Use of a Statistical Adaptive Treatment Strategy Approach for Emulating Randomized Controlled Trials Using Observational Data: The Example of Blood Pressure Control Strategies for the Prevention of Cardiovascular Events Among Individuals with Hypertension at High Cardiovascular Risk

Short Title: Adaptive Treatment Strategies for Trial Emulation

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ABSTRACT

Statistical approaches to adaptive treatment strategies (ATS) can be used to mimic the sequential decision-making inherently found in clinical practice. To illustrate the use of a statistical ATS approach, we emulated a target trial of different blood pressure (BP) control plans for the prevention of cardiovascular events among individuals with hypertension at high cardiovascular risk inspired by the Systolic Blood Pressure Intervention Trial (SPRINT). We included 103,708 patients with hypertension and an QRISK3 estimated 10-year risk of cardiovascular disease ≥20% who initiated an antihypertensive drug between 1998 and 2018. Dynamic marginal structural models estimated the comparative effects of treating patients with intensive (target BP: 130/80 mmHg), standard (140/90 mmHg), and conservative (150/90 mmHg) BP control strategies. The adjusted hazard ratios (95% confidence intervals) for the intensive versus standard strategy were 0.96 (0.92, 1.00) for major adverse cardiovascular events and 0.93 (0.88, 0.97) for death from cardiovascular causes. For the conservative versus standard strategy, they were 1.06 (1.02, 1.10) and 1.08 (1.03, 1.13), respectively. These results are largely compatible with SPRINT. ATS can be used to emulate randomized controlled trials (RCTs) of complex treatment strategies in an observational setting and represents an alternative approach for situations where RCTs are not feasible.

INTRODUCTION

Precision medicine embraces the concept of prescribing the right therapy to the right patient at the right time[1]. It typically relies on an adaptive treatment strategy (ATS) that tailors sequential treatment decisions according to patients' characteristics, disease history, and response to treatment[2]. While a sequential, multiple assignment, randomized controlled trial (RCT) is the gold standard to assess sequential decision-making, such trials are often cost-prohibitive given their sophisticated design, required long follow-up duration, large number of candidate treatment strategies, and large required sample size. Benefiting from innovations in data collection, the availability of detailed clinical information in electronic health records, and the development of novel statistical methods, this trial can be emulated using observational data[3]. Several studies[4-7] have demonstrated that explicitly emulated trials using observational data align more closely with the results from well-conducted RCTs. However, few examples are available regarding the use of ATS to emulate RCTs of sequential decision-making using observational data.

Cardiovascular disease (CVD) prevention among patients with hypertension represents a commonly occurring clinical situation that involves sequential decision-making given the ease of blood pressure (BP) measurement, disease progression, the availability of several antihypertensive drugs, and the potential for the most appropriate BP targets to vary with patient characteristics. However, the most appropriate BP target for patients with hypertension remains uncertain. Indeed, while the American Heart Association guidelines[8] recommend an aggressive treatment approach (systolic blood pressure [SBP]/diastolic blood pressure [DBP]) $\leq$ 130/80 mmHg), other guidelines[9-12] including those issued by the European Society of Cardiology and the European Society of Hypertension recommend this BP target only for patients with hypertension and previously-diagnosed CVD or at high CVD risk. Importantly, the rationale for intensive BP

lowering is largely based on the results of the Systolic Blood Pressure Intervention Trial (SPRINT)[13], which randomized 9,361 patients with hypertension at high CVD risk to an SBP target of <120 mmHg or <140 mmHg. To illustrate the use of a statistical approach to ATS, we emulated a target trial inspired by SPRINT using observational data. Specifically, we investigated whether following an intensive BP control strategy (≤ 130/80 mmHg) or a conservative BP control strategy (≤ 150/90 mmHg) is associated with a greater reduction in the rate of major adverse cardiovascular event (MACE) compared with following a standard treatment strategy (≤ 140/90 mmHg) among patients with hypertension at high CVD risk.

METHODS

We constructed a hypothetical RCT to compare three BP control strategies and then emulated it in an observational setting. The protocol for this target trial is compared to that of SPRINT[13] in **Table 1**.

Protocol of the Target Trial

Eligibility Criteria

Adult patients diagnosed with hypertension who did not receive a prescription for an antihypertensive medication for ≥ 1 year prior to diagnosis were included. Inclusion was restricted to patients at high CVD risk, defined by a 10-year risk of CVD ≥ 20% using the QRISK3 score[14]. Patients with a previous history of a CVD event, severe proteinuria, end stage renal disease, polycystic kidney disease, dementia, organ transplant, or cancer were excluded. Women with a pregnancy in the past year were also excluded.

Treatment Strategies

Eligible patients were randomly and evenly assigned to one of three BP control strategies: intensive (target BP ≤ 130/80 mmHg), standard (≤ 140/90 mmHg), or conservative (≤ 150/90 mmHg) BP control strategy. After randomization, the treating physician determined whether the target BP had been met at each quarterly visit, and adjusted medications if the target had not been met. Specifically, if the measured BP was higher than the target BP, the physician added or switched to a medication from an antihypertensive drug class that had not been prescribed previously. Use of any of following classes was permitted: thiazide diuretics, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), calcium channel blockers (CCB), beta blockers, loop diuretics, potassium-sparing diuretics, alpha blockers, central acting drugs, direct vasodilators, and renin inhibitors.

Outcomes

The primary outcome was time to MACE, defined as a composite endpoint of nonfatal myocardial infarction (MI), nonfatal stroke, and cardiovascular death. Secondary outcomes were an expanded macrovascular event (defined as a composite endpoint of MACE, revascularization, and hospitalization due to heart failure), the occurrence of MI, stroke, cardiovascular death, death from any cause, and hospitalization for heart failure as individual events, and the occurrence of adverse events related to antihypertensive medications (hypotension, syncope, bradycardia, electrolyte abnormal, injury falls, and acute kidney disease).

Follow-up

Follow-up occurred every 3 months. At each visit, patients' demographic characteristics, lifestyle variables (smoking, body mass index (BMI)), history of comorbidities, laboratory test results, SBP, DBP, and medication use were recorded. Patients were followed from baseline (randomization) until the occurrence of outcome or loss to follow-up (failure to show up for two consecutive visits)., or the end of study period (June 30th, 2019), whichever occurred first.

Causal Contrasts of Interest

To compare the per-protocol effect of these treatment strategies, we estimated the rate of CVD and safety outcomes among patients from baseline to failure to follow their assigned BP control strategy during follow-up of the target trial.

Statistical Analysis

To estimate the HR for MACE comparing the intensive and conservative strategies versus the standard strategy in this per-protocol analysis, we fitted a weighted dynamic marginal structural model[15-19]:

$$\text{logit}\ \Pr(Y_{t+1}^{\Theta} = 1 | \bar{Y}_t = 0, \bar{A}_{t+1} = 1, \bar{C}_t = 0, V, \theta) = \beta_0 + \beta_1 V + \beta_2 \Theta,$$

where =1, =0 indicate that, at time *t*, patients were following their assigned treatment strategy and were uncensored due to loss to follow-up or administrative end of study, respectively (1: Yes, 0: No). indicates that the patient had been following their assigned treatment strategy from baseline until time *t*, and indicates the patient remained uncensored between baseline and time *t*. is a vector of covariates indicating the 3 treatment strategies in the study. indicates that prior to the time t, patients have not experienced the outcome. *V* is a vector of covariates that were measured at baseline, which included demographic characteristics (sex, race, age, Index of Multiple Deprivation), lifestyle variables (smoking, BMI), history of comorbidities (erectile dysfunction, migraine, rheumatoid arthritis, severe mental illness), SBP, DBP, laboratory test results (estimated glomerular filtration rate), health resource utilization (number of general physician visits and number of hospitalizations in the previous year), and medication use (antidiabetic drugs, antihyperlipidemic drugs, anticoagulants).

Time-varying covariates were measured at each visit. In addition to covariates from *V*, we also measured additional lifestyle variables (alcohol use, family history of CVD), comorbidities (atrial fibrillation, human immunodeficiency virus, type 1 diabetes, type 2 diabetes, chronic kidney disease, systemic lupus erythematosus), BP information (relative change of SBP and DBP compared to the measurement at the previous visit), medication use (antipsychotics, aspirin, corticosteroids), and follow-up time (fitted with a restricted cubic spline with 5 knots).

We used inverse-probability treatment weighting (IPTW)[20] to adjust for potential time-varying selection bias induced by failure to follow the assigned treatment strategy in the per-protocol analysis. Stabilized IPTW was applied to enhance efficiency[3]. For each patient at time *t*, IPTW was estimated as =, . The denominator estimates the probability of patient remaining on the assigned treatment strategy at time *t*, conditioned on the patient having followed the treatment

strategy until *t-1* (and time-varying covariates until *t* (). Similarly, the numerator conditions on the treatment strategy until *t-1* (and time-independent covariates (*V*). We used inverse-probability of censoring weighting (IPCW) to adjust for selection bias due to loss to follow-up[21] or administrative censoring (June 30th, 2019). For each patient at time *t*, IPCW was defined as=. The denominator estimates the probability of the patient remaining uncensored at time *t*, conditioned on having followed the assigned treatment strategy until *t-1* (, remaining uncensored until *t-1* (, and time-varying covariates from baseline until *t* (). The denominators of both IPCW and IPTW were estimated using pooled multinomial logistic regression, numerators were estimated non-parametrically using the proportion of patients following the aforementioned treatment strategy at time *t*. The product of IPTW and IPCW was used as a weight at all visits in the model.

To better visualize results, we generated standardized cumulative hazards curves, which indicated the results that would have been observed if all patients had been counterfactually assigned to each treatment strategy and had followed it since baseline.

Emulating the Target Trial Using Observational Data

Data Source

To emulate the target trial, we used data from the Clinical Practice Research Datalink (CPRD) Gold. This data source has been described in detail elsewhere[22]. Briefly, the CPRD is a population-based clinical database that contains detailed electronic clinical records for >16 million patients seen at >700 general practitioner practices in the UK. The CPRD covers 1988 to present and contains demographic characteristics, medical diagnoses (based on Read Codes)[22,23], and prescription data (based on the British National Formulary), as well as laboratory test values and clinical measure that are not typically available in administrative databases. CPRD data are well

recorded[22,24]. CPRD data were linked to Hospital Episode Statistics (HES) data[25], which contain full hospitalization records (with ICD-10 diagnostic codes and OPCS-4 procedure codes), and to Office for National Statistics (ONS) vital statistics data, which contain the date and cause of death (defined using ICD-9 codes pre-2001 and ICD-10 codes thereafter)[22]. Linkage between the CPRD and these data sources has been well validated[26,27]. The protocol of this study received scientific and ethical approval from the Independent Scientific Advisory Committee in the CPRD (18_222RA) and Research Ethics Board in the Jewish General Hospital in Montreal, Canada.

Eligibility Criteria

We first created a base-cohort of patients with incident hypertension. Base-cohort entry date was defined by the date of a Read code indicating a diagnosis of hypertension or the date of an elevated BP reading (SBP ≥ 140 mmHg or DBP ≥ 90mmHg). We then identified all treatment-naïve patients (no prescription for an antihypertensive drug in the previous year) who received a new prescription for an antihypertensive drug between April 1, 1998 and June 30, 2018. The date of this prescription defined the study-cohort entry date. The study-cohort entry date may have occurred on or after the base-cohort entry date. All 11 previously mentioned antihypertensive drug classes were considered. We applied the same exclusion criteria as described for the target trial (**Table 1)**.

Treatment Strategies

We compared intensive (≤ 130/80 mmHg), standard (≤ 140/90 mmHg), and conservative (≤ 150/90 mmHg) strategies. To determine whether a patient followed a treatment strategy, we used SBP and DBP measured at their current visit, as well as antihypertensive drugs prescribed at their previous and current visits. A 30-day treatment gap was permitted between prescriptions for the same class. A patient was defined as following the strategy whenever: 1) the observed BP was

lower than target BP, or 2) the observed BP was higher than the target and the physician adjusted the antihypertensive drugs at the following visits until the BP was lower than the target level again. The definition of adjustment included the addition of antihypertensive drugs from classes not previously prescribed or switching treatment classes; **Figure 1** describes this process visually. Dosage changes were not considered.

Outcomes

The primary and secondary outcomes assessed in the hypothetical trial were the same as those in the target trial. Events were defined by the presence of relevant ICD-10 codes (listed in **Appendix A**) in HES (in the primary or secondary position) or ONS. The date of admission (for HES-defined events) or date of death (for ONS-defined events) defined the event date.

Follow-up

In the hypothetical trial, we mimicked the follow-up of the target trial by reformatting patient records to approximate quarterly visits. From the study cohort entry date, we built a hypothetical prescheduled routine clinic visit every 91 days. If a patient did not have a visit at the prescheduled date, we used the most recent visit that occurred within 90 days before the prescheduled date to capture time-varying covariates. We imputed time-varying covariates if there was no visit within the required time period. As in the target trial, patients were followed from their study-cohort entry date until the occurrence of outcome, loss to follow-up (defined by no recorded general practitioner visits, hospitalizations, or prescriptions in the 6 months after the last visit), or the end of study period, whichever occurred first.

Causal Contrasts of Interest

We compared the per-protocol effect of treating patients using intensive, standard, and conservative treatment strategies on the time to MACE among patients between study-cohort entry and deviation from their assigned strategy during follow-up in the reformatted cohort. A similar approach was used for each of the secondary outcomes.

Statistical Analysis

After reformatting the cohort, we imputed missing values. Given the small variation over time, we used a last-observation-carried-forward approach for most time-varying covariates. However, for missing values of SBP, DBP, smoking, and body weight, we imputed 10 datasets using multiple imputation with the fully conditional specification approach[28]. In the imputation model, we included demographic characteristics, history of comorbidities, and non-antihypertensive drug use at the current visit and values that were measured at the previous visit for these four variables. To reflect the inconsistent trajectory of these covariates after 10 years of follow-up, we used three models to impute missing values that occurred at baseline, from baseline to 10 years of follow-up, and thereafter, respectively.

To mimic the target trial, we fitted the previously described pooled logistic model to the observational data using an augmented dataset.[4,15,18] This dataset included three replicates of each patient and assigned them to follow three treatment strategies. We censored patients when they deviated from their assigned treatment strategy, were lost-to-follow-up, or reached the end of the study period. For tutorial purpose, we included a mockup dataset and relevant code (**Appendix G**).

The trial emulation involved three key assumptions: 1) no unmeasured confounding given variables used in the IPTW and IPCW models; 2) correctly specified models for the estimation of these weights; and 3) positivity. When these assumptions are satisfied, the outcomes of the

replicates in the augmented dataset represent the counterfactual result that we would have observed if we had randomly assigned three identical patients to follow each of the individual treatment strategies () in the target trial (. Data management and descriptive analyses were performed using SAS 9.4 (SAS Institute Inc.) and R 3.6.1 (https://cran.r-project.org).

We conducted three sensitivity analyses to examine the robustness of the results. First, we examined potential residual confounding by additionally adjusting for the Framingham risk score in the outcomes model. Second, we investigated potential outcome misclassification by restricting HES-defined events diagnostic or procedure codes in the primary position. Third, we examined the potential residual confounding due to changes in treatment guidelines by stratifying the calendar year of treatment initiation. We reported the antihypertensive medication prescribed among patients (with IPTW and IPCW) who followed the assigned treatment strategy at 1, 3 and 5 years of follow-up to demonstrate the variation of use of individual antihypertensive drugs across treatment groups.

RESULTS

The hypothetical trial included 103,708 patients (**Figure 2**). Their mean age was 75.1 years (standard deviation [SD]: 7.9), and 45.6% were male (**Table 2**). At baseline, the mean SBP and DBP were 172.0 mmHg (SD: 22.4) and 91.2 mmHg (SD: 13.0), respectively. Follow-up duration ranged from 1 day to 20 years. Replicates followed the intensive, standard, and conservative strategies for mean durations of 0.9, 1.5, and 2.6 years (SD: 1.4, 1.9, and 2.9), respectively (**Appendix B**).

All treatment strategies resulted in an initial rapid decrease in BP followed by a relatively slow decrease thereafter (**Appendix C**). The mean SBP for replicates in the intensive strategy group reached the target SBP after 2 years, while it took replicates who followed the standard or conservative strategies 9 months.

During the first 5 years of follow-up, there were 1,860 (incidence rate: 2.0/100 person-years), 2,550 (1.8/100 person-years), and 3,577 (1.7/100 person-years) events in the intensive, standard, and conservative strategy groups, respectively (**Table 3**). The incidence rates increased to 5.4, 5.8, and 6.1 per 100 person-years, respectively, after inverse probability weighting.

Figure 3 shows the standardized cumulative hazards during the first 5 years of follow-up. Compared to replicates in the standard strategy group, replicates in the intensive strategy group had a cumulative incidence ratio of 0.95 (95% CI, 0.91 to 0.99) and a cumulative incidence difference of -0.86/100 person-years (95% CI, -1.48 to -0.24/100 person-years) for MACE at 5 years. Replicates in conservative strategy group had a cumulative incidence ratio of 1.05 (95% CI, 1.01 to 1.09) and a cumulative incidence difference of 0.93/100 person-years (95% CI, 0.27 to 1.59/100 person-years) compared to replicates in the standard strategy group.

Compared to those who followed the standard strategy, replicates who followed the intensive strategy were less likely to develop the primary and secondary effectiveness outcomes (**Figure 4**), including MACE (HR, 0.96; 95% CI, 0.92 to 1.00), death from cardiovascular causes (HR, 0.93; 95% CI, 0.88 to 0.97), and death from any cause (HR, 0.96; 95% CI, 0.95 to 0.98). In contrast, replicates in the conservative strategy group were more likely to develop MACE (HR, 1.06; 95% CI, 1.02 to 1.10), death from cardiovascular causes (HR, 1.08; 95% CI, 1.03 to 1.13), and death from any cause (HR, 1.06; 95% CI, 1.04 to 1.09) compared to those who followed the standard strategy. Consistent results were obtained in sensitivity analyses (**Appendix D, E**). The use of antihypertensive drugs was consistent among treatment groups at 1, 3, and 5 years of follow-up (**Appendix F**).

At the end of the 5th year of follow-up, 3,204 (3.5/100 person-years), 4,609 (3.4/100 person-years), and 6,693 (3.1/100 person-years) serious adverse events occurred in the intensive, standard, and conservative strategy groups, respectively, with more than half caused by injury/falls or emergency room (ER) visits/hospitalizations related to electrolyte abnormalities. Incidence rates for most adverse events increased after adjustment for time-varying confounders and replicates lost-to-follow-up (**Table 4**). The adjusted incidence rates for serious adverse events were similar between replicates in intensive and standard strategy groups (4.8 vs 4.8/100 person-years; HR, 1.00; 95% CI, 0.96 to 1.04). Compared to replicates in the standard strategy group, those in the intensive strategy group were more likely to have ER visit/hospitalization related to bradycardia, injury/falls, and acute kidney disease. The adjusted incidence rate for serious adverse events was higher among replicates in the conservative strategy group (5.0 vs 4.8/100 person-years; HR, 1.07; 95% CI, 1.03 to 1.12) compared to replicates in the standard strategy group (**Figure 5**). The

incidence rates for all components of the serious adverse event composite outcome except syncope were higher in the conservative treatment group.

DISCUSSION

In this study, we demonstrate how a target trial that compares the per-protocol effect of adaptive BP control strategies for the primary prevention of CVD among patients with hypertension at high CVD risk can be emulated using observational data. This demonstration includes describing the target trial and the process used to emulate it using a statistical approach to ATS and observational data, including reformatting data to create replicates with fixed-interval clinic visits, missing value imputation, and models to adjust selection bias. Our results suggest that there is a benefit of treating patients with hypertension at high CVD risk with an intensive treatment strategy (target SBP/DBP ≤ 130/80 mmHg), with lower rates of MACE, death from any cardiovascular causes, and death from any cause relative to following a standard strategy. Compared to a standard strategy, the utilization of intensive strategy would prevent 25,879 MACE per year in the UK, assuming that 25% of the 12.5 million patients with hypertension were at high CVD risk[29]. Moreover, the risk of serious adverse event among patients who followed these two strategies was comparable. In contrast, the use of conservative treatment strategy increased the risk of cardiovascular and safety outcomes compared to a standard strategy.

We emulated a target trial inspired by SPRINT[13]. With their overlapping 95% CIs, our findings are compatible with those from SPRINT[13]. The incidence rates for MACE (2.0 and 1.8/100 person-years) among patients in the intensive and standard strategy, respectively, were similar to those in SPRINT (2.2 and 1.7/100 person-years, respectively). In addition, as in SPRINT, we found that, compared to using a standard BP control strategy, an intensive BP control strategy reduced the rates of MACE (HR, 0.96; 95% CI, 0.92 to 1.00), death from cardiovascular causes (HR, 0.93; 95% CI, 0.88 to 0.97), and death from any cause (HR, 0.96; 95% CI, 0.95 to 0.98). However, the benefits observed in our study were attenuated relative to those in SPRINT (**Figure**

6). These differences may be explained by differences in eligibility criteria, patient population, exposure, and the estimated causal contrast of interest. Unlike SPRINT, which enrolled patients with stable hypertension, our study included patients who were antihypertensive-treatment naïve. Thus, at baseline, patients in our cohort had a higher mean SBP and were less likely to have previously received prescriptions of antihypertensive drugs, statins, and aspirin. This difference may partially explain why it took longer for patients to reach the intensive BP target in our study, increasing the probability of patients being classified as not following the intensive strategy. Unlike SPRINT, we also included patients diagnosed with type 2 diabetes at baseline. Moreover, differences were present in the race/ethnicity of the study population; SPRINT included a racially diverse population while ours was predominantly White. Furthermore, the intensive BP treatment strategy differed slightly: SPRINT used 120/90 mmHg, and we used 130/80 mmHg. We applied this alternative definition given that treatment-naïve patients tend to be treated with a higher target BP in clinical practice. Importantly, we included patients over a 20-year study period, during which several changes in the UK guidelines occurred[30]. Yet, compared with a standard treatment strategy, the protective effect of following an intensive treatment strategy was consistent across the study period (**Appendix E**). Although some antihypertensive medications prevent the MACE directly, yet it would have minimum impact on the above results due to our unique design and the minor difference in drug use at years 1, 3, and 5 among the three groups (**Appendix F**). Finally, the causal parameter estimated in SPRINT was an intention-to-treat effect rather than per-protocol effect. This parameter reflects our interests of identifying the effect of continuously following these treatment strategies to treat patients with hypertension.

Using a statistical approach to emulate an RCT using observational data represents an important alternative to addressing the causal question of interest when the target trial is infeasible,

unethical, untimely, or cost prohibitive[3]. Compared to static interventions (including both interventions administered once such as surgery and those that are sustained over time), ATS evolve over time and thus require RCTs with larger sample sizes and longer durations of follow-up. Target trial emulation using observational data overcomes these limitations by leveraging the detailed information available in large, population-based data sources and recent advances in statistical approaches and computational power. Moreover, it helps researchers identify the most relevant treatment strategies to assess in subsequent trials. This approach also allows the adjustment for time-varying confounding and potential selection bias[15,18], increasing study validity. Another statistical approach, targeted maximum likelihood estimation[31,32], is also applicable.

This study has several strengths. Access to a longitudinal, population-based database with prescription data available for many patients allowed for the estimation of the per-protocol effect of 3 ATS among patients with hypertension at high CVD risk. Although the attrition rate was relatively high, our cohort included more patients after 3 years of follow-up than were included in SPRINT, and we applied rigorous models to adjust for selection bias due to informative censoring. We truncated the estimated weights at the 1st and 99th percentiles of the distribution to reduce potential bias due to model misspecification[4,20]. Finally, we developed a comprehensive protocol that mapped our target trial to SPRINT to help shape the research question.

Our study has potential limitations. First, the missing data may follow a pattern conditional on unobserved variables. If data were not missing at random, imputation could result in bias, which might impact three groups evenly. Second, we relied on the assumption of no unmeasured confounding. Although we used rigorous statistical approaches to reduce residual confounding and the CPRD contains detailed clinical data, we cannot rule this out. The existence of unmeasured confounders could attenuate the observed effect of the intensive BP strategy. The variation of drug

use across the three treatment strategies was modest at 1, 3, and 5 years of follow-up, suggesting that it is an unlikely explanation for our observed associations. Third, the CPRD records BP measured and prescriptions written by general practitioners, but not by specialists. Some exposure misclassification is thus possible, which leads to early censoring and underestimates the effect of intensive BP strategy. Fourth, in clinical practice, physicians may titrate doses rather than changing antihypertensive drugs or adding an additional hypertensive drug when BP is not well controlled. Due to the limited information available regarding dose titration, we did not include it as part of our definition of a treatment change. This may have resulted in some patients being censored earlier because of a deviation from the assigned treatment strategy. This issue may have affected the intensive treatment strategy more than the other treatment strategies given its lower target BP, and the protective effect for the intensive BP control strategy could be slightly overestimated. Fifth, the effectiveness of the intensive target BP was demonstrated in the intention-to-treat analysis, which could be different in a per-protocol analysis due to high rates of non-adherence. Fortunately, the rate of non-adherence to the assigned treatment strategy in our study was less than 10% higher than the related one in SPRINT. Sixth, we estimated HR, which has two main limitations: changing over time, and including built-in selection bias. However, to facilitate the understanding and comparison with the results in the SPRINT trial, together with the results of cumulative incidence ratio and cumulative incidence different reported in the paper, we believe that using the OR to estimate the HR is the best and most practical approach. Finally, outcome misclassification is also possible, particularly for the occurrence of serious adverse events. Routinely collected data tend to be less sensitive than events recorded in a trial setting, where patients are more closely followed and events are often adjudicated by an endpoint evaluation committee. These differences could

explain, in part, the attenuated incidence rate for serious adverse events reported in our study relative to that reported in SPRINT.

In conclusion, we emulated a target trial examining adaptive BP control strategies for CVD prevention among patients with hypertension at high CVD risk using observational data. We found that treating patients with hypertension at high CVD risk with an intensive treatment strategy results in lower rates of MACE, death from any cardiovascular causes, and death from any cause relative to a standard strategy. These results are compatible with those of SPRINT, the RCT that inspired our target trial. This study demonstrates the potential use of statistical approaches to examining ATS using observational data in situations where conducting an RCT is infeasible or impractical. The use of such approaches may also be considered when awaiting the results of ongoing trials.

DISCLOSURES

Dr. Platt has received personal fees from Amgen, Analysis Group, Biogen, Merck, Nant Pharma, Pfizer, and Reckitt Benckiser, all outside of the submitted work. The other authors have no potential conflicts to disclose.

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AUTHOR CONTRIBUTIONS

Dr. Jiao conceived of the study idea. Drs. Jiao, Platt, Douros, and Filion contributed to the study design. Dr. Jiao conducted the statistical analysis and drafted the manuscript. All authors were involved in the interpretation of data and critically reviewed the manuscript for important intellectual content. Dr. Filion is the guarantor of this work.

REFERENCES

1. National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. Washington (DC): National Academies Press (US); 2011.
2. Kosorok MR, Moodie EE. Adaptive Treatment Strategies in Practice: Planning Trials and Analyzing Data for Personalized Medicine: Society for Indusrial and Applied Mathematics, 2016.
3. Hernan MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol 2016;183(8):758-64. DOI: 10.1093/aje/kwv254.
4. Cain LE, Saag MS, Petersen M, et al. Using observational data to emulate a randomized trial of dynamic treatment-switching strategies: an application to antiretroviral therapy. Int J Epidemiol 2016;45(6):2038-2049. DOI: 10.1093/ije/dyv295.
5. Garcia-Albeniz X, Hsu J, Hernan MA. The value of explicitly emulating a target trial when using real world evidence: an application to colorectal cancer screening. Eur J Epidemiol 2017;32(6):495-500. DOI: 10.1007/s10654-017-0287-2.
6. Hernan MA, Alonso A, Logan R, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology 2008;19(6):766-79. DOI: 10.1097/EDE.0b013e3181875e61.
7. Neugebauer R, Fireman B, Roy JA, O'Connor PJ, Selby JV. Dynamic marginal structural modeling to evaluate the comparative effectiveness of more or less aggressive treatment intensification strategies in adults with type 2 diabetes. Pharmacoepidemiol Drug Saf 2012;21 Suppl 2:99-113. DOI: 10.1002/pds.3253.
8. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2017;71(6):e13-e115. DOI: 10.1161/HYP.0000000000000065.
9. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;34(28):2159-219. DOI: 10.1093/eurheartj/eht151.
10. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129(25 Suppl 2):S49-73. DOI: 10.1161/01.cir.0000437741.48606.98.
11. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311(5):507-20. DOI: 10.1001/jama.2013.284427.
12. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens (Greenwich) 2014;16(1):14-26. DOI: 10.1111/jch.12237.

13. Sprint Research Group, Wright JT, Jr., Williamson JD, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015;373(22):2103-16. DOI: 10.1056/NEJMoa1511939.
14. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017;357:j2099. DOI: 10.1136/bmj.j2099.
15. Jiao T. Investigation of the Optimal Timing of Treatment Change to Maximize the Delay of Onset Mucoid Pseudomonas Aeruginosa Pulmonary Infection in Pediatric Cystic Fibrosis Patients. Pharmacotherapy. University of Utah: University of Utah; 2019.
16. Orellana L, Rotnitzky A, Robins JM. Dynamic regime marginal structural mean models for estimation of optimal dynamic treatment regimes, Part II: proofs of results. Int J Biostat 2010;6(2):Article 9. DOI: 10.2202/1557-4679.1242.
17. Orellana L, Rotnitzky A, Robins JM. Dynamic regime marginal structural mean models for estimation of optimal dynamic treatment regimes, Part I: main content. Int J Biostat 2010;6(2):Article 8. (https://www.ncbi.nlm.nih.gov/pubmed/21969994).
18. Shortreed SM, Moodie EE. Estimating the optimal dynamic antipsychotic treatment regime: Evidence from the sequential multiple assignment randomized CATIE Schizophrenia Study. J R Stat Soc Ser C Appl Stat 2012;61(4):577-599. DOI: 10.1111/j.1467-9876.2012.01041.x.
19. van der Laan MJ, Petersen ML. Causal effect models for realistic individualized treatment and intention to treat rules. Int J Biostat 2007;3(1):Article 3. DOI: 10.2202/1557-4679.1022.
20. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008;168(6):656-64. DOI: 10.1093/aje/kwn164.
21. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med 2012;367(14):1355-60. DOI: 10.1056/NEJMsr1203730.
22. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44(3):827-36. DOI: 10.1093/ije/dyv098.
23. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol 2010;69(1):4-14. DOI: 10.1111/j.1365-2125.2009.03537.x.
24. Sarrazin MS, Rosenthal GE. Finding pure and simple truths with administrative data. JAMA 2012;307(13):1433-5. DOI: 10.1001/jama.2012.404.
25. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). Int J Epidemiol 2017;46(4):1093-1093i. DOI: 10.1093/ije/dyx015.
26. Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ 2013;346:f2350. DOI: 10.1136/bmj.f2350.
27. Gallagher AM, Puri S, Van Staa TP. Linkage of the General Practice Research Database (GPRD) with other data sources. Pharmacoepidemiology and Drug Safety 2011;20:S230-S1.
28. Lee KJ, Carlin JB. Multiple imputation for missing data: fully conditional specification versus multivariate normal imputation. Am J Epidemiol 2010;171(5):624-32. DOI: 10.1093/aje/kwp425.

29. Public Health England. Hypertension prevalence estimates in England, 2017. Public Health England: 2020. (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/873605/Summary_of_hypertension_prevalence_estimates_in_England__1_.pdf).
30. Jiao T, Platt RW, Douros A, Filion KB. Prescription Patterns for the Use of Antihypertensive Drugs for Primary Prevention Among Patients With Hypertension in the United Kingdom. Am J Hypertens 2022;35(1):42-53. DOI: 10.1093/ajh/hpab137.
31. van der Laan MJ, Rose S. Targeted Learning in Data Science : Causal Inference for Complex Longitudinal Studies. Springer Series in Statistics,. 1st ed. Cham: Springer International Publishing : Imprint: Springer,; 2018:1 online resource (XLII, 640 pages 37 illustrations).
32. Chaffee PH, van der Laan MJ. Targeted Maximum Likelihood Estimation for Dynamic Treatment Regimes in Sequentially Randomized Controlled Trials. International Journal of Biostatistics 2012;8(1) (In English). DOI: Artn 1410.1515/1557-4679.1406.

Table 1. A comparison of the protocols of SPRINT[13] and a target trial examining blood pressure control plans.

Protocol Component	SPRINT	Target trial
Eligibility criteria		
Included	≥ 50 years old	≥ 18 years old
	SBP: 130-180 mmHg (the upper bound varied according to the number of antihypertensive medications a patient received)	Patients who were treatment naïve for ≥ 1 year
	Increased CVD risk (subclinical cardiovascular disease other than stroke; chronic kidney disease; 10-year risk of cardiovascular disease ≥ 15% on the basis of the Framingham risk score; ≥ 75 years old)	High CVD risk (10-year risk of cardiovascular disease ≥ 20% on the basis of the QRISK3 score)
Excluded	Proteinuria in the past 6 months	Proteinuria in the past 6 months
	Diabetes	NA
	History of stroke	History of stroke
	History of polycystic kidney disease	History of polycystic kidney disease
	History of end stage renal disease	History of end stage renal disease
	Cardiovascular event or procedure (MI, PCI, CABG, CE, carotid stenting, or PAD with revascularization) or hospitalization for unstable angina within last 3 months hospitalization for unstable angina within last 3 months	Cardiovascular event or procedure (MI, revascularization for CHF) or hospitalization for angina
	Symptomatic heart failure within the past 6 months or left ventricular ejection fraction (by any method) < 35%	Hospitalization for congestive heart failure
	A cancer diagnosed and treated within the past two years other than non-melanoma skin cancer, early-stage prostate cancer, localized breast cancer	A cancer diagnosed and treated within the past two years other than non-melanoma skin cancer, early-stage prostate cancer, localized breast cancer

	Any factors judged by the clinic team to be likely to limit adherence to interventions (residence in a nursing home, dementia etc.)	Diagnosis of dementia
	Any organ transplant	Any organ transplant
	Pregnancy, currently trying to become pregnant, or of child-bearing potential and not using birth control	Recorded pregnancy
Treatment strategies	Standard treatment strategy: SBP target ≤ 140 mmHg & DBP target ≤ 100 mmHg	Standard treatment strategy: SBP target ≤ 140 mmHg & DBP target ≤ 90 mmHg
	Intensive treatment strategy: SBP target ≤ 120 mmHg & DBP target ≤ 100 mmHg	Intensive treatment strategy: SBP target ≤ 130 mmHg & DBP target ≤ 80 mmHg
	NA	Conservative treatment strategy: SBP target ≤ 150 mmHg & DBP target ≤ 90 mmHg
Assignment procedures	Randomization was randomly stratified according to clinical site.	Patients were randomly and evenly assigned to each strategy at baseline statistically.
Follow-up period	Patients were seen monthly for the first 3 months and every 3 months thereafter. They were followed until the occurrence of outcome, or end of study (maximum 6 years since baseline), whichever occurred first.	Patients were seen every 3 months. They were followed until the occurrence of outcome, or administrative end of study (June 2019), whichever occurred first.
Outcome		
Primary outcome	Major CVD events, defined as the composite endpoint of the first occurrence of a MI, non-MI ACS, stroke, HF, or death attributable to CVD.	Major CVD events, defined as the composite endpoint of the first occurrence of a MI, stroke, or death attributable to CVD.
Secondary outcomes	MI, ACS, stroke, CHF, death from cardiovascular causes, death from any causes, primary outcome or death	MI, stroke, hospitalization or death due to CHF, death from cardiovascular causes, death from any causes
	Serious adverse events (includes hypotension, syncope, electrolyte abnormalities, bradycardia, and acute kidney injury or failure)	Serious adverse events (includes hypotension, syncope, electrolyte abnormalities, bradycardia, and acute kidney injury or failure)

	NA	Expanded macrovascular event (defined as a composite endpoint of MACE, revascularization and hospitalization due to congestive heart failure)
Causal contrasts of interest	Intention-to-treat effect	Per-protocol effect
Analysis plan	Intention-to-treat effect estimated via the first occurrence of an outcome event among patients assigned to each treatment strategy with stratification accordingly to clinic	Per-protocol effect estimated via the first occurrence of an outcome event among patients assigned to each treatment strategy. Inverse probability weights were applied to adjust selection bias due to failure to follow the assigned treatment strategy, loss to follow-up, or administrative end of study respectively

Abbreviations: ACS: Acute Coronary Syndrome, CABG: Coronary Artery Bypass Grafting, CE: Carotid Endarterectomy, CHF: Congestive Heart Failure, CVD: Cardiovascular Disease, MI: Myocardial Infarction, PAD: Peripheral Artery Disease, PCI: Percutaneous Coronary Intervention.

Table 2. Baseline characteristics of patients with hypertension at high cardiovascular risk who are initiating an antihypertensive drug.

Characteristic	Number of Patients or Mean	Percentage or Standard Deviation
Total	103,708	100
Female	56,377	54.4
Age, years		
Mean, SD	75.1	7.9
Mean among those ≥ 75 years of age, SD	80.9	4.9
Race or ethnic group		
Non-Hispanic white	25,969	25.0
Non-Hispanic black	138	0.1
Hispanic	13	0.0
Asian	1,112	1.1
Unknown/missing	76,476	73.7
Smoking status		
Non-smoker	33,230	32.0
Former smoker	26,240	25.3
Light smoker (<10 cigarettes/day)	2,875	2.8
Moderate smoker (10~19 cigarettes/day)	3,913	3.8
Heavy smoker (≥ 20 cigarettes/day)	3,656	3.5
Unknown/missing	33,794	32.6
Measured baseline blood pressure	89,424	86.2
Systolic blood pressure, mmHg (mean, SD)	172.0	22.4
Diastolic blood pressure, mmHg (mean, SD)	91.2	13.0
Distribution of systolic blood pressure		
< 132 mmHg	2,646	2.6
≥ 132 to < 145 mmHg	6,886	6.6
≥ 145 mmHg	79,892	77.0
Measured BMI	40,183	38.7
Mean, SD (kg/m^2)	27.2	4.9
Underweight (< 18.5 kg/m^2)	919	0.9
Normal weight (18.5 to 24.9 kg/m^2)	12,776	12.3
Overweight (25 to 29.9 kg/m^2)	16,424	15.8
Obese (30 to 39.9 kg/m^2)	9,467	9.1
Extremely obese (≥ 40 kg/m^2)	597	0.6
Family history of CVD	186	0.2
Comorbidities		
Atrial fibrillation	5,265	5.1
Chronic kidney disease	4,538	4.4

Characteristic	Number of Patients or Mean	Percentage or Standard Deviation
Type 2 diabetes	15,160	14.6
Drug use		
Number of antihypertensive agents (Mean, SD)	1.1	0.3
Statin	13,127	12.7
Aspirin	13,644	13.2
Anticoagulants	3,232	3.1
Antihyperlipidemic drugs	13,472	13.0
Antidiabetics	5,274	5.1

Abbreviations: BMI: Body Mass Index, CVD: Cardiovascular Disease, SD: Standard Deviation.

Table 3. Five-year incidence rates for cardiovascular events by blood pressure control strategy among patients with hypertension at high cardiovascular risk.

Outcome	Intensive treatment strategy (target BP: 130/80 mmHg)			Standard treatment strategy (target BP: 140/90 mmHg)			Conservative treatment strategy (target BP: 150/90 mmHg)		
	Number	Incidence*	Adjusted incidence*	Number	Incidence*	Adjusted incidence*	Number	Incidence*	Adjusted incidence*
MACE[a]	1,860	2.0	5.4	2,550	1.8	5.8	3,577	1.7	6.1
Secondary outcomes									
Expanded macrovascular event[b]	4,235	4.7	8.0	5,632	4.2	8.3	7,562	3.6	8.5
Major coronary disease event[c]	3,457	3.8	6.3	4,584	3.4	6.3	6,096	2.9	6.4
Myocardial infarction	723	0.8	1.5	998	0.7	1.6	1,484	0.7	1.8
Stroke	961	1.0	2.3	1,312	0.9	2.5	1,818	0.8	2.7
Death from cardiovascular causes	577	0.6	4.1	798	0.6	4.5	1,033	0.5	4.8
Death from any cause	5,003	5.3	9.9	6,888	4.8	10.6	9,305	4.1	11.2
Hospitalization or death due to congestive heart failure	1,900	2.1	4.1	2,510	1.8	4.1	3,240	1.5	4.2
Diagnosis restricted to the primary position[d]	1,860	2.0	5.4	2,550	1.8	5.8	3,577	1.7	6.1

*The unit for incidence and adjusted incidence is per 100 person-years. We included IPTW and IPCW to calculate the adjusted incidence rate. Initially, there were 103,708 patients who followed each treatment strategy.

[a] This composite endpoint included nonfatal MI, nonfatal stroke, death from cardiovascular causes.

[b] This composite endpoint included nonfatal MI, nonfatal stroke, death from cardiovascular causes, revascularization or hospitalization for congestive heart failure.

[c] This composite endpoint included fatal coronary event, nonfatal MI, hospitalization for angina, or congestive heart failure.

[d] This composite endpoint included nonfatal MI, nonfatal stroke, death from cardiovascular causes, which were recorded only in the primary position for the diagnostic and procedure codes.

Abbreviations: BP: Blood Pressure, CVD: Cardiovascular Disease, IPCW: Inverse Probability Censoring Weighting, IPTW: Inverse Probability Treatment Weighting, MI: Myocardial Infarction.

Table 4. Five-year incidence rates for serious adverse events and other conditions of interest by blood pressure control strategy among patients with hypertension at high cardiovascular risk.

Outcome	Intensive treatment strategy (target BP: 130/80 mmHg)			Standard treatment strategy (target BP: 140/90 mmHg)			Conservative treatment strategy (target BP: 150/90 mmHg)		
	Number	Incidence*	Adjusted incidence*	Number	Incidence*	Adjusted incidence*	Number	Incidence*	Adjusted incidence*
Serious adverse event[a]	3,204	3.5	4.8	4,609	3.4	4.8	6,693	3.1	5.0
Conditions of interest									
Hypotension	596	0.6	0.8	881	0.6	0.8	1,265	0.6	0.8
Syncope	778	0.8	0.8	1,128	0.8	0.8	1,631	0.8	0.8
Bradycardia	200	0.2	0.2	288	0.2	0.2	413	0.2	0.2
Electrolyte abnormal	904	1.0	1.6	1,295	0.9	1.6	1,880	0.9	1.7
Injury/falls	943	1.0	0.9	1,417	1.0	0.9	2,196	1.0	0.9
Acute kidney disease	800	0.9	1.8	1,226	0.9	1.9	1,800	0.8	2.0

*The unit for incidence and adjusted incidence is per 100 person-year. We included IPTW and IPCW to calculate the adjusted incidence. Initially, there were 103,708 patients followed each treatment strategy.

[a] This composite endpoint included hospitalizations or emergency visits that are caused by any conditions of interest or antihypertensive treatment related severe adverse event.

FIGURE LEGENDS

Figure 1. Illustration of mapping of a hypothetical patient's record to following blood pressure control strategies investigated in the target trial.

We have a hypothetical patient A. Three replicates of their record were created to follow each individual treatment strategy, respectively. At t_1, the patient was prescribed to an additional CCB. They followed intensive and standard strategies, since a treatment change occurred when the observed BP was higher than the target BP (specifically SBP in this scenario). They also followed the conservative strategy since any prescription decision was acceptable (regardless of the occurrence of treatment change) when the observed BP was lower than the target BP. At t_2, the patient was prescribed with same treatments, ACE inhibitor and CCB, as at t_1. However, given the observed SBP was higher than the target in intensive strategy, a treatment change should be observed if the patient kept following the strategy. Thus, they deviated from intensive treatment strategy and were considered to still be following the other two strategies. A similar situation occurred at t_4, where they deviated from standard treatment strategy and continued to follow the conservative strategy. Abbreviations: ACE inhibitors: angiotensin-converting-enzyme inhibitors; BP: blood pressure; CCB: calcium channel blockers; DBP: diastolic blood pressure; SBP: systolic blood pressure; TD: thiazide diuretics.

Figure 2. Flow diagram describing construction of the study cohort of patients with hypertension at high cardiovascular risk initiating antihypertensive drugs. Abbreviations: HES: Hospital Episode Statistics.

Figure 3. Major adverse cardiovascular events among patients with hypertension at high cardiovascular risk following three blood pressure control strategies during first 5 years of follow-up. A) Standardized survival curve (by baseline covariates and IPTW for time-varying covariates); B) Cumulative hazards.

Abbreviations: MACE: major cardiovascular event.

Figure 4. Forest plot of the association between blood pressure control treatment strategies and the risk of cardiovascular events during the first 5 years of follow-up among patients with hypertension at high cardiovascular risk. A) Intensive vs. Standard strategy; B) Conservative vs. Standard strategy. Abbreviations: CI: confidence interval; MACE: major cardiovascular event.

Figure 5. Forest plot of the association between blood pressure control treatment strategies and the risk of serious adverse events during the first 5 years of follow-up among patients with hypertension at high cardiovascular risk. A) Intensive vs. Standard strategy; B) Conservative vs. Standard strategy. Abbreviations: CI: confidence interval.

Figure 6. Comparison of hazard ratios for cardiovascular events during the first 5 years of follow-up with different blood pressure control strategies between SPRINT and our observational study. Abbreviations: CI: confidence interval; MACE: major cardiovascular event; SPRINT: Systolic Blood Pressure Intervention Trial.

Figure 1.

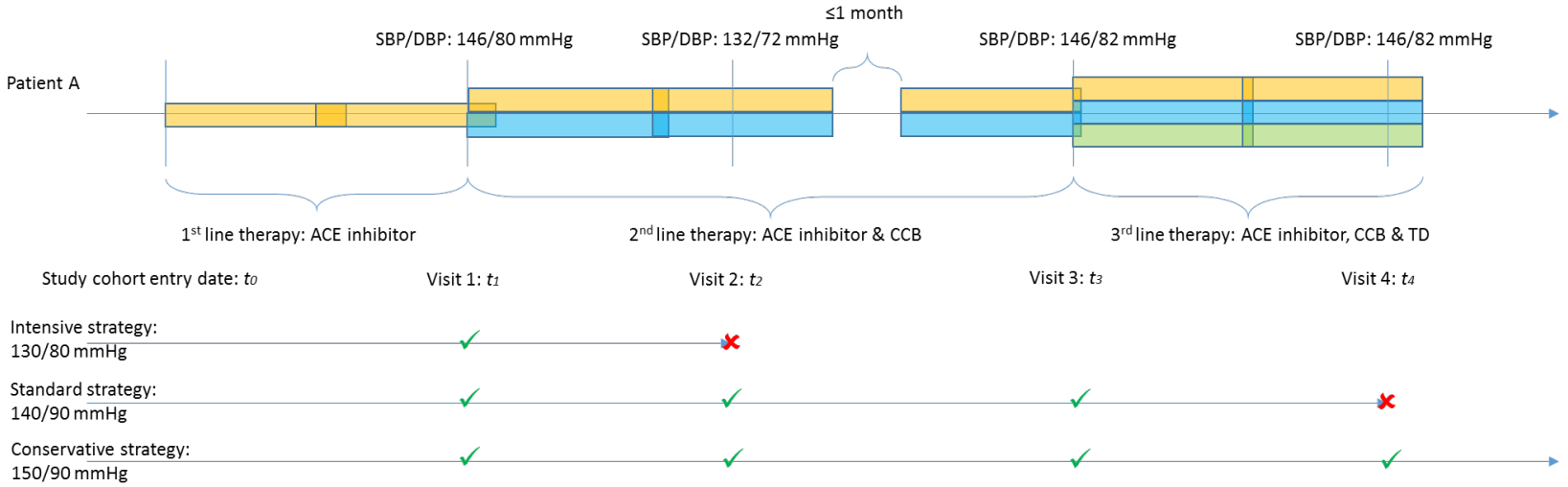

≤1 month
SBP/DBP: 146/80 mmHg
SBP/DBP: 132/72 mmHg
SBP/DBP: 146/82 mmHg
SBP/DBP: 146/82 mmHg
Patient A
1st line therapy: ACE inhibitor
2nd line therapy: ACE inhibitor & CCB
3rd line therapy: ACE inhibitor, CCB & TD
Study cohort entry date: t0
Visit 1: t1
Visit 2: t2
Visit 3: t3
Visit 4: t4
Intensive strategy:
130/80 mmHg
Standard strategy:
140/90 mmHg
Conservative strategy:
150/90 mmHg

Figure 2.

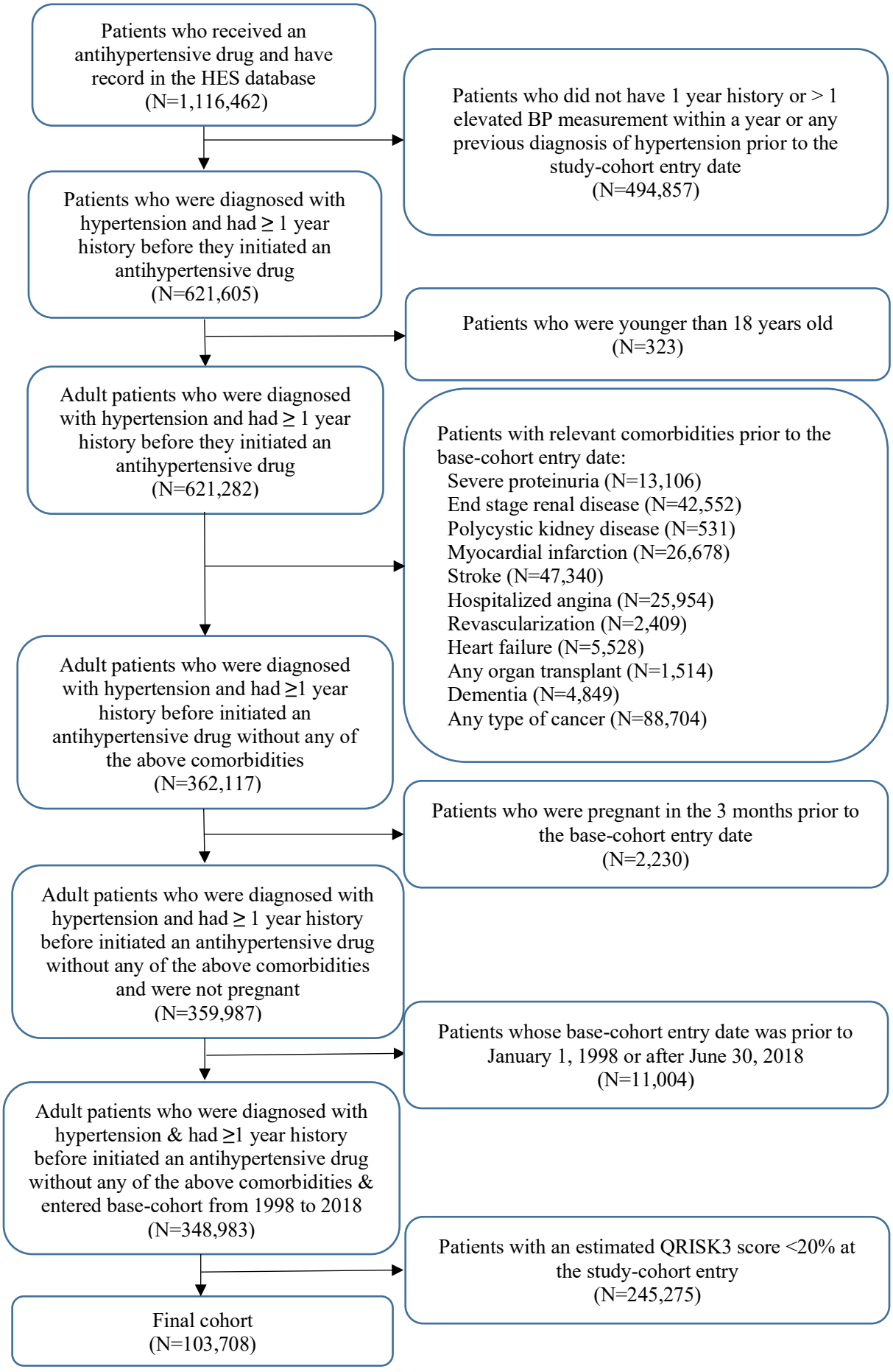

Patients who received an antihypertensive drug and have record in the HES database (N=1,116,462)
Patients who did not have 1 year history or > 1 elevated BP measurement within a year or any previous diagnosis of hypertension prior to the study-cohort entry date (N=494,857)
Patients who were diagnosed with hypertension and had ≥ 1 year history before they initiated an antihypertensive drug (N=621,605)
Patients who were younger than 18 years old (N=323)
Adult patients who were diagnosed with hypertension and had ≥ 1 year history before they initiated an antihypertensive drug (N=621,282)
Patients with relevant comorbidities prior to the base-cohort entry date:
Severe proteinuria (N=13,106)
End stage renal disease (N=42,552)
Polycystic kidney disease (N=531)
Myocardial infarction (N=26,678)
Stroke (N=47,340)
Hospitalized angina (N=25,954)
Revascularization (N=2,409)
Heart failure (N=5,528)
Any organ transplant (N=1,514)
Dementia (N=4,849)
Any type of cancer (N=88,704)
Adult patients who were diagnosed with hypertension and had ≥1 year history before initiated an antihypertensive drug without any of the above comorbidities (N=362,117)
Patients who were pregnant in the 3 months prior to the base-cohort entry date (N=2,230)
Adult patients who were diagnosed with hypertension and had ≥ 1 year history before initiated an antihypertensive drug without any of the above comorbidities and were not pregnant (N=359,987)
Patients whose base-cohort entry date was prior to January 1, 1998 or after June 30, 2018 (N=11,004)
Adult patients who were diagnosed with hypertension & had ≥1 year history before initiated an antihypertensive drug without any of the above comorbidities & entered base-cohort from 1998 to 2018 (N=348,983)
Patients with an estimated QRISK3 score <20% at the study-cohort entry (N=245,275)
Final cohort (N=103,708)

Figure 3a.

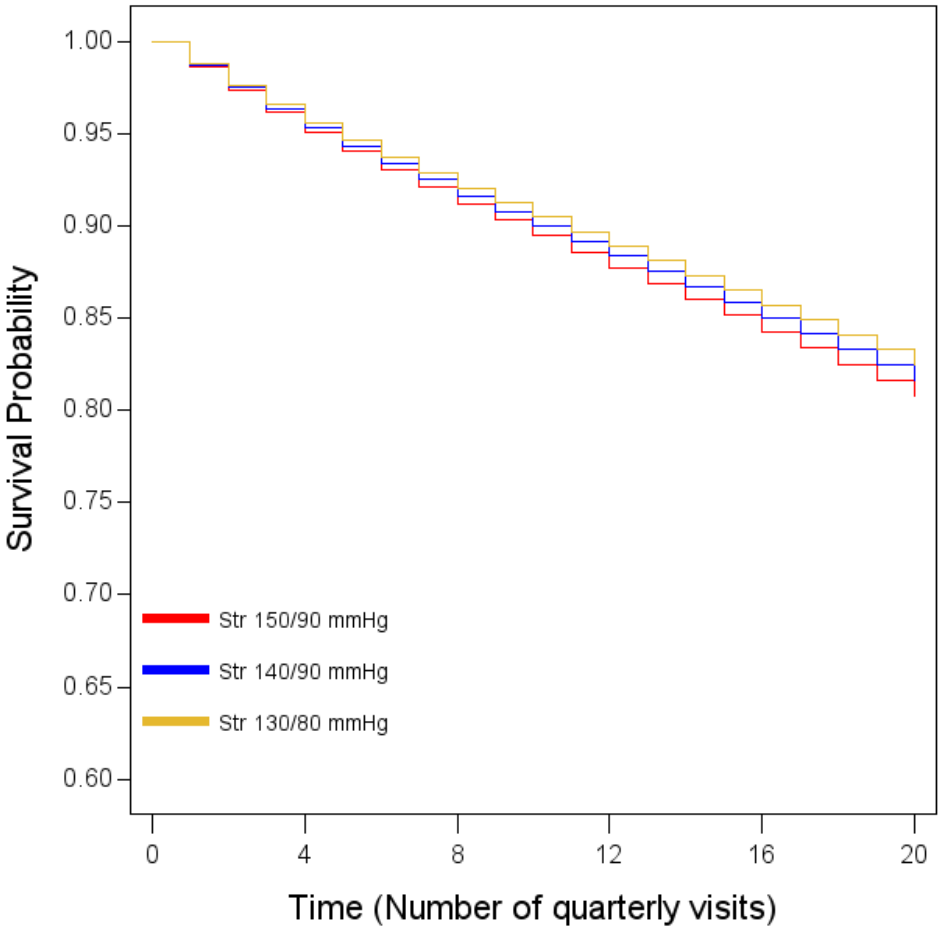

1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
Survival Probability
Str 150/90 mmHg
Str 140/90 mmHg
Str 130/80 mmHg
0
4
8
12
16
20
Time (Number of quarterly visits)

Figure 3b.

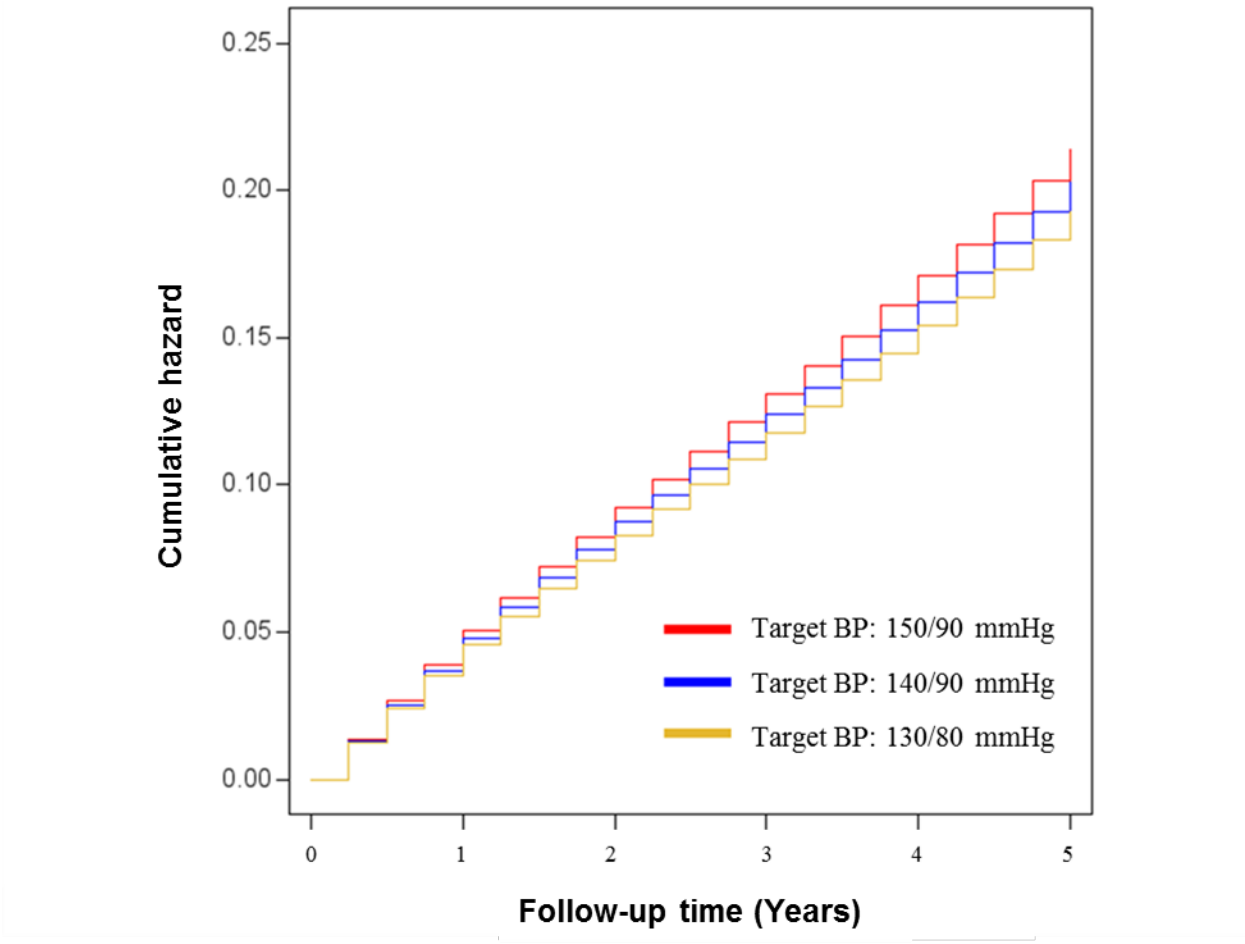

0.25
0.20
0.15
0.10
0.05
0.00
Cumulative hazard
0
1
2
3
4
5
Follow-up time (Years)
Target BP: 150/90 mmHg
Target BP: 140/90 mmHg
Target BP: 130/80 mmHg

Figure 4a.

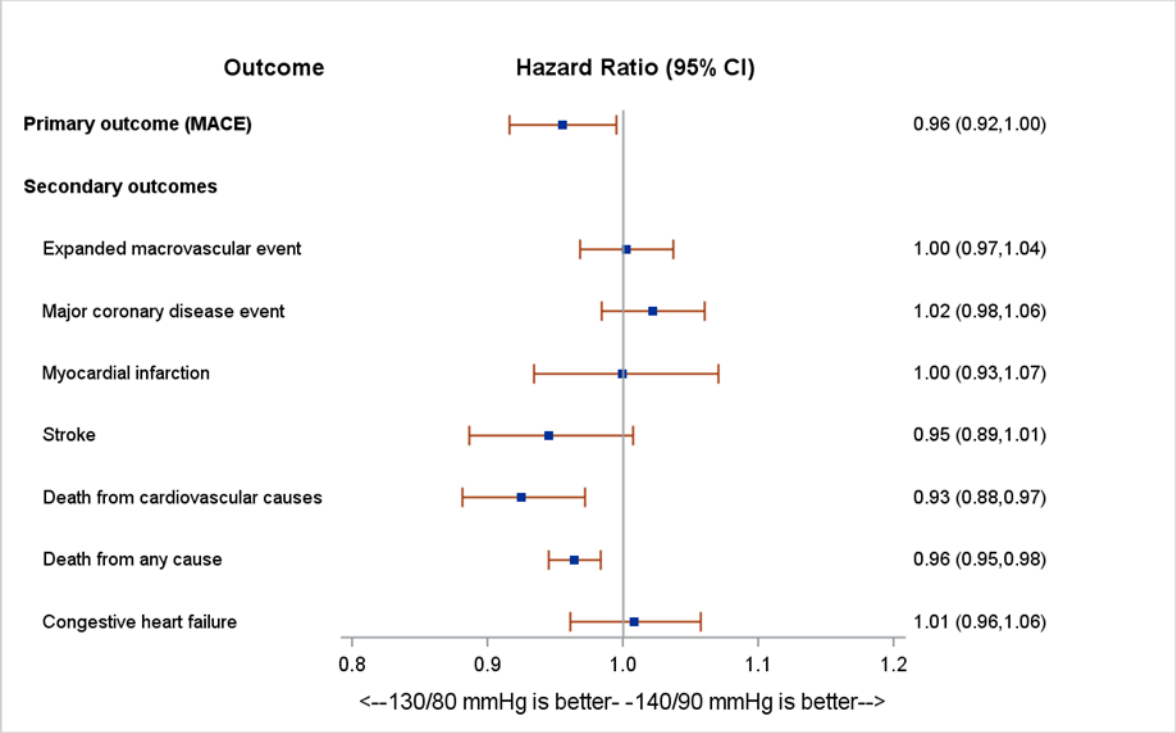


Figure 4b.

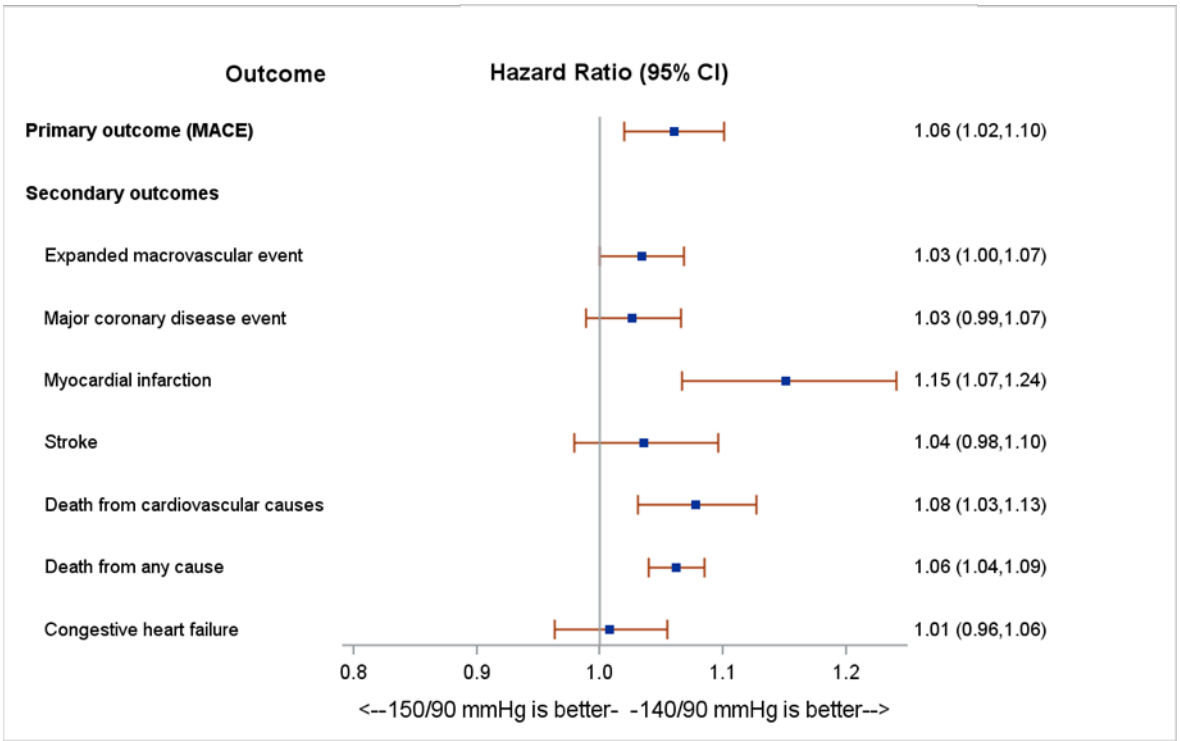


Figure 5a.

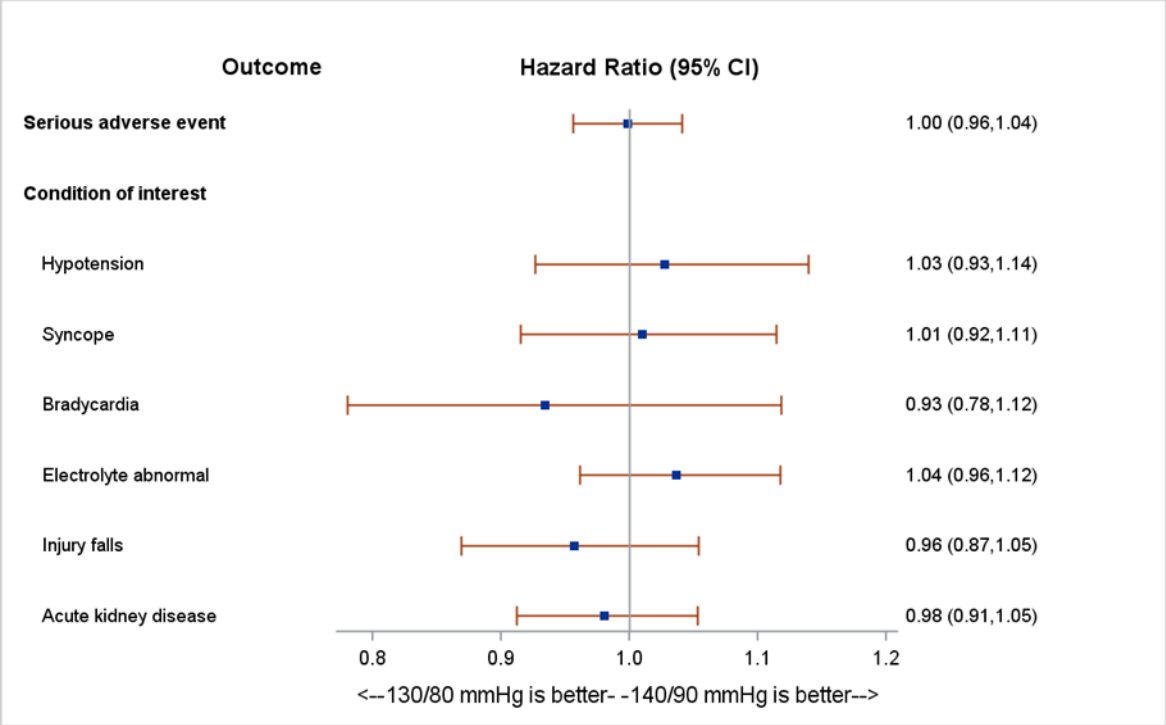


Figure 5b.

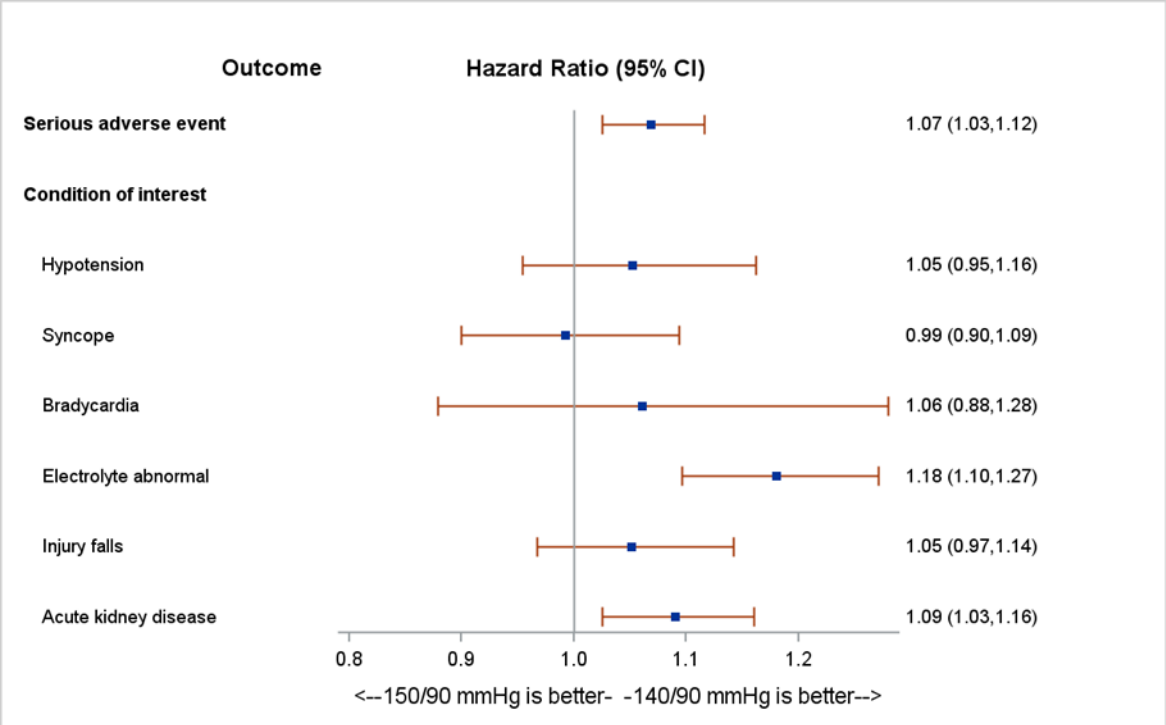
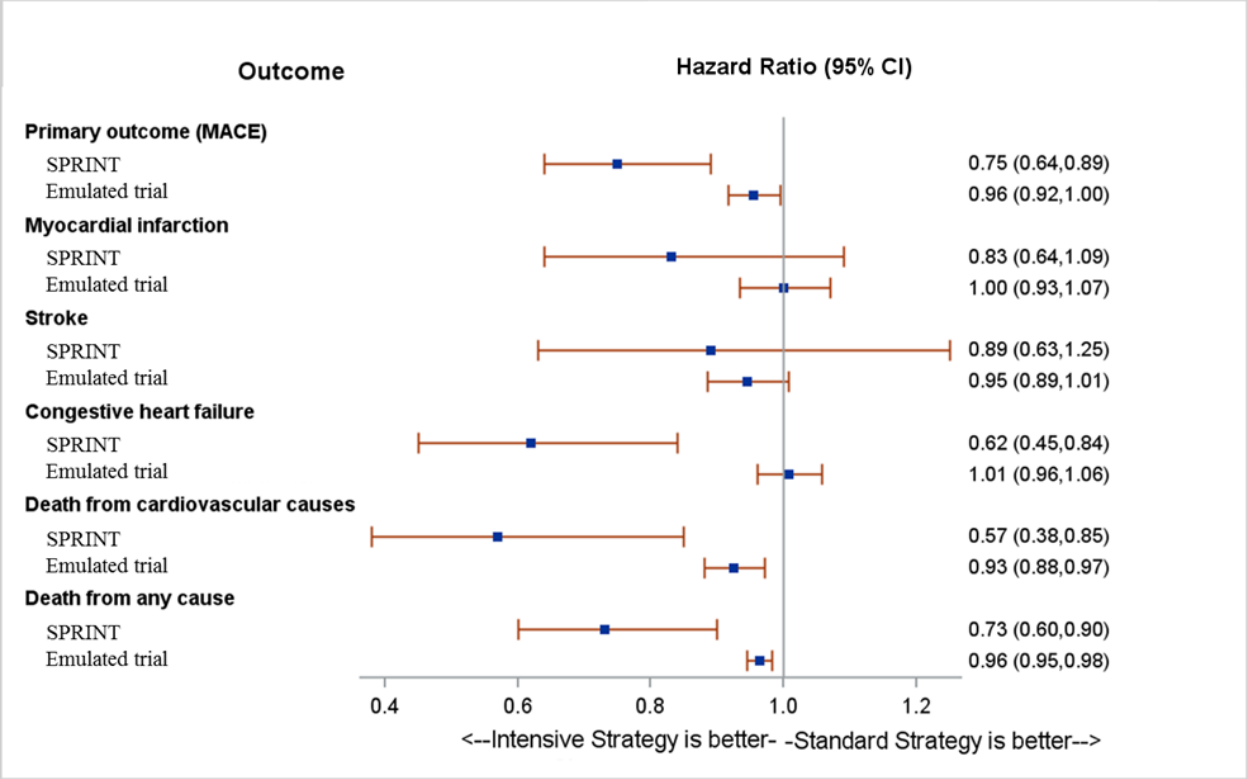


Figure 6.


Outcome
Hazard Ratio (95% CI)
Primary outcome (MACE)
SPRINT
0.75 (0.64,0.89)
Emulated trial
0.96 (0.92,1.00)
Myocardial infarction
SPRINT
0.83 (0.64,1.09)
Emulated trial
1.00 (0.93,1.07)
Stroke
SPRINT
0.89 (0.63,1.25)
Emulated trial
0.95 (0.89,1.01)
Congestive heart failure
SPRINT
0.62 (0.45,0.84)
Emulated trial
1.01 (0.96,1.06)
Death from cardiovascular causes
SPRINT
0.57 (0.38,0.85)
Emulated trial
0.93 (0.88,0.97)
Death from any cause
SPRINT
0.73 (0.60,0.90)
Emulated trial
0.96 (0.95,0.98)
0.4
0.6
0.8
1.0
1.2
<--Intensive Strategy is better- -Standard Strategy is better-->