Nature Communications

https://doi.org/10.1038/s41467-026-74041-9

Article in Press

Optimal blood pressure target in patients with uncomplicated hypertension: a target trial emulation study

Received: 22 April 2025

Accepted: 27 May 2026

Cite this article as: Zhang, R., Lam, I.C., Emilsson, L. *et al.* Optimal blood pressure target in patients with uncomplicated hypertension: a target trial emulation study. *Nat Commun* (2026). https://doi.org/10.1038/s41467-026-74041-9

Ran Zhang, Ivan Chun Hang Lam, Louise Emilsson, Feng Sun, Siyan Zhan, Kai Hang Yiu, Daniel Yee Tak Fong, Esther Yee Tak Yu, Celine Sze Ling Chui, Esther Wai Yin Chan, Ian Chi Kei Wong, Cindy Lo Kuen Lam, Goodarz Danaei & Eric Yuk Fai Wan

Title: Optimal blood pressure target in patients with uncomplicated hypertension: a target trial emulation study

Ran Zhang, MPH[1], Ivan Chun Hang Lam, PhD[2], Louise Emilsson, MD, PhD[3,4,5], Feng Sun, PhD[6,7], Siyan Zhan, PhD[6,7], Kai Hang Yiu, MD, PhD[8,9,10], Daniel Yee Tak Fong, PhD[11], Esther Yee Tak Yu, MBBS[12], Celine Sze Ling Chui, PhD[11,13], Esther Wai Yin Chan, PhD[14,15,16], Ian Chi Kei Wong, PhD[14,17,18,19], Cindy Lo Kuen Lam, MD[1,20], Goodarz Danaei, PhD[21], Eric Yuk Fai Wan, PhD[1,10,14,22*]

1 Department of Family Medicine and Primary Care, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.

2 Pharmaco- and Device Epidemiology, Health Data Sciences, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

3 Department of General Practice & General Practice Research Unit (AFE), Institute of Health and Society, University of Oslo, Oslo, Norway.

4 Vårdcentralen Nysäter and Centre for Clinical Research, County Council of Värmland, Värmland, Sweden.

5 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden.

6 Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, 100191, China

7 Key Laboratory of Epidemiology of Major Diseases (Peking University), Ministry of Education, Beijing, 100191, China

8 Cardiology Division, Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.

9 Cardiology Division, Department of Medicine, The University of Hong Kong Shenzhen Hospital, Shenzhen City, China.

10 The Institute of Cardiovascular Science and Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China.

11 School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong SAR, Hong Kong, China.

12 Primary Healthcare Office, Health Bureau, Hong Kong SAR, China.

13 School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.

14 Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.

15 Department of Pharmacy, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China.

16 The University of Hong Kong Shenzhen Institute of Research and Innovation, Hong Kong SAR, China.

17 Aston Pharmacy School, Aston University, Birmingham, United Kingdom.

18 Macau University of Science and Technology, Macau Special Administrative Region, China

19 Advanced Data Analytics for Medical Science Limited, Hong Kong SAR, China

20 Department of Family Medicine, The University of Hong Kong Shenzhen Hospital, Shenzhen City, China.

21 Department of Global Health and Population, Harvard TH Chan School of Public Health, Boston, MA, USA.

22 Comprehensive Primary Healthcare Collaboratory, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

Full professors: Siyan Zhan, Kai Hang Yiu, Esther Wai Yin Chan, Ian Chi Kei Wong and Cindy Lo Kuen Lam.

Correspondence to:

Dr Eric Yuk Fai Wan

Postal Address: Room 105M, 1/F, The Hong Kong Jockey Club Building for Interdisciplinary Research, 5 Sassoon Road, Pokfulam, Hong Kong SAR

Email: yfwan@hku.hk

Tel: +852 28315057

Keywords: Hypertension, Blood pressure, Antihypertension management, Target trial emulation

Abstract

The limited real-world evidence on the clinical benefits of intensive blood pressure (BP) management demonstrated in randomised controlled trials has led to its poor adoption in primary care settings. Here we conducted a target trial emulation study on 118,271 patients with uncomplicated hypertension to evaluate the effectiveness and safety managed by lower (below 130/80mmHg) compared to standard (130-140/80-90 mmHg) BP targets using a territory-wide public healthcare database in Hong Kong. Patients in the lower blood pressure target group were observed to incur a lower risk of hypertension related complications and all-cause mortality with no significant increased risk of the serious adverse events reported. The findings of this study provide evidence on the clinical benefits of an intensive BP management in real-world settings, supporting the adoption of a BP target of less than 130/80 mmHg in clinical guidelines for the treatment of adult patients with hypertension in primary care.

Introduction

Hypertension is a common cardiovascular disease affecting approximately one third of the global population.[1] Patients with hypertension are at greater risk of developing severe complications such as acute coronary syndrome and end-stage renal disease, which are leading causes of mortality worldwide.[2] Effective control of blood pressure has been widely regarded as an effective clinical strategy in preventing hypertension-related complications.[3]

Early recommendations from existing treatment guidelines have recommended a conservative treatment target of 140/90 mmHg for systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively.[4] Nonetheless, findings from subsequent randomised controlled trials (RCTs) and meta-analyses have provided evidence supporting a more intensive treatment targeting of SBP below 130 mmHg and even below 120 mm Hg, given the marked reduction in risk of cardiovascular events in patients treated with more intensive management targets.[5, 6, 7, 8, 9, 10] For instance, early clinical trials comparing standard and intensive blood pressure targets have reported a 27% and 25% reduction in risk of cardiovascular events and mortality in individuals managed on lower SBP targets.[5, 7] The risk reduction of cardiovascular event and mortality was more profound among elder patients aged 75 years or over, with reductions of 33% and 34%, respectively.[6] More recent trials, including BPROAD and ESPRIT trials have further demonstrated comparable benefits in risk reduction of major cardiovascular events in selected patient groups, including patients with diabetes and a history of stroke, supporting the clinical benefits of intensive blood pressure management across patient groups with different underlying health conditions.[11, 12] The observed clinical benefits have since led to the adoption of a more intensive blood pressure target recommendations across various guidelines committees, including The American College

of Cardiology and American Heart Association (ACC/AHA)[13] and European Society of Hypertension (ESH)[14].

Whilst previous RCTs have demonstrated the clinical benefits of intensive blood pressure management in selected populations, the scarcity of real-world evidence on the benefits and potential adverse effects associated with patients with uncomplicated hypertension has limited the adoption of such treatment regimen in clinical settings. This study aimed to evaluate the long-term benefits of intensified blood pressure control in reducing hypertension-related complications and all-cause mortality rates. The results can inform clinical decisions on the optimal blood pressure target for patients with uncomplicated hypertension.

Results

A total of 118,271 patients with hypertension were included in this study (Figure 1). After censoring due to treatment deviation over the grace period, 82,753 patients initiated an optimal BP target of BP 130-140/80-90 mmHg and 15,992 initiated BP of below 130/80 mmHg. Table 1 summarised the baseline characteristics of the participants. The mean age was 57.6 (SD 10.2) and 58.6 (SD 9.7), and BP was 157.1 (16.6)/92.3(8.9) mmHg and 155.1 (15.9)/90.6(8.0) mmHg for patients in traditional treatment strategy and in the intensive treatment strategy, respectively. Truncation at the 99.5th percentile did not change the overall distribution of the weight (Supplementary Table 4). The crude incidence rates for each outcome were summarised in Table 2. Adherence was around 60% for patients in intensive treatment strategy versus 80% in traditional treatment strategy (Supplementary Figure 2). Over an average follow-up of 7 years, patients with

lower BP target were observed to incur a lower risk of hypertension related complications (Figure 2), including major CVD [HR (95%CI):0.85 0.79-0.91)], CHD [HR (95%CI): 0.81 (0.72-0.90)], stroke [HR (95%CI): 0.89 (0.80-0.99)], end-stage renal disease [HR (95%CI): 0.79 (0.64-0.97)], and all-cause mortality [HR (95%CI): 0.88 (0.80-0.97)]. The risk reduction (Table 2) was observed for major CVD (absolute risk difference, -0.58 % [95%CI, -0.63 to -0.53 %]), and all-cause mortality (absolute risk difference, -0.60 % [CI, -0.62 to -0.57 %]). There was an average of 35 attended office blood pressure measurements per patient.

There was no significant increased risk for the serious adverse events requiring hospital admission (Figure 2) in the lower blood pressure group compared to the traditional treatment target were observed, including falls [HR (95%CI): 1.00 (0.92-1.09) and dizziness [HR (95%CI): 1.01 (0.92-1.10)]. The cumulative incidence curves of major CVD and all-cause mortality were summarised in the Figure 3. Sensitivity and subgroup analyses reported largely consistent findings for aforementioned outcomes (Supplementary Table 5-26). Notably, a similar risk lowering benefit in CVD was observed across patients with different estimated 10-year risk of CVD. The risk reduction effects in CHD associated with intensive blood pressure monitoring target were more profound among patients aged between 65 and 80 compared to patients from other age-subgroups. Despite age not being an interaction term with complications examined in this study, the greater risk of adverse events such as dizziness warrant the need for closer attention in older patients with lower blood pressure target (Supplementary Table 8). The blood pressure levels and proportion of intensification in the two treatment strategies over the follow-up period were shown in the Supplementary Figure 3 and Supplementary Table 27. The lower blood pressure target group identified more instances of drug escalation or dosage increases, suggesting an intensification of

treatment in the lower blood pressure treatment arm. The mean number of anti-hypertensive medications used by patients in each arm by the follow-up year was shown in Supplementary Table 28. The model estimates in the inverse probability weighting were summarized in Supplementary Table 29.

Discussion

Our study on adults with uncomplicated hypertension reported a lower risk of CVD related complications, end-stage renal disease and mortality in patients managed by an intensive blood pressure target of less than 130/80 mmHg compared to the standard blood pressure target over an up-to 11 years of follow-up. The observed CVDs and all-cause mortality risk reduction benefits were broadly consistent across various subgroups, supporting the clinical benefits from lower blood pressure target applies over a diverse population of patients.

Hypertension has been widely regarded as a major risk factor for CVD due to the potential damage to the vascular and myocardial tissues imposed by the prolonged high blood pressure resulting in damage to vital organs and atherosclerosis.[15] The cumulative evidence from previous RCTs demonstrating a risk reduction in CVD complications in patients treated with a lower blood pressure target has supported the "lower the better" approach in determining the optimal blood pressure for individual patients. Nonetheless, the limited follow-up period and the recruitment of under-representative study populations have led to disputes over such approach in clinical settings. For instance, the considerable proportion of elderly participants in the SPRINT trial, comprising over 25% of participants aged over 75, could lead to an over-estimation of the treatment efficacy

of the lower blood pressure management target and limited its generalisability across the general population.[5, 16, 17] Subsequent evidence from a meta-analysis including a broader population of hypertensive patients demonstrated a markedly lower risk of myocardial infraction and stroke in patients managed by a lower blood pressure target compared the standard blood pressure target.[18] Despite the clinical benefits observed, the arbitrary definition of the lower blood pressures of (<140/90 and <135/85 mmHg) have led to poor interpretability of its findings in clinical settings.[14] The consistent findings of this study, based on a wider coverage of patients with wider age range and CVD risk, further emphasised the clinical benefits in preventing CVD complications and all-cause mortality across the general population over the long-term as well as supporting the adoption of a lower blood pressure target of 130/80 mmHg for patients with uncomplicated hypertension.

Despite the marked reduction in the risk of CVD, existing observational studies and RCTs have reported the significant increased risk of the adverse events[17, 19, 20], including hypotension, electrolyte imbalances, acute kidney diseases and falls associated with aggressive blood pressure management. In contrast, we did not observe among patients managed with intensive blood pressure target of 130/80mmHg a greater risk of the serious adverse effects. Our findings regarding the safety profile are generally consistent with those of the latest RCT conducted in China.[12] The low observed incidence of serious adverse events could be partially attributed to the selection of a healthier population. However, the results from the subgroup analyses of patients with a high Charlson Comorbidity Index (CCI) did not indicate an increased risk of serious adverse events, supporting the lack of risk of serious adverse events across a diverse patient group with varying health conditions and comorbidity statuses. The low incidence rates of electrolyte abnormality might be due to the low use of diuretics in our study population, which is consistent with the

practice among other Chinese populations. [21, 22] Additionally, we excluded the patients with chronic kidney disease, who are more likely to develop acute kidney injury.[23] While there was no significant increase in serious adverse events that requiring hospitalisation associated with intensified blood pressure target <130/80 mmHg reported in our study, the slight increase in risk of syncope and dizziness observed during outpatient consultation implicated that a careful balance of potential benefits and risks of intensive blood pressure control should be considered on individual patients in clinical settings. Future study using more detailed and systematic adverse events monitoring are needed to better evaluate the safety of the intensive blood pressure target.

This is the first study to investigate the effects of intensive blood pressure targets among the patients with uncomplicated hypertension with varying characteristics in real-world clinical settings. The population-based observational data, with at most 11-year follow-up period, allowed us to reveal the relationship between different optimal blood pressure targets and long-term health effects adjusted by the major potential confounders. In addition, the emulated RCT design used as the analytical approach on the per-protocol effect where the evolvement of the post-baseline confounders was adjusted. Furthermore, the patients with younger age and lower CVD risks were included in our study compared to the precious trials, extending the current evidence on the benefits of lower blood pressure target in all population for the primary prevention of hypertension related complications.

However, we acknowledged several limitations in this study. Firstly, the information on the desired blood pressure target was not recorded in the CMS database. We assumed the blood pressure target

based on the blood pressure records and the concurrent antihypertensive drugs prescription data, which might have introduced a misclassification of the treatment target groups. Besides, the treatment assignment after the long grace period could potentially introduce further misclassification bias. However, given the prolonged follow-up in this study of over 7 years, the duration of grace period included in relation to the total follow-up period was in-line with previous study employing the clone-censor-weight design.[24, 25] Nevertheless, the results of the sensitivity analysis with a short grace period of six-months and the sensitivity analysis using different numbers of consecutive records of BP readings concurrent with the prescription records have majorly yielded consistent findings, showing that any potential misclassification bias using this definition should not have a major impact on the overall results. Secondly, the target-based definition of the treatment assignment may violate the assumption of consistency since patients can achieve the optimal blood pressure target through treatment modification, but attributed to treatment intensification in this study. Thirdly, some potential confounders such as hypertension duration, lifestyle factors (including diet and physical activity), socioeconomic status, and educational level were unavailable in our study, which may have introduced bias to our results. Additionally, despite our efforts to emulate a target trial and account for various clinical scenarios, certain confounders and patients' complexities in real-world practice may not have been fully captured, similar to other observational studies. Therefore, the findings reported in this study should be interpreted with caution in patients with specific clinical conditions or complexities. Future research incorporating additional real-world variables is warranted to further examine the benefits of intensive BP monitoring in other patient groups. Furthermore, the in our dataset, only the primary cause of death was recorded, which may lead to potential misclassification of the cause of death when considering the competing risks of the non-CVD mortality in this study. Further

studies with more precise and comprehensive cause-of-death data are necessary to better understand the relationship between intensive blood pressure management and related complications. Lastly, ICPC-2 and ICD-9-CM codes were used to identify the diagnosis in the CMS database, which might lead to the misclassification. However, as demonstrated in the previous studies using this database, the history of chronic diseases in the HKHA has been recorded with a high coding accuracy.[26, 27]

The findings of the study provided comprehensive real-world evidence supporting the association of the clinical benefits of reduced risk of hypertension related cardiovascular complications and all-cause mortality with an intensive blood pressure management target among patients with uncomplicated hypertension without significant increased risk of serious adverse events. Nevertheless, the optimal blood pressure management target should also take into consideration of individual's characteristics, comorbidities, and potential risk factors for associated adverse events.

Methods

This study was approved by the Institutional Review Board of the University of HK/HA HK West Cluster (UW19-361) with an exemption for informed consent from participants since all data used in this study were anonymized and obtained from the electronic health records from the HA.

Data Sources

We conducted a trial emulation using data from the Clinical Management System (CMS) provided by the Hong Kong Hospital Authority (HKHA) to evaluate the effects of different blood pressure targets on the risks of hypertension-related complications and adverse events among patients with hypertension. The HKHA manages all public healthcare services in the Hong Kong, China. The service is available to all Hong Kong residents, covering over 80% of all routine healthcare management. The electronic medical records maintained by the HKHA include the disease diagnoses recorded during doctor consultations from in- and out-patient hospital and emergency visits. [28] The blood pressure readings in this data source are from attended office measurements.

Eligible criteria for study participants

All patients aged⩾18 with a documented diagnosis of hypertension on or before December 2013 were included in our study. The baseline was defined as the date of the first prescription adjustment for patients with hypertension whose blood pressure records were⩾130/80mmHg on that date, between 01 January 2008 to 31 December 2013. The treatment adjustment in these patients with uncontrolled blood pressure were regarded as an indication that the clinicians were attempting to modify and monitor their treatment plans to achieve the potential optimal BP target. Patients on 4 or more regular antihypertensive medications on or within 3 months before baseline, as well as patients with history of CKD, DM or CVD were excluded in this study. Complete case analysis was conducted, and patients with incomplete data for the used covariates at the baseline were also excluded. Individuals with a prescription for aspirin on or before baseline were excluded to avoid the underdiagnosis of CVD history, as aspirin is used primarily for recurrence prevention in patients with cardiovascular diseases.[29] The details of the study design and RCT emulation were summarised in Supplementary Figure 1 and Supplementary Table 1.

Treatment strategies

According to the Hong Kong Reference Framework[30], the optimal blood pressure treatment goal for patients without CKD, DM or CVD is below 140/90mmHg, and a lower goal can be considered for those individuals who can tolerate. Therefore, two treatment targets were considered for comparison: (1) Continue being treated according to the current Hong Kong Reference Framework[30]: SBP 130-140 mmHg and DBP 80-90 mmHg; (2) a more intensive treatment goal: SBP <130 mmHg and DBP <80 mmHg. The initiation of the treatment strategy was defined based on the BP readings and the concurrent prescription records of antihypertensive regimens during 12-month grace period.

Patients with two consecutives records of BP <130/80 mmHg without de-escalation, or BP readings of 130-140/ 80-90 mmHg with escalation of drug treatment, were considered to be treated to reach the intensive treatment target. The rest of the patients who already achieved the standard blood pressure target were considered to continue treatment according to the current treatment guideline with target of 130-140/80-90 mmHg. Therefore, patients who did not achieve the traditional treatment target after grace period, or patients without follow-up after baseline, were censored from the study during the grace period.

Outcome measures and follow-up period

The outcomes of this study included the incidences of major cardiovascular diseases (a composite outcomes of coronary heart disease, heart failure and stroke), coronary heart disease (CHD), stroke, heart failure, end-stage renal disease (ESRD), all-cause mortality and seven serious adverse events of intensive treatment (hypotension, syncope, bradycardia, electrolyte abnormality, fall(s), acute

kidney injury or acute renal failure and dizziness). Disease diagnoses were based on the International Classification of Primary Care, 2nd edition (ICPC-2), International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), or relevant clinical parameters (Supplementary Table 2). The serious adverse events of blood pressure treatment were defined as the diagnosis requiring hospital admission. All patients were followed from the baseline until the outcome events, death or the end of the study (31 Dec 2018), whichever occurred first.

Statistical Analysis

We adopted the cloning, artificial censoring and weighting approach to minimise the potential selection bias and immortal time bias because the treatment strategy of interest includes a grace period of 1 year for initiation of the optimal blood pressure target. [31] Firstly, we created the dataset of the eligible patients at baseline with 2 replicates (clones), and each of the replicates was randomly assigned to one of the treatment strategies. After that, we assessed whether the replicates adhered to their assigned treatment strategy at monthly intervals. To estimate the per-protocol effect of the optimal BP target, replicates who actually deviated from their assigned strategy were censored unless the deviation was explained by a medical reason. For example, if replicates were assigned to the traditional treatment strategy, but (1) were not treated with the traditional treatment initially by the end of 12 months, or (2) received the intensive treatment after the grace period (identified as patients with five consecutive records of with BP below 140/90mmHg with prescription escalation), except for changes due to the diagnosis of DM or CKD, or (3) did not maintain the standard treatment target after the grace period (defined as patients with five consecutive records of BP records which were higher than 140/90mmHg without prescription escalation), they were censored at that time point; Conversely, if replicates were assigned to the intensive treatment target, but (1) were not treated with the intensive treatment target initially by

the end of 12 months, or (2) were treated with the higher BP target after the grace period (defined as patients with five consecutive of BP records below 130/80mmHg with prescription de-escalation; or of BP records higher than 130/80 without prescription escalation), they were be censored at that time point. The possible censoring mechanisms in our emulated trial setting were illustrated in Supplementary Figure 1.

A panel dataset was created for all time-varying indicators (by month) for each eligible patient. The last observation carried forward was used for time-varying clinical parameters during the follow-up period. To adjust for the selection bias introduced by the aforementioned artificial censoring process, we conducted the inverse probability weighting to account for the difference in baseline and time-varying covariates, including sex; age; smoking status; fasting glucose level; low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC); triglyceride (TG) level; estimated glomerular filtration rate (eGFR); obesity status; and usage of ACEI/ARB, β-blocker, calcium channel blockers, diuretic, CCI score; history of adverse events; and in the past year the number of attendances for doctor consultations in general outpatient clinics, specialist outpatient clinics, accident and emergency services, and overnight hospitalisation between separate cohorts. The weighted score of individuals at each specific time points were calculated by the sum of the cumulative weighted score of previous time points.

Finally, the cumulative inverse probability weight at each time point was truncated at the 0.5^{th} and 99.5^{th} percentile. A pooled logistic model was fitted to estimate the hazard ratio for the effect of the continuous blood pressure target on the incidence of outcome events. The indicators for the

assigned treatment strategy, month of follow-up (linear and quadratic term), and baseline covariates were included in the models with time-varying weights.

The absolute risk difference and cumulative incidence of each outcome were estimated using the aforementioned pooled logistic model with interaction terms between treatment and follow-up time after standardising the outcomes using the joint distribution of the covariates in the entire study population. The 95% CIs for the absolute risk difference and cumulative incidence were obtained from a nonparametric bootstrap with 200 samples.

Subgroup analysis and sensitivity analysis

Subgroup analyses were predefined taking account of the risk factors of hypertension complications identified. Patients were stratified by 1) age (<65, 65-79, ≥80), 2) gender, 3) CCI (<4, ≥4), 4) smoking status, 5) CVD risk using Framingham risk score formula (<10,10-20 ≥20), and 6) obesity status. Interaction between treatment and each subgroup were also evaluated. Several sensitivity analyses were performed as: (1) Applying the same RCT emulation without adjustment for time-varying confounders to estimate the intention-to-treat effect, that is, the effect of being assigned to intensive treatment compared with standard treatment at baseline on the risk of outcomes[32]; (2) Censoring patients with missing SBP records (defined as an interval of more than 1 year between two SBP records) during follow-up to assess the influence of carrying forward the last SBP value for missing data; (3) Changing the grace period from 12 months to 6 months; (4) Using single or three, instead of two, consecutive BP readings and prescription records of antihypertensive regimens to define the treatment strategy, in order to investigate the robustness of outcomes to the definition of treatment assignment; (5) Evaluating the safety of the treatment

target by assessing the incidences of adverse events from both inpatient and outpatient settings; (6) Using cancer as a negative control outcome; (7) Including baseline BP readings in the weighting model; (8) Adjusting for competing risks in the per-protocol analysis: each clone additionally received a time-varying inverse probability weight for not dying of non-cardiovascular events; (9) Including patients with low-dose aspirin prescriptions on or before baseline; (10) Including the year of the enrolment in the weighting model; (11) Using two, three, four, or six consecutive records to define deviation from the assigned treatment strategy after the grace period; (12) Considering adverse effects due to advanced age (defined as older than 65 years), frailty (defined as a change in CCI greater than 2 compared to baseline), and polypharmacy (defined as taking more than three types of drugs) during the follow-up period as contraindications.

All analyses were performed in Stata/MP 17.0. All significance tests were two-tailed. We followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklists to guide transparent reporting of the cohort study.

Data Availability

The data used in this article were provided by the Hospital Authority of Hong Kong. Due to the data sharing policy, the data containing confidential information cannot be shared with the public. Local academic institutions, government departments, or non-governmental organizations interested in accessing the data may apply through the Hospital Authority's data-sharing portal (https://www3.ha.org.hk/data).The investigators are responsible for the archiving and safekeeping of the personal and study data during and after the study.

Code Availability

The code used in this study is available on Zenodo (https://doi.org/10.5281/zenodo.17033442).

References

1. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol* **16**, 223-237 (2020).

2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet* **389**, 37-55 (2017).

3. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **388**, 1659-1724 (2016).

4. Saiz LC*, et al.* Blood pressure targets for the treatment of people with hypertension and cardiovascular disease. *Cochrane Database of Systematic Reviews*, (2017).

5. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* **373**, 2103-2116 (2015).

6. Williamson JD*, et al.* Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ⩾75 Years: A Randomized Clinical Trial. *JAMA* **315**, 2673-2682 (2016).

7. SPRINT Research Group. Final Report of a Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* **384**, 1921-1930 (2021).

8. Zhang W*, et al.* Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension. *N Engl J Med* **385**, 1268-1279 (2021).

9. He J*, et al.* Effectiveness of a non-physician community health-care provider-led intensive blood pressure intervention versus usual care on cardiovascular disease (CRHCP): an open-label, blinded-endpoint, cluster-randomised trial. *The Lancet* **401**, 928-938 (2023).

10. Erviti J*, et al.* Blood pressure targets for hypertension in people with chronic renal disease. *Cochrane Database of Systematic Reviews*, (2024).

11. Bi Y*, et al.* Intensive Blood-Pressure Control in Patients with Type 2 Diabetes. *New England Journal of Medicine* **392**, 1155-1167 (2025).

12. Liu J*, et al.* Lowering systolic blood pressure to less than 120 mm Hg versus less than 140 mm Hg in patients with high cardiovascular risk with and without diabetes or previous stroke: an open-label, blinded-outcome, randomised trial. *The Lancet* **404**, 245-255 (2024).

13. Whelton PK*, 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: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* **71**, 1269-1324 (2018).

14. Mancia G*, et al.* 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens* **41**, 1874-2071 (2023).

15. Gambardella J, Morelli MB, Wang XJ, Santulli G. Pathophysiological mechanisms underlying the beneficial effects of physical activity in hypertension. *J Clin Hypertens (Greenwich)* **22**, 291-295 (2020).

16. Benavente OR*, et al.* Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* **382**, 507-515 (2013).

17. Cushman WC*, et al.* Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* **362**, 1575-1585 (2010).

18. Arguedas JA, Leiva V, Wright JM. Blood pressure targets in adults with hypertension. *Cochrane Database of Systematic Reviews*, (2020).

19. Ambrosius WT*, et al.* The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials* **11**, 532-546 (2014).

20. Frey L, Gravestock I, Pichierri G, Steurer J, Burgstaller JM. Serious adverse events in patients with target-oriented blood pressure management: a systematic review. *J Hypertens* **37**, 2135-2144 (2019).

21. Suchard MA*, et al.* Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. *The Lancet* **394**, 1816-1826 (2019).

22. Yang R, Tang J, Zhuo Y, Kuang M, Liu H. Current prescription status of antihypertensive drugs in Chinese patients with hypertension: analysis by type of comorbidities. *Clinical and Experimental Hypertension* **44**, 240-248 (2022).

23. Rocco MV*, et al.* Effects of Intensive Blood Pressure Treatment on Acute Kidney Injury Events in the Systolic Blood Pressure Intervention Trial (SPRINT). *Am J Kidney Dis* **71**, 352-361 (2018).

24. Chen A*, et al.* Impact of beta-blockers on mortality and cardiovascular disease outcomes in patients with obstructive sleep apnoea: a population-based cohort study in target trial emulation framework. *Lancet Reg Health Eur* **33**, 100715 (2023).

25. Trevisan M*, et al.* Stopping mineralocorticoid receptor antagonists after hyperkalaemia: trial emulation in data from routine care. *Eur J Heart Fail* **23**, 1698-1707 (2021).

26. Wong AY*, et al.* Cardiovascular outcomes associated with use of clarithromycin: population based study. *BMJ* **352**, h6926 (2016).

27. Wong MC, Jiang JY, Tang JL, Lam A, Fung H, Mercer SW. Health services research in the public healthcare system in Hong Kong: an analysis of over 1 million antihypertensive prescriptions between 2004-2007 as an example of the potential and pitfalls of using routinely collected electronic patient data. *BMC Health Serv Res* **8**, 138 (2008).

28. Lai FTT*, et al.* Carditis After COVID-19 Vaccination With a Messenger RNA Vaccine and an Inactivated Virus Vaccine. *Annals of Internal Medicine* **175**, 362-370 (2022).

29. The Hong Kong Department of Health. Information on oral Non-Steroidal Anti-Inflammatory Drugs. https://www.drugoffice.gov.hk/eps/do/en/consumer/news_informations/dm_03.html (2012).

30. Lim MK, Ha SCN, Luk KH, Yip WK, Tsang CSH, Wong MCS. Update on the Hong Kong Reference Framework for Hypertension Care for Adults in Primary Care Settings-review of evidence on the definition of high blood pressure and goal of therapy. *Hong Kong Med J* **25**, 64-67 (2019).

31. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol* **183**, 758-764 (2016).

32. Dickerman BA, García-Albéniz X, Logan RW, Denaxas S, Hernán MA. Avoidable flaws in observational analyses: an application to statins and cancer. *Nat Med* **25**, 1601-1606 (2019).

Acknowledgements

This study was supported by Health Bureau [No. 18192571; E.Y.F.W.], the Government of Hong Kong Special Administrative Region, China. The funder had no role in study design, data collection, data analysis, and data interpretation. We would like to thank the Central Panel on Administrative Assessment of External Data Requests of the Hospital Authority for approval of the data extraction for our study. The data analysis was performed using research computing facilities provided by Information Technology Service, The University of Hong Kong. We would like to thank them for their ongoing support of this project.

Author Contributions Statement

E.Y.F.W., and R.Z. had the original idea for the study, contributed to the development of the study, extracted data from the source database, constructed the study design and the statistical model, reviewed the literature, and act as guarantors for the study. R.Z., and E.Y.F.W. accessed and verified the data, and performed statistical analysis. I.C.H.L., R.Z., and E.Y.F.W. wrote the first draft of the manuscript. E.Y.F.W. is the principal investigator and provided oversight for all aspects of this project. L.E., F.S., S.Y.Z., K.H.Y., D.Y.T.F., E.Y.T.Y, C.S.L.C., E.W.Y.C., I.C.K.W., C.L.K.L., G. D. and E.Y.F.W. provided critical input to the analyses, study design, and discussion. All authors contributed to the interpretation of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript to be submitted.

Competing Interests Statement

All authors declare no known competing interests that directly impact the study and its findings.

Table 1 Baseline Characteristics

Demographic	Overall (N = 118,271)	SBP 130-140mmHg and DBP 80-90 mmHg (N = 82,753) [a]	SBP<130mmHg and DBP<80 mmHg (N = 15,992) [a]
Sex (male)	56,296 (47.6%)	40,005 (48.3%)	6,449 (40.3%)
Age	57.8 (10.4)	57.6 (10.2)	58.6 (9.7)
Smoking status	8,119 (6.9%)	5,814 (7.0%)	1,041.0 (6.5%)
SBP	157.6 (16.8)	157.1 (16.6)	155.1 (15.9)
DBP	92.2 (8.9)	92.3 (8.9)	90.6 (8.0)
Fasting glucose	5.5 (1.1)	5.5 (1.1)	5.5 (1.1)
Low-density lipoprotein cholesterol	3.3 (0.9)	3.4 (0.9)	3.4 (0.9)
Total cholesterol	5.4 (1.0)	5.4 (1.0)	5.4 (1.0)
High-density lipoprotein cholesterol	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)
Triglyceride level	1.6 (1.1)	1.6 (1.1)	1.5 (1.0)
Body Mass Index	26.1 (4.0)	26.2 (4.0)	25.6 (3.8)
Estimated glomerular filtration rate	87.8 (14.4)	88.0 (14.4)	87.6 (13.9)
Charlson Comorbidity Index	0.1 (0.5)	2.3 (1.2)	2.4 (1.1)
Use of ACEI/ARB	7,593 (6.4%)	5,117 (6.2%)	859 (5.4%)
Use of β-blocker	19,243 (16.3%)	13,094 (15.8%)	2,522 (15.8%)
Use of calcium channel blockers	25,244 (21.3%)	17,711 (21.4%)	2,946 (18.4%)
Use of diuretic	7,150 (6.0%)	5,038 (6.1%)	874 (5.5%)
Use of other antihypertensive drugs	5,101 (4.3%)	3,496 (4.2%)	696 (4.4%)
Use of lipid-lowering agents	21,852 (18.5%)	15,058 (18.2%)	2,956 (18.5%)
Dementia	3.5 (3.2)	65 (0.1%)	13 (0.1%)
Doctor consultations in general outpatient clinics [b]	2.6 (1.7)	3.5 (3.1)	3.8 (3.4)
Doctor consultations in specialist outpatient clinics[b]	1.4 (1.3)	2.6 (1.6)	2.5 (1.6)
Accident and emergency services [b]	1.3 (0.8)	1.4 (1.3)	1.4 (1.1)
Inpatient Visit [b]	3.5 (3.2)	1.3 (0.8)	1.3 (0.7)

[a] These numbers do not add up to the total number of patients as some patients experienced study outcomes or administrative censoring over the grace period; [b] Number of Specialist, General Outpatient Clinics attendance, accident and emergency and hospitalization were counted within 1 year before baseline.

Table 2 Crude incidence rate and adjusted risk difference of different blood pressure treatment targets on the risk of hypertension related complications and serious adverse events

	SBP 130-140mmHg and DBP 80-90 mmHg		SBP <130mmHg and DBP <80 mmHg		
Outcome	**Events/Follow-up time**	**Crude incidence Rate (95% CI)**	**Events/Follow-up time**	**Crude incidence Rate (95% CI)**	**Adjusted Risk Difference (95% CI)**
Major CVD	4,603 /6.6	8.50 (8.26-8.75)	770 /6.2	7.81 (7.28-8.39)	-0.58 (-0.63, -0.53)
CHD	2,188 /6.6	3.99 (3.82-4.16)	362 /6.3	3.63 (3.28-4.03)	-0.23 (-0.26, -0.20)
Heart Failure	741 /6.7	1.34 (1.24-1.44)	109 /6.3	1.08 (0.90-1.31)	-0.15 (-0.18, -0.12)
Stroke	2,153 /6.7	3.92 (3.76-4.09)	368 /6.3	3.69 (3.33-4.08)	-0.25 (-0.29, -0.22)
ESRD	73 /6.7	0.13 (0.10-0.17)	7 /6.3	0.07 (0.03-0.15)	-0.55 (-0.57, -0.52)
Mortality	2,857 /6.7	5.14 (4.96-5.33)	496 /6.3	4.92 (4.50-5.37)	-0.60 (-0.62, -0.57)
Serious adverse event					
Composite of seven serious adverse event	6,432 /6.5	12.02 (11.73-12.32)	1,212 /6.1	12.47 (11.79-13.19)	-0.15 (-1.64,1.34)
Hypotension	328 /6.7	0.59 (0.53-0.66)	58 /6.3	0.58 (0.45-0.75)	-0.00 (-0.65,0.59)
Syncope	1,069 /6.7	1.94 (1.82-2.06)	205 /6.3	2.05 (1.78-2.35)	-0.30 (-0.89,0.28)
Bradycardia	82 /6.7	0.15 (0.12-0.18)	16 /6.3	0.16 (0.10-0.26)	0.03 (-0.03,0.04)
Electrolyte abnormality	9 /6.7	0.02 (0.01-0.03)	2 /6.3	0.02 (0.00-0.08)	NA*
Falls	2,903 /6.6	5.31 (5.12-5.51)	559 /6.2	5.63 (5.18-6.11)	0.11 (-1.20, 1.43)
Acute kidney disease	486 /6.7	0.88 (0.80-0.96)	72 /6.3	0.71 (0.57-0.90)	-0.41 (-1.26,0.43)
Dizziness	2,340 /6.6	4.27 (4.10-4.45)	459 /6.2	4.62 (4.21-5.06)	0.10 (-0.96,1.16)

Note: Major CVD: composite outcomes of heart failure, chronic heart disease and stroke; CHD: chronic heart disease; ESRD: end-stage renal disease; Analyses adjusted for sex, age, smoking status, fasting glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, total cholesterol, eGFR, Charlson Comorbidities Index, usage of ACEI/ARB, β-blocker, calcium channel blockers, diuretic; history of fall, syncope and electrolyte abnormality, Specialist, General Outpatient Clinics attendance, accident and emergency and hospitalization (within 1 year before baseline).

*The model can not converge due to limited number of events

Figure Legends

Figure 1. Flowchart of patient selection

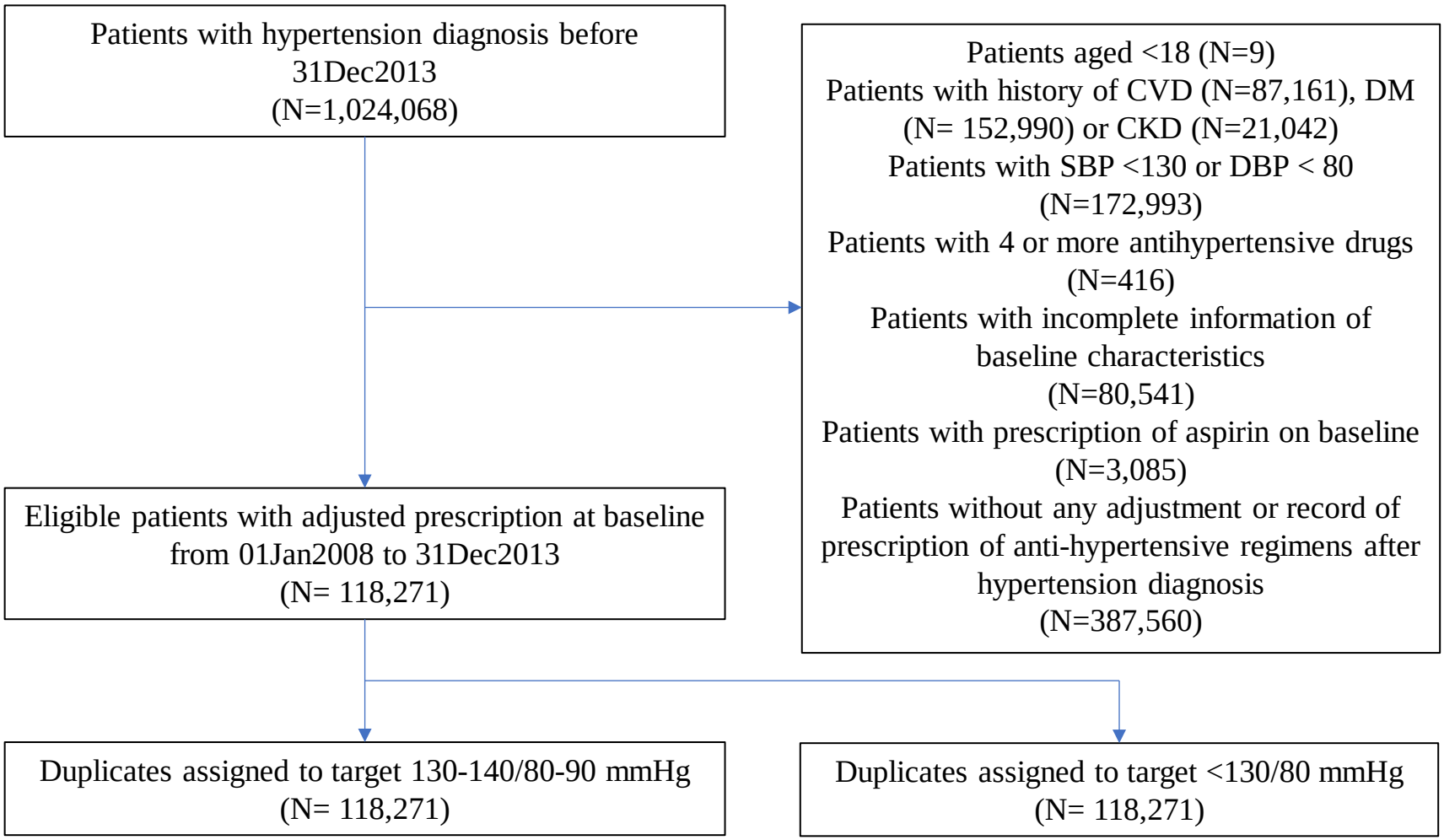
Figure 2. Estimated hazard ratios (and 95% confidence interval) of hypertension related complications, all-cause mortality and serious adverse events between intensive treatment target group and traditional treatment target group.

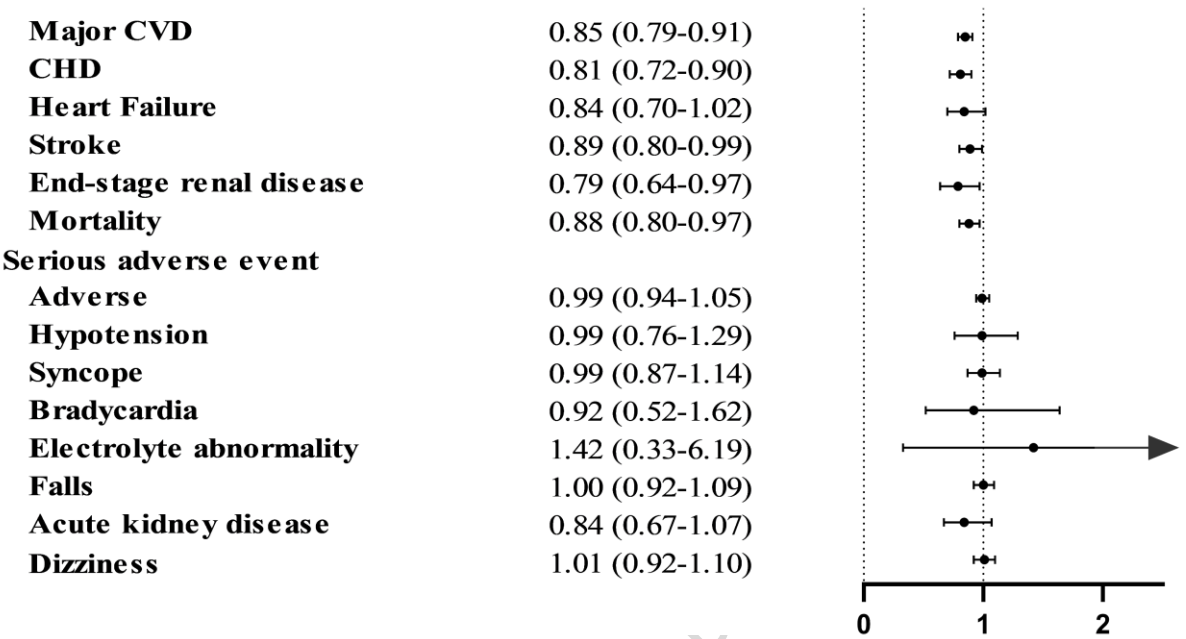
Figure 3. Cumulative incidence of cardiovascular diseases and all-cause mortality

Editorial summary:

Optimal blood pressure target is the cornerstone in hypertension management. Here the authors evaluated the effectiveness and safety of the intensive blood pressure target <130/80mmHg in patients with uncomplicated hypertension.

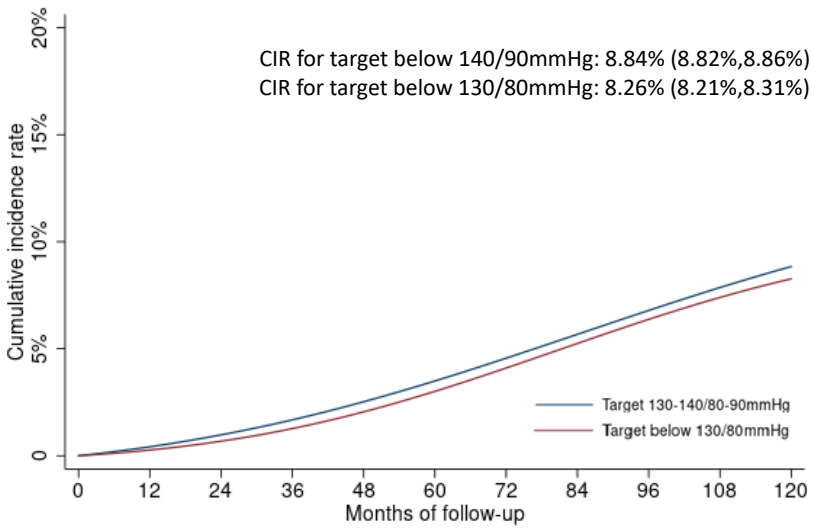
Peer review information: *Nature Communications* thanks Jing Liu, and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. A peer review file is available.


Patients with hypertension diagnosis before 31Dec2013 (N=1,024,068)
Patients aged <18 (N=9)
Patients with history of CVD (N=87,161), DM (N= 152,990) or CKD (N=21,042)
Patients with SBP <130 or DBP < 80 (N=172,993)
Patients with 4 or more antihypertensive drugs (N=416)
Patients with incomplete information of baseline characteristics (N=80,541)
Patients with prescription of aspirin on baseline (N=3,085)
Patients without any adjustment or record of prescription of anti-hypertensive regimens after hypertension diagnosis (N=387,560)
Eligible patients with adjusted prescription at baseline from 01Jan2008 to 31Dec2013 (N= 118,271)
Duplicates assigned to target 130-140/80-90 mmHg (N= 118,271)
Duplicates assigned to target <130/80 mmHg (N= 118,271)

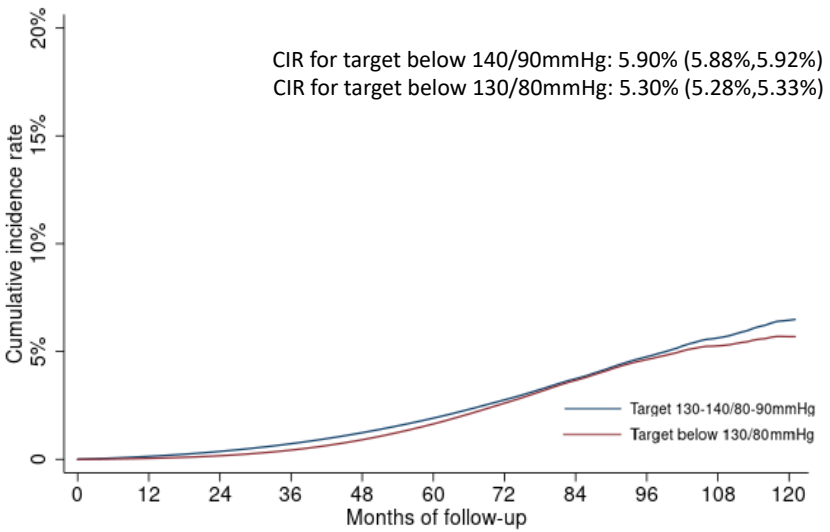


Note: Major CVD: composite outcomes of heart failure, chronic heart disease and stroke; CHD: chronic heart disease; ESRD: end-stage renal disease; Analyses adjusted for sex, age, smoking status, fasting glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, total cholesterol, eGFR, Charlson Comorbidities Index, usage of ACEI/ARB, β-blocker, calcium channel blockers, diuretic; history of fall, syncope and electrolyte abnormality, Specialist, General Outpatient Clinics attendance, accident and emergency and hospitalization (within 1 year before baseline). Statistical significance was defined as a two-tailed *p*-value.

Major CVD



Mortality



*CIR: cumulative incidence rate