreviations: AUC, area under the curve; CKD, chronic kidney disease; CVD, cardiovascular disease; NICE, National Institute of Health and Care Excellence; RCT, randomized clinical trial; ROC, receiver operating characteristic; SIGN, Scottish Intercollegiate Guidelines Network; SPRINT, Systolic Blood Pressure Intervention Trial; THIN, The Health Improvement Network primary care database

INTRODUCTION

High SBP ($\geq$140 mmHg) is one of the leading risk factors of the global burden of disease, attributing to an estimated 122.2 million disease-adjusted life-years in men and 89.9 million in women in 2016 [1]. High SBP has consistently been associated with increased risks of cardiovascular disease (CVD) and related comorbidities such as chronic kidney disease (CKD) [1–3].

The results of the Systolic Blood Pressure Intervention Trial (SPRINT) in the United States showed considerable survival benefits of treatment of SBP to a target of less than 120 mmHg compared with a target of less than 140 mmHg [4]. Following this, the American Heart Association changed its guideline on hypertension in 2017 [3]. In its previous version of 2003, hypertension was defined as having a SBP of at least 140 mmHg, whereas now hypertension is defined as having a SBP of at least 130 mmHg. With the change in hypertension definition, its prevalence in the United States increased from 32 to 46% [5].

The UK National Institute of Health and Care Excellence (NICE) is currently reviewing its hypertension guideline [2]. Hypertension is defined as having a SBP of at least 140 mmHg, which is prevalent in nearly 30% in the United Kingdom [6]. The Scottish Intercollegiate Guidelines Network (SIGN) is accredited by NICE to develop clinical guidelines [7]. The SPRINT results were not taken up in its latest guideline on the prevention of CVD published in 2017, as SIGN found that several aspects of SPRINT made the results difficult to interpret with respect to routine clinical practice in Scotland [7]. These were among others the short follow-up of 3.3 years compared with treatment regimes in routine practice and the way blood pressure (BP) was measured resulting in lower readings than if they were measured in routine practice. SIGN, however, did acknowledge that tighter BP targets should be considered in high-risk patients.

NICE identified several gaps in the research evidence around the management of hypertension when the guidance was updated in 2016 [2]. It recommended further research into the optimal SBP in people with treated hypertension by means of a large randomized clinical trial (RCT) that has sufficient power to assess clinical outcomes in people with different SBP targets [2]. An RCT, however, is expensive and due to its strict targets that are tightly controlled, its results can be difficult to translate to routine

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practice [7]. A large observation study could complement RCTs by testing the effect of treatments associated with clinical outcomes in the general population [8]. This led to the research question: what are the survival and CKD prospects of intensive treatment of SBP to less than 120 mmHg versus standard treatment to less than 140 mmHg in the US clinical trial SPRINT in comparison with similar hypertensive patients managed in routine primary care in the United Kingdom?

METHODS

Study design

SPRINT is an RCT which included people aged 50–90 years with a SBP of 130–180 mmHg and an increased risk of CVD (Framingham risk score ≥15%) [4]. The study population excluded people with a history of cancer, dementia, diabetes, heart failure, or stroke. Patients were enrolled in November 2010–March 2013 and followed-up to August 2015. Patients were either assigned the standard treatment regime of lowering SBP to less than 140 mmHg or the intensive to less than 120 mmHg. For more information on SPRINT, refer to [4]. For our study, SPRINT patients were excluded if they had a history of CKD at baseline, were not prescribed antihypertensive drugs at trial entry, or did not reach the target SBP in 6 months, refer to Supplementary File Table S1, http://links.lww.com/HJH/B19.

Two retrospective cohorts were studied using health records of The Health Improvement Network (THIN) primary care database. THIN records are representative of the UK population when adjusted for sex, age, and deprivation [9,10]. The first cohort had the same study period as SPRINT. The second cohort had an extended study period to increase the power of the study and to estimate the long-term effects of SBP targets; enrolment in January 2005–December 2013 and follow-up to January 2017. The first cohort was a subset of the second cohort, with a maximum follow-up of almost 5 and 12 years, respectively. The cohorts had the same inclusion and exclusion criteria as SPRINT with the exception of no criterion on cardiac risk. In addition, the selected patients had to have their SBP reduced from 141 to 180 mmHg (baseline, first measurement) to either 121–140 mmHg (standard treatment) or 70–120 mmHg (intensive treatment) within 6 months (second measurement). The cut-off values of BP categories in THIN were 1 mmHg higher than in SPRINT because there was a terminal digit bias towards zero in BP recording in primary care [11]. The selection criteria also specified that the patient had to have a diagnosis of hypertension at baseline or at least one ongoing antihypertensive drug prescription in the month prior to the baseline, and a change in antihypertensive treatment in the month prior to the second measurement. A change in treatment was defined as a change in dose, drug, or number of drugs.

SPRINT data were made available by the National Heart, Lung, and Blood Institute for the SPRINT Data Analysis Challenge hosted by the *New England Journal of Medicine* [12]. By qualifying for the challenge, we were permitted to publish our analyses of SPRINT data. This study was approved by THIN Scientific Review Committee and the University of East Anglia Computing Sciences Research Ethics Committee. Informed consent was not required for research based on routine data.

Medical history

The outcomes were time to all-cause mortality and time to CKD [estimated glomerular filtration rate (eGFR) to <60 ml/min per 1.73 m^2], measured in days. The primary exposure was treatment of SBP. In SPRINT, BP was measured by an automated device while unattended by a healthcare professional after the patient rested for 5 min alone in a room [4]. In contrast, in UK routine clinical practice, BP is measured by a sphygmomanometer used by a healthcare professional with no rest period for the patient (i.e., office BP) [2]. The secondary exposures were the number of antihypertensive drugs prescribed at baseline and change in the number of antihypertensive drugs prescribed at trial entry (SPRINT) or prior to the second BP measurement (THIN). Potential confounders were selected based on SPRINT's baseline measures: SBP, CVD, aspirin, statin, smoking status, and BMI. The demographic measures included sex, age, ethnicity (SPRINT only), and deprivation (THIN only). To have a meaningful reference group, baseline SBP was centred at 140 mmHg and age at 65 years. In THIN, ethnicity is not consistently recorded with 65% being unknown [13], therefore it was not included. In SPRINT, deprivation was not recorded [4]. For more information on the selected medical history, refer to Table S2, http://links.lww.com/HJH/B19.

In SPRINT, there were less than 1% missing values in aspirin, statin, smoking status, and BMI. In THIN, there were missing values in smoking status (23%) and BMI (45%). Due to the high prevalence of missing values in BMI in THIN and the insignificant association of BMI with the outcomes time to death or CKD in SPRINT, BMI was excluded from the analyses. Patients with missing values in aspirin, statin, or smoking status were excluded from the study (SPRINT < 1%; THIN = 23%).

Statistical analyses

Cox's regression models were fitted to estimate the effect of intensive treatment associated with the hazard of all-cause mortality and the hazard of CKD. The competing risk adaptation of a Cox's model was examined, but disregarded as the adapted models provided similar results with the same conclusions as the simple Cox's models. The final models included the covariates and interactions with treatment arm that were significant ($P < 0.05$) or of substantial effect size ($|\beta| > 0.20$) in either SPRINT or THIN using backward elimination. The main exposures and demographic covariates were included regardless of their significance level or effect size. The linearity of the effect of the continuous covariates SBP and age were tested by including their quadratic form. The proportional hazards assumption was checked by Grambsch and Therneau's test [14]; the effect of a violating covariate was made time-dependent. The models included a frailty term on clinical site to take into account the interdependence of patients from the same site. The models were assessed on overall performance, discrimination, and external validation, using Royston's R^2, Harrell's concordance, and 10-fold cross-validation, respectively [15].

A sensitivity analysis was performed based on the propensity score of receiving intensive treatment in routine

clinical practice as observed in THIN. This score was predicted by a logistic regression that included all baseline information described above and a frailty term on clinical site. The accuracy of the prediction was quantified by the area under the curve (AUC) of the receiver operating characteristic (ROC) [15]. By means of nearest neighbour matching [16], patients on intensive treatment were matched one on one to patients on standard treatment. The final survival models were refitted on the matched propensity score datasets of THIN.

RESULTS

Cohorts' characteristics

With our additional selection criteria, SPRINT's sample size was reduced to 4165 patients, where 45% was assigned the intensive treatment of lowering SBP to less than 120 mmHg, refer to Table 1. At each stage of the selection process, the unadjusted hazard of mortality or CKD associated with intensive treatment was estimated, refer to Table S1, http://links.lww.com/HJH/B19. Comparing the results in the original sample with our final sample, the hazards were not significantly different.

The THIN cohort with the same SPRINT dates included 8361 patients, where 43% had their SBP reduced to 120 mmHg or less, refer to Table 1. The THIN cohort with the extended dates included 54 683 patients, where 36% had their SBP reduced to less than 120 mmHg, refer to Table S3, http://links.lww.com/HJH/B19.

The baseline SBP was on average 11 mmHg lower in SPRINT than in THIN. This could be explained by the different selection criteria, where in SPRINT the baseline SBP had to be between 130 and 180 mmHg whereas in THIN this had to be between 141 and 180 mmHg. In SPRINT, the average SBP during follow-up stayed stable after reaching the treatment target within 6 months; 135–137 mmHg in the standard and 116–120 mmHg in the intensive treatment arm, refer to Fig. 1. In THIN, however, the average SBP increased after the treatment target was reached within 6 months and remained levelled thereafter; 142–143 mmHg in the standard and 137–138 mmHg in the intensive treatment arm, refer to Fig. 1.

Comparing the characteristics of the SPRINT cohort and the THIN cohort with the same SPRINT dates, the average follow-up was 3.3 and 3.4 years, respectively. The incidence of death during follow-up was similar in both standard treatment arms (2–3%), but was higher in the intensive treatment arm of THIN (5%). The incidence of CKD during follow-up was higher in the intensive treatment arms and in THIN (1–6%). The prevalences of CVD and prescribed drugs

TABLE 1. Characteristics of Systolic Blood Pressure Intervention Trial and The Health Improvement Network cohorts with the same study period

	SPRINT		THIN	
	Standard treatment[a]	Intensive treatment[b]	Standard treatment[a]	Intensive treatment[b]
Number of participants	2285	1880	4743	3618
Total person-years follow-up (mean)	7439 (3.3)	6173 (3.3)	16 475 (3.5)	12 417 (3.4)
Death during follow-up	76 (3%)	45 (2%)	104 (2%)	171 (5%)
Chronic kidney disease during follow-up	32 (1%)	73 (4%)	162 (3%)	206 (6%)
SBP at baseline				
Mean (SD)	145.0 (11.2)	144.3 (10.9)	159.4 (10.1)	155.9 (9.8)
Number of antihypertensive drugs at baseline				
1	756 (33%)	602 (32%)	750 (16%)	915 (25%)
2	791 (35%)	626 (33%)	374 (8%)	637 (18%)
3+	519 (23%)	418 (22%)	177 (4%)	457 (13%)
Change in number of antihypertensive drugs at entry				
More	577 (25%)	908 (48%)	4010 (85%)	2422 (67%)
Less	156 (7%)	59 (3%)	228 (5%)	494 (14%)
Aspirin				
Yes	1097 (48%)	929 (49%)	267 (6%)	555 (15%)
Statin				
Yes	905 (40%)	759 (40%)	621 (13%)	1021 (28%)
Cardiovascular disease				
Yes	324 (14%)	292 (16%)	277 (6%)	407 (11%)
Sex				
Male	1501 (66%)	1212 (64%)	2730 (58%)	1760 (49%)
Age				
Mean (SD)	66.5 (9.0)	66.5 (9.1)	63.5 (8.5)	65.3 (9.7)
Ethnicity				
Black	806 (35%)	610 (32%)	NA	NA
Deprivation quintile				
2	NA	NA	1131 (24%)	815 (23%)
3	NA	NA	1106 (23%)	808 (22%)
4	NA	NA	865 (18%)	689 (19%)
5 Least	NA	NA	626 (13%)	484 (13%)
Smoking status				
Ex	928 (41%)	762 (41%)	1558 (33%)	1320 (36%)
Yes	326 (14%)	286 (15%)	940 (20%)	644 (18%)

SPRINT, Systolic Blood Pressure Intervention Trial; THIN, The Health Improvement Network.
[a]Standard treatment of SBP less than 140 mmHg.
[b]Intensive treatment of SBP less than 120 mmHg.

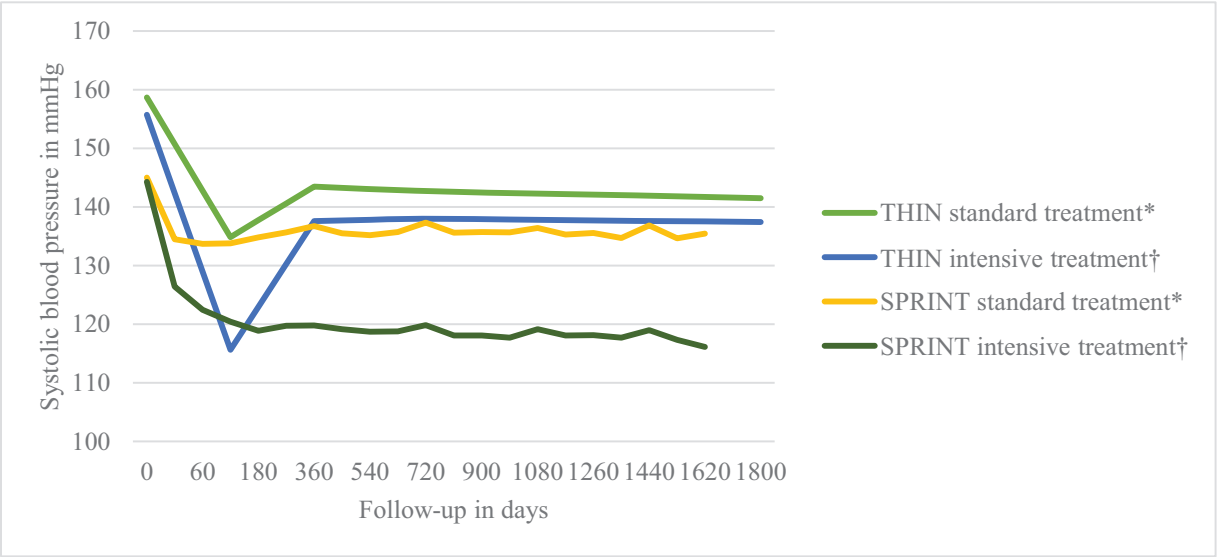

FIGURE 1 SBP during follow-up by treatment arm and cohort. *Standard treatment of SBP less than 140 mmHg. †Intensive treatment of SBP less than 120 mmHg.

were higher in SPRINT than in THIN. This could be explained by the different selection criteria, where SPRINT patients had to be at an increased risk of CVD and were therefore more likely to be prescribed-related drugs. Furthermore, in SPRINT these prevalences were balanced across treatment arms, but in THIN the prevalences in the intensive treatment arm were twice of those in the standard treatment arm. In SPRINT, there was a similar percentage of men in each treatment arm (64–66%), however in THIN, there were more men in the standard (58%) than in the intensive treatment arm (49%). The average age was 66.5 in SPRINT and 64.5 in THIN. In SPRINT, the treatment arms consisted of 32–35% black minority. Given that THIN is representative of the UK population, 93% of the cohort is expected to be white [17], and it was assumed this was balanced across treatment arms. In THIN, the treatment arms had similar distribution of deprivation (<2% difference per quintile). SPRINT and THIN had similar prevalence of nonsmokers, however, SPRINT had more ex-smokers while THIN had more current-smokers.

The THIN cohort with extended dates had a longer study period with an average follow-up of 7.8 and 7.2 years in the standard and intensive treatment arm, respectively. This resulted in a higher percentage deaths and CKD observed; the standard treatment arm had 11% deaths and 14% CKD, while the intensive treatment arm had 13% deaths and 16% CKD. The baseline characteristics of the extended THIN cohort were similar to those of the THIN cohort with the same SPRINT dates, with the exception that sex was balanced across treatment arms and the prevalences of CVD and prescribed drugs were higher in the extended cohort. This is in accordance with the literature, which showed that the incidence of CVD has fallen in the past decades [18,19] and therefore related drugs has fallen as well.

All-cause mortality

The leanest survival model of all-cause mortality included treatment arm, number of antihypertensive drugs at baseline, change in the number of antihypertensive drugs at trial entry, aspirin, statin, CVD, sex, age, ethnicity (only SPRINT), deprivation (only THIN), smoking status, and clinic, refer to Fig. 2 and Table S4, http://links.lww.com/HJH/B19. In SPRINT, compared with the standard treatment, the intensive treatment was associated with a decreased hazard of mortality of 0.63 (0.43–0.92). In THIN, the intensive treatment had a time-dependent effect, where it was associated with higher increased hazard in the first

Factor	Category	SPRINT HR (95%CI)	THIN_spr HR (95%CI)	THIN_ext HR (95%CI)
Antihypertensive	Standard			
treatment	Intensive <1 yr	0.63 (0.43–0.92)	2.40 (1.35–4.24)	1.35 (1.11–1.65)
	Intensive >=1 yr		1.51 (1.14–2.02)	1.20 (1.14–1.27)
Number of antihyp.	0/1 drug			
drugs at baseline	2+ drugs	1.35 (0.88–2.05)	1.33 (0.96–1.84)	1.19 (1.11–1.26)
Change in number of	Same/less			
antihyp. drugs at entry	More	1.54 (1.01–2.34)	1.01 (0.74–1.38)	0.93 (0.88–0.99)

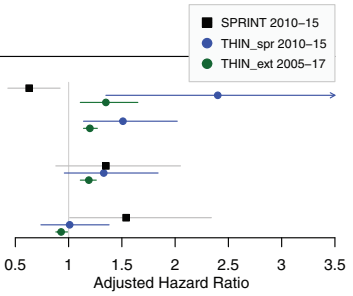

FIGURE 2 Adjusted effects of antihypertensive treatment associated with the hazard of all-cause mortality. The Health Improvement Network_spr is the Health Improvement Network cohort with the same study period as Systolic Blood Pressure Intervention Trial of 2010–15. The Health Improvement Network_ext is the Health Improvement Network cohort with extended study period of 2005–2017. Standard treatment of lowering SBP to less than 140 mmHg. Intensive treatment of lowering SBP to less than 120 mmHg. In Systolic Blood Pressure Intervention Trial, there was no time-dependent effect of antihypertensive treatment. Hazards ratios adjusted for listed factors, cardiovascular disease, aspirin, statin, sex, age, ethnicity (only Systolic Blood Pressure Intervention Trial), deprivation (only The Health Improvement Network), smoking status, and clinic.

year [SPRINT dates: 2.40 (1.35–4.24), extended dates: 1.35 (1.11–1.65)] than in subsequent years [SPRINT dates: 1.51 (1.14–2.02), extended dates: 1.20 (1.14–1.27)]. Compared with no or one antihypertensive drug prescription at baseline, two or more prescriptions was associated with an increased hazard of mortality of 1.35 (0.88–2.05) in the SPRINT cohort, 1.33 (0.96–1.84) in the THIN cohort with SPRINT dates, and 1.19 (1.11–1.26) in the THIN cohort with extended dates. Compared with the same number or fewer antihypertensive drug prescriptions at trial entry, additional prescriptions was associated with an increased hazard of mortality of 1.54 (1.01–2.34) in the SPRINT cohort. However, in the THIN cohort with SPRINT dates it was not associated with the hazard of mortality [1.01 (0.74–1.38)] and in the THIN cohort with extended dates it was associated with a decreased hazard of mortality of 0.93 (0.88–0.99). Finally, in both SPRINT and THIN, there were no interaction effects between treatment arm and the other covariates, indicating that the effect of intensive treatment associated with the hazard of mortality was the same for different groups of patients, such as for men and women. For model performance statistics, refer to Table S4, http://links.lww.com/HJH/B19.

Chronic kidney disease

The leanest survival model of CKD included treatment arm, number of antihypertensive drugs at baseline, change in the number of antihypertensive drugs at trial entry, SBP, aspirin, CVD, sex, age, ethnicity (only SPRINT), deprivation (only THIN), smoking status, and clinic, refer to Fig. 3 and Table S5, http://links.lww.com/HJH/B19. In the THIN cohort with extended dates, the hazard of CKD associated with intensive treatment depended on the number of antihypertensive drugs prescribed at baseline. The hazard of CKD increased with the number of drugs prescribed at baseline and was higher with the intensive treatment if less than two drugs were prescribed at baseline. Compared with the standard treatment and no antihypertensive drug prescription at baseline, the standard treatment with 1, 2, or 3+ prescriptions was associated with an increased hazard of CKD of 1.37 (1.27–1.49), 1.86 (1.71–2.02), or 2.51 (2.28–2.75), respectively. Compared with the standard treatment and no antihypertensive drug prescription at baseline, the intensive treatment with 0, 1, 2, or 3+ prescriptions was associated with an increased hazard of CKD of 1.15 (1.05–1.25), 1.44 (1.32–1.58), 1.77 (1.61–1.95), or 2.26 (2.04–2.50), respectively. In the THIN cohort with SPRINT dates, compared with the standard treatment with 0/1 antihypertensive drug prescription at baseline, the standard treatment with 2+ prescriptions, the intensive treatment with 0/1 prescription, or the intensive treatment with 2+ prescription was associated with an increased hazard of CKD of 1.09 (0.67–1.75), 1.35 (1.05–1.73), or 1.80 (1.28–2.53), respectively. These hazards were higher in the SPRINT cohort; with an increased hazard of CKD of 1.19 (0.57–2.46), 2.57 (1.35–4.90), or 3.38 (1.81–6.32), respectively. Additional antihypertensive drug prescription at trial entry was associated with an increased hazard of CKD, ranging from 1.13 (0.85–1.50) in the THIN cohort with SPRINT dates to 1.23 (1.16–1.30) in the THIN cohort with extended dates to 1.49 (0.94–2.34) in the SPRINT cohort. For model performance statistics, refer to Table S5, http://links.lww.com/HJH/B19.

Sensitivity analysis

The ROC curve of the predicted propensity score of receiving intensive treatment in the THIN cohorts had an AUC of 63–70%, meaning that the prediction of intensive treatment was of low accuracy. The propensity score matching reduced the THIN cohort with SPRINT dates by 14% to 7236 patients and the THIN cohort with extended dates by 28% to 39 512 patients. The final survival models of all-cause mortality and CKD fitted on the matched propensity score datasets produced very similar hazard ratios as the ones presented above and had slightly wider confidence intervals due to the reduced sample sizes, refer to Tables S4 and S5, http://links.lww.com/HJH/B19.

DISCUSSION

The current study estimated the survival and CKD prospects of intensive treatment of SBP to less than 120 mmHg versus

Factor	Category	SPRINT HR (95%CI)	THIN_spr HR (95%CI)	THIN_ext HR (95%CI)
Antihypertensive treatment	Standard 0 drug			
& number of antihyp.	Standard 1 drug			1.37 (1.27–1.49)
drugs at baseline	Standard 2 drugs	1.19 (0.57–2.46)	1.09 (0.67–1.75)	1.86 (1.71–2.02)
	Standard 3+ drugs			2.51 (2.28–2.75)
	Intensive 0 drug	2.57 (1.35–4.90)	1.35 (1.05–1.73)	1.15 (1.05–1.25)
	Intensive 1 drug			1.44 (1.32–1.58)
	Intensive 2 drugs	3.38 (1.81–6.32)	1.80 (1.28–2.53)	1.77 (1.61–1.95)
	Intensive 3+ drugs			2.26 (2.04–2.50)
Change in number of	Same/less			
antihyp. drugs at entry	More	1.49 (0.94–2.34)	1.13 (0.85–1.50)	1.23 (1.16–1.30)

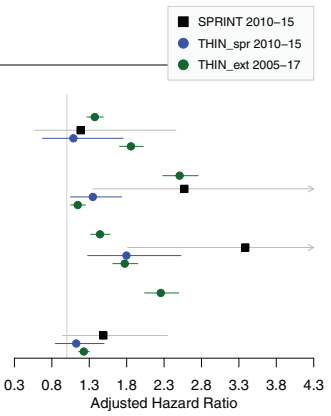

FIGURE 3 Adjusted effects of antihypertensive treatment associated with the hazard of chronic kidney disease. The Health Improvement Network_spr is the Health Improvement Network cohort with the same study period as Systolic Blood Pressure Intervention Trial of 2010–2015. The Health Improvement Network_ext is the Health Improvement Network cohort with extended study period of 2005–2017. Standard treatment of lowering SBP to less than 140 mmHg. Intensive treatment of lowering SBP to less than 120 mmHg. In Systolic Blood Pressure Intervention Trial and The Health Improvement Network_spr, the interaction of antihypertensive treatment with number of antihypertensive drugs at baseline had the levels: standard treatment with 0/1 drug (reference category), standard treatment with 2+ drugs, intensive treatment with 0/1 drug, and intensive treatment with 2+ drugs. Hazards ratios adjusted for listed factors, cardiovascular disease, aspirin, SBP, sex, age, ethnicity (only Systolic Blood Pressure Intervention Trial), deprivation (only The Health Improvement Network), smoking status, and clinic.

standard treatment to less than 140 mmHg in hypertensive patients aged 50–90 without cancer, CKD, dementia, diabetes, heart failure, or stroke using RCT data and electronic health records.

The current study found that intensive treatment was associated with survival benefits in SPRINT, but survival harms in THIN. Furthermore, there was a time-dependent effect of intensive treatment in THIN, with higher hazards in the first year than in subsequent years. This finding might be explained by the fact that after the SBP reached the target level, it levelled off to an average of 142 and 137 mmHg in the standard and intensive treatment groups, respectively. The UK clinical guideline recommends a SBP target of 140 mmHg in hypertensive patients [2], therefore there is no apparent reason to keep SBP below 120 mmHg. This study also found that intensive treatment was associated with an increased hazard of CKD. The reason for higher estimated hazards in SPRINT might be explained by the fact that in SPRINT the average SBP of the treatment groups remained at the target levels during follow-up whereas in THIN they converged after the target levels were reached. Furthermore, this study found that patients with polypharmacy tended to have worse survival and CKD prospects. In both SPRINT and THIN, treatment effects did not differ by sex or age. Finally, the models fitted on the THIN cohort with an average follow-up of 7.8 years estimated smaller hazards and performed better than the models fitted on the other cohorts with an average follow-up of 3.3 years.

SPRINT BP readings are not directly comparable with BP readings obtained in other trials and routine clinical practice, due to its unusual way of measuring BP by an automated device unattended by a healthcare professional [4]. The benefit of an unobserved automated BP measurement is that it removes the 'white-coat' effect where BP spikes in a clinical setting [20]. Removing this effect meant that BP measurements were standardized across the sites of the SPRINT study [20]. Health professionals expect that the BP readings of SPRINT are between 5 and 20 mmHg lower than the usual office BP readings [21]. In the extreme case of 20 mmHg difference, SPRINT's standard treatment target is of reducing SBP to less than 160 mmHg and its intensive treatment target to less than 140 mmHg. In this extreme case, we would expect that the intensive treatment would improve clinical outcomes. SPRINT reported that intensive treatment improved the risk of heart failure and mortality, but did not improve the risk of stroke [4], which is a peculiar finding as the risk of stroke is more responsive to BP [21]. A meta-analysis of 32 clinical trials including approximately 105 000 patients, studied the effect of reducing SBP to less than 150, 140, or 130 mmHg on the risk of stroke, coronary events, and death [22]. This meta-analysis reported improved outcomes associated with SBP reduced to less than 150 or 140 mmHg, but only improved stroke outcomes with SBP reduced to less than 130 mmHg. Another meta-analysis of 19 clinical trials including approximately 45 000 patients with a mean follow-up of 3.8 years, studied the effect of intensive lowering of SBP on the risk of cardiovascular events, renal events, and death [23]. Here, the intensive and standard treatment group had a mean SBP of 133 and 140 mmHg, respectively. This meta-analysis reported no significant difference between treatment groups with respect to the risk of heart failure, cardiovascular death, all-cause mortality, and CKD. An observational study based on US electronic health records including approximately 400 000 patients with a mean follow-up of 4.0 years, found that the hazards of mortality and chronic kidney disease associated with SBP is a U-shaped function with the lowest hazards being at a SBP of 130–139 mmHg [24], which is equivalent to our standard treatment group. In SPRINT, this U-shaped function was not possible to test due to the two-group design with widely different BP targets [25]. Finally, in the latest hypertension guideline of SIGN, reducing SBP to less than 130 mmHg is not recommended as 'this brings limited additional benefits and causes significant adverse effects' [7,22]. In the SPRINT cohort, intensive treatment was associated with a three-fold increase in chronic kidney disease. In SPRINT, patients were closely monitored and the adverse effects did not coincide with loss in follow-up. However, in routine clinical practice, the adverse effects could lead to discontinuation of the intensive treatment and thereby losing the cardiac benefit it gave in the first place [25]. The presence of adverse effects could also lead to polypharmacy and increase in healthcare utilization with unknown long-term kidney outcomes [26]. Thus, previous research supports our THIN results that on average clinical outcomes are not improved with the intensive treatment of SBP compared with the standard treatment and that the optimal SBP target seems to be less than 140 mmHg in treated hypertensive patients.

Strengths and limitations

The current study had access to SPRINT data [4] and primary care data that were representative of the United Kingdom [9,10]. This study selected THIN patients who were similar to those treated in SPRINT, where one cohort had the exact same study period and one cohort had an extended study period. This meant that the short-term and long-term survival and CKD prospects associated with intensive treatment of SBP could be estimated in patients seen in routine clinical practice in the United Kingdom and compared with the original clinical trial.

The main limitation of this study is the difficulty of directly comparing results of a clinical trial with that of an observational cohort study based on administrative data due to the different study designs [8]. With clinical trials, treatments are randomly assigned, although in SPRINT this was not blinded for the patients or professionals. In theory, randomization ensures that all factors affecting the outcome are evenly balanced across treatment arms, so that the difference in outcome between the arms is due to the effect of the treatment. With clinical studies based on administrative data, treatments are not randomly assigned and there could be selection bias where treatment groups differ in factors affecting the outcome. In our THIN cohorts, the main known difference between patients with a SBP reduced to 140 mmHg or less or to 120 mmHg or less was that a higher percentage of the latter group were treated for CVD, which included antihypertensive treatment. In our study, selection bias was minimized by regression analyses adjusting for known confounders of the effect of antihypertensive treatment associated with survival and CKD prospects, including CVD and related treatments.

Furthermore, the sensitivity analysis based on the propensity score of receiving intensive treatment suggests that the results are robust to selection bias. Even though the survival models performed well, there will be some residual confounding. In THIN, prescription changes could signify sicker patients and lower BP readings could signify unwell patients. Other differences between the SPRINT and THIN cohorts were that SPRINT patients had to be at an increased cardiac risk at baseline; BP was measured differently; and follow-up BP stayed at target levels in SPRINT but not in THIN. Finally, the statistical analyses excluded patients with missing values. The percentage of patients excluded was limited in SPRINT and would not have altered the results. In THIN, however, a larger percentage of patients were excluded due to missing smoking status, which may have resulted in selecting sicker study population [27].

Recommendations

The study's findings suggest that in a country where there is universal access to healthcare, such as the UK National Health Services, routine patients aged 50–90 years with hypertension but who are otherwise healthy with respect to cancer, CKD, dementia, diabetes, heart failure, or stroke, do not benefit from intensive treatment of SBP. In fact, lowering the SBP too far down, such as less than 120 mmHg, could increase the hazard of CKD and mortality. However, if patients are closely monitored as with SPRINT, hypertensive patients who are at high cardiac risk might benefit from intensive antihypertensive treatment.

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Data sharing statement: For all interested researchers, THIN data are available via QuintilesIMS, subject to ethical approval of the THIN Scientific Review Committee and governance controls. SPRINT data are available in the NHLBI data repository, Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC, https://biolincc.nhlbi.nih.gov/studies/sprint_pop/) for further secondary analyses by the scientific community.

Conflicts of interest

There are no conflicts of Interest.

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