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# Impact of achieved blood pressure on renal function decline and first stroke in hypertensive patients with chronic kidney disease

Youbao Li[1], Min Liang[1], Chongfei Jiang[1], Guobao Wang[1], Jianping Li[2], Yan Zhang[2], Fangfang Fan[2], Ningling Sun[3], Yiming Cui[4], Mingli He[5], Genfu Tang[6,7], Delu Yin[8], Xiaoshu Cheng[9], Binyan Wang[1], Yong Huo[2], Xin Xu[1], Fan Fan Hou[1], Xiping Xu[1,10] and Xianhui Qin[1]

[1]Division of Nephrology, Nanfang Hospital, Southern Medical University, National Clinical Research Center for Kidney Disease, State Key Laboratory of Organ Failure Research, Guangdong Provincial Institute of Nephrology, Guangzhou, China, [2]Department of Cardiology, Peking University First Hospital, Beijing, China, [3]Department of Cardiology, Peking University People's Hospital, Beijing, China, [4]Department of Pharmacy, Peking University First Hospital, Beijing, China, [5]Department of Neurology, First People's Hospital, Lianyungang, China, [6]Institute for Biomedicine, Anhui Medical University, Hefei, China, [7]Department of Health Administration, School of Health Administration, Anhui Medical University, Hefei, China, [8]Department of Cardiology, First People's Hospital, Lianyungang, China, [9]Department of Cardiology, Second Affiliated Hospital, Nanchang University, Nanchang, China and [10]AUSA Research Institute, Shenzhen AUSA Pharmed Co. Ltd, Shenzhen, China

Correspondence and offprint requests to: Xianhui Qin; E-mail: pharmaqin@126.com and Xiping Xu; E-mail: xipingxu126@126.com



ORIGINAL ARTICLE

## ABSTRACT

**Background.** The effect of achieved blood pressure (BP) on first stroke and renal function decline among hypertensive patients with mild to moderate chronic kidney disease (CKD) is still uncertain.

**Methods.** In total, 3230 hypertensive patients with estimated glomerular filtration rate 30–60 mL/min/1.73 $m^2$ and/or proteinuria were included in the present analyses. Eligible participants were randomly assigned to a daily treatment of a combined enalapril 10 mg and folic acid 0.8 mg tablet or an enalapril 10 mg tablet alone. Participants were followed up every 3 months. The study outcomes included first stroke and the progression of CKD.

**Results.** The median antihypertensive treatment duration was 4.7 years. Compared with participants with a time-averaged on-treatment systolic blood pressure (SBP) of 135 to ≤140 mmHg, the incidence of total first stroke [1.7% versus 3.3%; hazard ratio (HR), 0.51; 95% confidence interval (CI): 0.26–0.99] and ischemic stroke (1.3% versus 2.8%; HR, 0.46; 95% CI: 0.22–0.98) decreased significantly in those with a time-averaged SBP of ≤135 mmHg. Furthermore, a time-averaged diastolic blood pressure (DBP) of ≤80 mmHg, compared with a time-averaged DBP level of 80 to ≤90 mmHg, was significantly related to a decreased risk of hemorrhagic stroke (0.2% versus 0.9%; HR, 0.18; 95% CI: 0.04–0.80). However, compared with participants with a time-averaged SBP of 135 to ≤140 mmHg, a lower but non-significant trend of CKD progression was found in those with a time-averaged SBP of ≤130 mmHg.

**Conclusions.** A BP treatment level of ≤135/80 mmHg, compared with a BP treatment level of 135–140/80–90 mmHg, could lead to a decreased risk of first stroke in hypertensive patients with mild-to-moderate CKD.

**Keywords:** blood pressure, chronic kidney disease, hypertension, renal function decline, stroke

## INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem [1, 2], leading to a considerably increased risk of end-stage renal disease (ESRD), cardiovascular disease (CVD) and mortality [3–5]. High blood pressure (BP) is the most important risk factor for CVD and development of ESRD [6–8], and lowering BP may reduce the risk of CVD and all-cause mortality in the general population [9, 10]. Because CKD is common and BP levels are often elevated in CKD patients, the management of BP in CKD patients would have an enormous global impact [11]. However, uncertainty remains over the appropriate BP levels for the primary prevention of CVD and renal function decline in hypertensive patients with mild-to-moderate CKD [11].

Stroke is the leading cause of death in China [12]. The China Stroke Primary Prevention Trial (CSPPT) [13] found that the combined use of enalapril and folic acid, compared with enalapril alone, significantly reduced the risk of first stroke by 21% [hazard ratio (HR), 0.79; 95% confidence interval (CI): 0.68–0.93] in Chinese hypertensive patients without a history of major CVDs. The renal sub-study of the CSPPT further found that enalapril–folic acid therapy, compared with enalapril alone, can significantly delay the progression of CKD [odds ratio (OR),

0.45; 95% CI: 0.27–0.76] among patients with mild-to-moderate CKD [14]. Furthermore, a previous *post hoc* analysis of the CSPPT reported that a low systolic blood pressure (SBP) level of 120–130 mmHg, when compared with the higher target SBP range of 130–140 mmHg and the lower SBP range of <120 mmHg, resulted in the lowest risk of first stroke in general hypertensive patients with normal renal function and without CVD or diabetes [15]. The current study, a *post hoc* analysis of the CSPPT and the renal sub-study of the CSPPT, aimed to test the impact of achieved BP on first stroke and renal function decline among hypertensive patients with mild-to-moderate CKD.

## MATERIALS AND METHODS

### Study participants and design

The rationale and study design for the CSPPT and the renal sub-study of the CSPPT have been described previously [13]. Briefly, the CSPPT was a multi-community, randomized, double-blind, controlled trial conducted from 19 May 2008 to 24 August 2013 in 32 communities in Jiangsu (20 communities) and Anhui (12 communities) provinces. The study enrolled a total of 20 702 hypertensive adults without a history of CVD. The renal sub-study enrolled CSPPT participants from the 20 communities in Jiangsu province, excluding those with an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 $m^2$ or who were missing eGFR at baseline. The CSPPT was approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (FWA assurance number: FWA00001263) and registered with ClinicalTrials.gov, NCT00794885.

Detailed inclusion and exclusion criteria for the CSPPT are described elsewhere [13]. Participants with an eGFR <60 mL/min/1.73 $m^2$ and/or proteinuria at baseline were classified as having CKD [14].

The present study was a *post hoc* analysis of the CSPPT (stroke outcomes) and the renal sub-study of the CSPPT (renal outcomes). Participants with eGFR 30–60 mL/min/1.73 $m^2$ and/or proteinuria at baseline were included.

### Intervention and follow-up

Eligible participants were randomly assigned, in a 1:1 ratio, to one of two treatment groups: a daily oral dose of one tablet containing 10 mg enalapril and 0.8 mg folic acid (single tablet combination, the enalapril–folic acid group), or a daily oral dose of one tablet containing 10 mg enalapril only (the enalapril alone group). If BP was not properly controlled during the study period, other classes of antihypertensive medications could be prescribed concomitantly, with the exception of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin type I receptor blockers (ARBs). However, BP control within a normal range [SBP <140 mmHg and diastolic blood pressure (DBP) <90 mmHg] was not mandatory.

Participants were followed up every 3 months. At each visit, BP measurements for each participant were taken, the number of pills taken between visits was counted, and concomitant medications and adverse events were recorded. Seated BP measurements were obtained by trained research staff after the patients had rested for 10 min using a mercury manometer, according to standard methods and using appropriately sized cuffs. Triplicate measurements on the same arm were taken, with at least 2 min between readings. The mean SBP and DBP of the three independent measures were used in analysis.

### Laboratory assays

Methylenetetrahydrofolate reductase (MTHFR) C677T (rs1801133) polymorphisms were detected on an ABI Prism 7900HT sequence detection system (Life Technologies, Carlsbad, CA, USA) using the TaqMan assay. Serum creatinine, lipids, fasting glucose and total homocysteine were measured using automatic clinical analyzers (Beckman Coulter, Brea, CA, USA) at the core laboratory of the National Clinical Research Center for Kidney Disease, Guangzhou, China. Specifically, serum creatinine was measured using an enzymatic assay that had been calibrated to be isotope dilution mass spectrometry traceable. Proteinuria was determined using a dipstick test (Dirui-H100, Changchun, Jilin, China). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [16].

### Outcomes

The primary outcome was a first nonfatal or fatal stroke (ischemic or hemorrhagic), excluding subarachnoid hemorrhage and silent stroke. Secondary outcomes included a composite of cardiovascular events consisting of cardiovascular death, myocardial infarction (MI) and stroke and all-cause death.

Renal outcomes include the following: (i) progression of CKD, defined as a decrease in eGFR of 30% or more and to a level of <60 mL/min/1.73 $m^2$ at the exit visit, or ESRD (eGFR <15 mL/min/1.73 $m^2$ or need for dialysis) and (ii) rapid decline in eGFR, defined as an average decline in eGFR of 5 mL/min/1.73 $m^2$ or more per year.

### Statistical analysis

Of the 20 702 randomized participants in the CSPPT, 3230 participants with eGFR 30–60 mL/min/1.73 $m^2$ and/or proteinuria were included in the current analysis. There were missing values on serum total cholesterol (TC) ($n = 42$), body mass index (BMI, $n = 2$), smoking status ($n = 2$), drinking status ($n = 2$), serum total homocysteine ($n = 31$), serum fasting glucose ($n = 43$) and eGFR levels ($n = 44$) at baseline. Of the 15 104 randomized participants in the renal sub-study of the CSPPT, 1403 participants with eGFR 30–60 mL/min/1.73 $m^2$ and/or proteinuria were included in the final renal outcome analyses. Multiple imputation was used to deal with missing values in the outcome multivariate-adjusted analyses.

Time-averaged BP levels during the treatment period were calculated for each participant using all post-baseline results up to the last visit prior to the date of an event or at the end of follow-up in those without an event. Participants were divided into groups according to time-averaged SBP levels of ≤130, 130 to ≤135, 135 to ≤140 (reference), 140 to ≤145 and >145 mmHg. Moreover, to avoid the potential of arbitrary grouping, we also divided participants according to quintiles of

time-averaged SBP. Time-averaged DBP was categorized into ≤80, 80 to ≤90 (reference) and >90 mmHg.

Means [standard deviation (SD)] or medians (25th percentile and 75th percentile) and proportions were calculated for population characteristics using time-averaged SBP categories (≤130, 130 to ≤135, 135 to ≤140, 140 to ≤145 and >145 mmHg). The differences in population characteristics were compared using ANOVA, the Kruskal–Wallis H test (continuous variables) or Chi-square tests (categorical variables), as appropriate. The Student's *t*-test, the Wilcoxon–Mann–Whitney test (continuous variables) or logistic regression models (categorical variables) were also used to determine any differences between the reference group 135 to ≤140 mmHg and the other time-averaged SBP categories with the Bonferroni correction. Cox proportional hazards models were used to estimate the HRs and 95% CI for the risk of study outcomes including stroke, ischemic stroke, hemorrhagic stroke, composite cardiovascular events and all-cause death; logistic regression models were used to estimate the ORs and 95% CI for the risk of renal outcomes associated with the time-averaged BP levels and were presented as both crude models and adjusted models after adjustment for age, sex, study centers, MTHFR C677T polymorphism, study treatment groups, BMI, SBP, eGFR, fasting glucose, TC and urinary protein at baseline.

A two-tailed $P < 0.05$ was considered to be statistically significant in all analyses. R software, version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/) was used for all statistical analyses.

## RESULTS

### Study participants and baseline characteristics

A total of 3230 participants in the CSPPT with eGFR 30–60 mL/min/1.73 $m^2$ and/or proteinuria at baseline were included in the analyses. The flow of the participants is presented in Supplementary data, Figure S1. Compared with the entire cohort of the CSPPT ($n = 20\,702$), patients with CKD tended to have higher levels of SBP, DBP, fasting glucose and homocysteine, and were more likely to be older, male, smokers and under antihypertensive treatment at baseline (Table 1). Of the 3230 participants, 2987 (92.8%) had proteinuria. Baseline characteristics of the five groups of CKD participants according to the time-averaged SBP levels (≤130, 130 to ≤135, 135 to ≤140, 140 to ≤145 and >145 mmHg) during the treatment period are summarized in Table 1. Comparing highest to lowest, participants were more likely to be older, female and to have higher baseline BP levels and fasting glucose concentrations.

A total of 1403 participants in the renal sub-study of the CSPPT with eGFR 30–60 mL/min/1.73 $m^2$ and/or proteinuria at baseline was included in the analyses of renal outcomes (Supplementary data, Figure S2). Baseline characteristics of these participants are presented in Supplementary data, Table S1.

### Impact of time-averaged BP during the treatment period on renal outcomes

For the primary renal outcome (progression of CKD), the median length of follow-up was 4.3 years (interquartile range, 4.1–4.6). A median of 16 (interquartile range, 14–18) BP measurements was taken during the treatment period.

The associations between time-averaged BP and the progression of CKD or rapid decline in eGFR are presented in Supplementary data, Figure S3 and Table S2 and Table 2. Overall, no significant associations between time-averaged BP and renal outcomes were observed. However, compared with participants with a time-averaged SBP of 135 to ≤140 mmHg, those with a time-averaged SBP of <130 mmHg showed a lower trend (2.7% versus 3.7%; OR, 0.89; 95% CI: 0.28–2.80) and those with a time-averaged SBP of >145 mmHg showed a higher trend (5.8% versus 3.7%; OR, 1.45; 95% CI: 0.66–3.20) for the risk of CKD progression (Table 2).

### Impact of time-averaged BP during the treatment period on first stroke

For the primary outcome (first stroke), the median length of follow-up was 4.7 years (interquartile range, 4.3–4.9). A median of 16 (interquartile range, 12–18) BP measurements was taken during the treatment period.

Overall, the risks of total first stroke (per 5 mmHg decrement; HR, 0.79; 95% CI: 0.75–0.83) and ischemic stroke (per 5 mmHg decrement; HR, 0.82; 95% CI: 0.77–0.87) decreased with the reduction of time-averaged SBP during the treatment period. Compared with participants with a time-averaged SBP of 135 to ≤140 mmHg, the incidence of total first stroke (1.7% versus 3.3%; HR, 0.51; 95% CI: 0.26–0.99) and ischemic stroke (1.3% versus 2.8%; HR, 0.46; 95% CI: 0.22–0.98) decreased significantly in those with a time-averaged SBP of ≤135 mmHg. Furthermore, a greater risk reduction was observed in participants with a time-averaged SBP of ≤130 mmHg (total first stroke: 1.3% versus 3.3%; HR, 0.39; 95% CI: 0.15–0.98; ischemic stroke: 1.1% versus 2.8%; HR, 0.39; 95% CI: 0.14–1.08) (Table 3). Consistently, the risk of total first stroke and ischemic stroke increased along with the increase in quintiles of time-averaged SBP during the treatment period (P for trend <0.001) (Figure 1). Similar trends were observed for hemorrhagic stroke, the composite of cardiovascular events and all-cause death (Table 3 and Supplementary data, Table S3 and Figure S4). Moreover, similar results were found in participants with proteinuria (Supplementary data, Table S4) or eGFR <60 mL/min/1.73 $m^2$ (Supplementary data, Table S5) at baseline.

The risk of total first stroke (per 5 mmHg decrement; HR, 0.67; 95% CI: 0.61–0.73), ischemic stroke (per 5 mmHg decrement; HR, 0.68; 95% CI: 0.62–0.76) and hemorrhagic stroke (per 5 mmHg decrement; HR, 0.58; 95% CI: 0.48–0.69) also decreased with the reduction of time-averaged DBP during the treatment period. Compared with participants with a time-averaged DBP of 80 to ≤90 mmHg, the incidence of hemorrhagic stroke decreased significantly in those with a time-averaged DBP of ≤80 mmHg (0.2% versus 0.9%; HR, 0.18; 95% CI: 0.04–0.80) (Table 4). Similar trends were observed for the composite of cardiovascular events and all-cause death (Supplementary data, Table S6).

**Table 1. Characteristics of CKD patients by time-averaged on-treatment SBP categories in the CSPPT[a]**

| | All CSPPT participants ($n = 20\,702$) | CKD patients ($n = 3230$) | Time-averaged on-treatment SBP (mmHg) | | | | | P-value |
|---|---|---|---|---|---|---|---|---|
| | | | ≤130 ($n = 474$) | 130 to ≤135 ($n = 468$) | 135 to ≤140 ($n = 577$) | 140 to ≤ 145 ($n = 515$) | >145 ($n = 1196$) | |
| Age (years) | 60.0 (7.5) | 61.2 (7.8) | 59.1 (8.2)[b] | 60.8 (7.5) | 61.2 (7.7) | 62.1 (7.8) | 61.8 (7.8) | <0.001 |
| Male, *n* (%) | 8497 (41.0) | 1489 (46.1) | 219 (46.2) | 254 (54.3)[b] | 266 (46.1) | 245 (47.6) | 505 (42.2) | <0.001 |
| BMI (kg/m$^2$) | 24.9 (3.7) | 24.6 (3.8) | 24.2 (3.5) | 24.3 (3.8) | 24.6 (3.6) | 24.6 (3.8) | 24.9 (4.0) | 0.008 |
| MTHFR C677T genotypes, *n* (%) | | | | | | | | 0.072 |
| CC | 5652 (27.3) | 936 (29.0) | 121 (25.5) | 137 (29.3) | 191 (33.1) | 141 (27.4) | 346 (28.9) | |
| CT | 10 176 (49.2) | 1589 (49.2) | 248 (52.3) | 234 (50.0) | 279 (48.4) | 241 (46.8) | 587 (49.1) | |
| TT | 4874 (23.5) | 705 (21.8) | 105 (22.2) | 97 (20.7) | 107 (18.5) | 133 (25.8) | 263 (22.0) | |
| Enalapril group, *n* (%) | 10 354 (50.0) | 1560 (48.3) | 238 (50.2) | 232 (49.6) | 264 (45.8) | 238 (46.2) | 588 (49.2) | 0.441 |
| Baseline blood pressure (mmHg) | | | | | | | | |
| Systolic | 166.9 (20.4) | 168.5 (23.0) | 153.7 (18.4)[b] | 160.4 (18.7)[b] | 165.0 (18.3) | 169.5 (19.9)[b] | 178.9 (24.5)[b] | <0.001 |
| Diastolic | 94.1 (11.9) | 94.8 (13.1) | 92.1 (11.4) | 92.9 (12.5) | 93.7 (12.1) | 93.9 (12.5) | 97.5 (14.2)[b] | <0.001 |
| Cardiovascular risk factors, *n* (%) | | | | | | | | |
| Current smoker | 4869 (23.5) | 809 (25.1) | 103 (21.7) | 126 (27.0) | 134 (23.2) | 146 (28.4) | 300 (25.1) | 0.021 |
| Self-reported hyperlipidemia | 562 (2.7) | 85 (2.6) | 16 (3.4) | 16 (3.4) | 9 (1.6) | 13 (2.5) | 31 (2.6) | 0.311 |
| Diabetes | 2288 (11.2) | 494 (15.5) | 65 (13.9) | 58 (12.4) | 80 (14.0) | 90 (17.6) | 201 (17.1) | 0.053 |
| Laboratory results | | | | | | | | |
| Fasting glucose (mmol/L) | 5.8 (1.7) | 6.0 (2.2) | 5.7 (2.0) | 5.8 (1.9) | 5.8 (2.1) | 6.2 (2.5) | 6.1 (2.2)[b] | <0.001 |
| TC (mmol/L) | 5.5 (1.2) | 5.4 (1.3) | 5.3 (1.3) | 5.3 (1.2) | 5.4 (1.3) | 5.5 (1.4) | 5.5 (1.3) | 0.046 |
| HDL-C (mmol/L) | 1.3 (0.4) | 1.3 (0.4) | 1.3 (0.4) | 1.3 (0.4) | 1.3 (0.4) | 1.3 (0.4) | 1.3 (0.4) | 0.503 |
| Triglycerides[c] (mmol/L) | 1.4 (1.1–2.0) | 1.4 (1.1–2.0) | 1.4 (1.1–1.8) | 1.4 (1.1–1.9) | 1.4 (1.1–2.0) | 1.4 (1.1–2.0) | 1.4 (1.1–2.0) | 0.012 |
| eGFR (mL/min/1.73 m$^2$) | 93.5 (13.2) | 87.5 (18.4) | 88.2 (18.7) | 88.6 (17.6) | 87.5 (18.7) | 86.7 (17.7) | 87.2 (18.7) | 0.306 |
| Homocysteine[c] (μmol/L) | 12.5 (10.5–15.5) | 13.6 (11.3–17.1) | 13.4 (11.0–16.7) | 13.8 (11.6–17.0) | 13.5 (11.0–16.4) | 13.5 (11.3–17.9) | 13.7 (11.3–17.6) | 0.039 |
| Proteinuria, *n* (%) | 3010 (15.1) | 2987 (92.8) | 437 (92.8) | 442 (94.8)[b] | 517 (90.1) | 469 (91.6) | 1122 (93.9)[b] | 0.013 |
| eGFR categories (mL/min/1.73 m$^2$) | | | | | | | | 0.792 |
| ≥90 | 13909 (68.6) | 1747 (54.8) | 259 (55.5) | 265 (56.9) | 319 (55.9) | 264 (51.8) | 640 (54.6) | |
| 60 to <90 | 5986 (29.5) | 1046 (32.8) | 151 (32.3) | 152 (32.6) | 177 (31.0) | 180 (35.3) | 386 (32.9) | |
| 30 to <60 | 393 (1.9) | 393 (12.3) | 57 (12.2) | 49 (10.5) | 75 (13.1) | 66 (12.9) | 146 (12.5) | |
| Medication use, *n* (%) | | | | | | | | |
| Antihypertensive drugs | 9536 (46.1) | 1602 (49.6) | 246 (51.9) | 215 (45.9) | 275 (47.7) | 261 (50.7) | 605 (50.6) | 0.279 |
| Glucose-lowering drugs | 317 (1.5) | 73 (2.3) | 14 (3.0) | 5 (1.1) | 14 (2.4) | 19 (3.7) | 21 (1.8) | 0.036 |
| Lipid-lowering drugs | 166 (0.8) | 26 (0.8) | 6 (1.3) | 5 (1.1) | 4 (0.7) | 3 (0.6) | 8 (0.7) | 0.671 |
| Antiplatelet drugs | 607 (2.9) | 83 (2.6) | 8 (1.7) | 7 (1.5) | 19 (3.3) | 13 (2.5) | 36 (3.0) | 0.217 |

[a]For continuous variables, values are presented as mean (SD).
[b]$P < 0.01$ when compared with SBP 135 to ≤ 140 mmHg group.
[c]Median (25th–75th).
FA, folic acid; HDL-C, high-density lipoprotein cholesterol.

### Stratified analyses for first stroke

Stratified analyses were performed by sex, age (<60 versus ≥60 years), baseline SBP levels (<160 versus ≥160 mmHg), eGFR levels (30–90 versus ≥90 mL/min/1.73 m$^2$) and study treatment groups (enalapril versus enalapril + folic acid). A lower risk of first stroke was observed in patients with a time-averaged SBP ≤135 mmHg (versus 135 to ≤140 mmHg) in all subgroups (Figure 2).

## DISCUSSION

This study demonstrates for the first time that a SBP treatment level of ≤135 mmHg, compared with a SBP treatment level of 135 to ≤140 mmHg, was significantly associated with a decreased risk of first stroke, especially ischemic stroke. Furthermore, a DBP treatment level of ≤80 mmHg, compared with a DBP treatment level of 80 to ≤90 mmHg, was related to

**Table 2. The associations between time-averaged on-treatment SBP and renal outcomes in hypertensive patients with mild or moderate CKD in the renal sub-study of the CSPPT**

| Time-averaged SBP categories (mmHg) | Time-averaged SBP, mean (SD) (mmHg) | Events (%) | Unadjusted | | Adjusted[a] | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | P | OR (95% CI) | P |
| Progression of CKD | | | | | | |
| Continuous measure (per 5 mmHg decrement) | 142.8 (12.4) | 69 (4.9) | 0.96 (0.87–1.06) | 0.387 | 1.00 (0.89–1.12) | 0.968 |
| Categorical measure | | | | | | |
| ≤135 | 129.1 (4.7) | 17 (4.4) | 1.20 (0.54–2.85) | 0.668 | 1.38 (0.59–3.23) | 0.463 |
| ≤130 | 125.2 (4.0) | 5 (2.7) | 0.73 (0.22–2.15) | 0.579 | 0.89 (0.28–2.80) | 0.841 |
| 130 to ≤135 | 132.6 (1.5) | 12 (5.9) | 1.63 (0.68–4.08) | 0.277 | 1.75 (0.71–4.35) | 0.226 |
| 135 to ≤140 | 137.5 (1.4) | 9 (3.7) | Ref | – | Ref | – |
| 140 to ≤145 | 142.4 (1.4) | 12 (5.0) | 1.38 (0.57–3.44) | 0.474 | 1.21 (0.49–3.00) | 0.678 |
| >145 | 155.1 (9.0) | 31 (5.8) | 1.60 (0.54–2.85) | 0.668 | 1.45 (0.66–3.20) | 0.360 |
| Rapid decline in eGFR | | | | | | |
| Continuous measure (per 5 mmHg decrement) | 142.8 (12.4) | 150 (10.7) | 0.94 (0.88–1.00) | 0.062 | 0.97 (0.90–1.05) | 0.423 |
| Categorical measure | | | | | | |
| ≤135 | 129.1 (4.7) | 39 (10.1) | 1.25 (0.72–2.24) | 0.433 | 1.27 (0.71–2.26) | 0.425 |
| ≤130 | 125.2 (4.0) | 13 (7.1) | 0.85 (0.40–1.75) | 0.667 | 0.87 (0.41–1.83) | 0.706 |
| 130 to ≤135 | 132.6 (1.5) | 26 (12.8) | 1.64 (0.89–3.06) | 0.116 | 1.61 (0.86–3.02) | 0.134 |
| 135 to ≤140 | 137.5 (1.4) | 20 (8.2) | Ref | – | Ref | – |
| 140 to ≤145 | 142.4 (1.4) | 19 (8.0) | 0.97 (0.50–1.87) | 0.921 | 0.86 (0.44–1.68) | 0.667 |
| >145 | 155.1 (9.0) | 72 (13.4) | 1.73 (1.05–2.98) | 0.039 | 1.45 (0.85–2.50) | 0.175 |

[a]Adjusted for age, sex, study treatment groups, MTHFR C677T polymorphisms, BMI, SBP, eGFR, fasting glucose, TC and urinary protein at baseline.

**Table 3. The associations between time-averaged on-treatment SBP and first stroke in hypertensive patients with mild or moderate CKD in the CSPPT**

| Time-averaged SBP categories (mmHg) | Time-averaged SBP, mean (SD) (mmHg) | Events (%) | Unadjusted | | Adjusted[a] | |
|---|---|---|---|---|---|---|
| | | | HR (95% CI) | P | HR (95% CI) | P |
| First stroke | | | | | | |
| Continuous measure (per 5 mmHg decrement) | 142.4 (12.8) | 135 (4.2) | 0.77 (0.74–0.81) | <0.001 | 0.79 (0.75–0.83) | <0.001 |
| Categorical measure | | | | | | |
| ≤135 | 128.9 (4.8) | 16 (1.7) | 0.51 (0.26–1.00) | 0.048 | 0.51 (0.26–0.99) | 0.049 |
| ≤130 | 125.1 (3.9) | 6 (1.3) | 0.38 (0.15–0.95) | 0.039 | 0.39 (0.15–0.98) | 0.045 |
| 130 to ≤135 | 132.7 (1.4) | 10 (2.1) | 0.64 (0.30–1.39) | 0.261 | 0.63 (0.29–1.35) | 0.231 |
| 135 to ≤140 | 137.5 (1.4) | 19 (3.3) | Ref | – | Ref | – |
| 140 to ≤145 | 142.5 (1.4) | 17 (3.3) | 1.00 (0.52–1.93) | 0.988 | 0.89 (0.46–1.71) | 0.722 |
| >145 | 155.4 (9.9) | 83 (6.9) | 2.22 (1.35–3.65) | 0.002 | 1.77 (1.06–2.95) | 0.028 |
| Ischemic stroke | | | | | | |
| Continuous measure (per 5 mmHg decrement) | 142.4 (12.8) | 104 (3.2) | 0.79 (0.75–0.83) | <0.001 | 0.82 (0.77–0.87) | <0.001 |
| Categorical measure | | | | | | |
| ≤135 | 128.9 (4.8) | 12 (1.3) | 0.46 (0.22–0.96) | 0.040 | 0.46 (0.22–0.98) | 0.043 |
| ≤130 | 125.1 (3.9) | 5 (1.1) | 0.38 (0.14–1.03) | 0.057 | 0.39 (0.14–1.08) | 0.069 |
| 130 to ≤135 | 132.7 (1.4) | 7 (1.5) | 0.54 (0.22–1.30) | 0.170 | 0.52 (0.21–1.27) | 0.153 |
| 135 to ≤140 | 137.5 (1.4) | 16 (2.8) | Ref | – | Ref | – |
| 140 to ≤145 | 142.5 (1.4) | 14 (2.7) | 0.98 (0.48–2.01) | 0.963 | 0.82 (0.40–1.70) | 0.599 |
| >145 | 155.4 (9.9) | 62 (5.2) | 1.96 (1.13–3.39) | 0.017 | 1.50 (0.85–2.64) | 0.158 |
| Hemorrhagic stroke | | | | | | |
| Continuous measure (per 5 mmHg decrement) | 142.4 (12.8) | 31 (1.0) | 0.77 (0.71–0.83) | <0.001 | 0.75 (0.68–0.83) | <0.001 |
| Categorical measure | | | | | | |
| ≤135 | 128.9 (4.8) | 4 (0.4) | 0.81 (0.18–3.63) | 0.786 | 0.83 (0.18–3.75) | 0.811 |
| ≤130 | 125.1 (3.9) | 1 (0.2) | 0.40 (0.04–3.88) | 0.432 | 0.40 (0.04–3.86) | 0.427 |
| 130 to ≤135 | 132.7 (1.4) | 3 (0.6) | 1.23 (0.25–6.08) | 0.803 | 1.30 (0.26–6.47) | 0.749 |
| 135 to ≤140 | 137.5 (1.4) | 3 (0.5) | Ref | – | Ref | – |
| 140 to ≤145 | 142.5 (1.4) | 3 (0.6) | 1.12 (0.23–5.57) | 0.886 | 1.22 (0.24–6.07) | 0.810 |
| >145 | 155.4 (9.9) | 21 (1.8) | 3.50 (1.04–11.75) | 0.042 | 3.34 (0.98–11.37) | 0.054 |

[a]Adjusted for age, sex, study centers, study treatment groups, MTHFR C677T polymorphisms, BMI, SBP, eGFR, fasting glucose, TC and urinary protein at baseline.

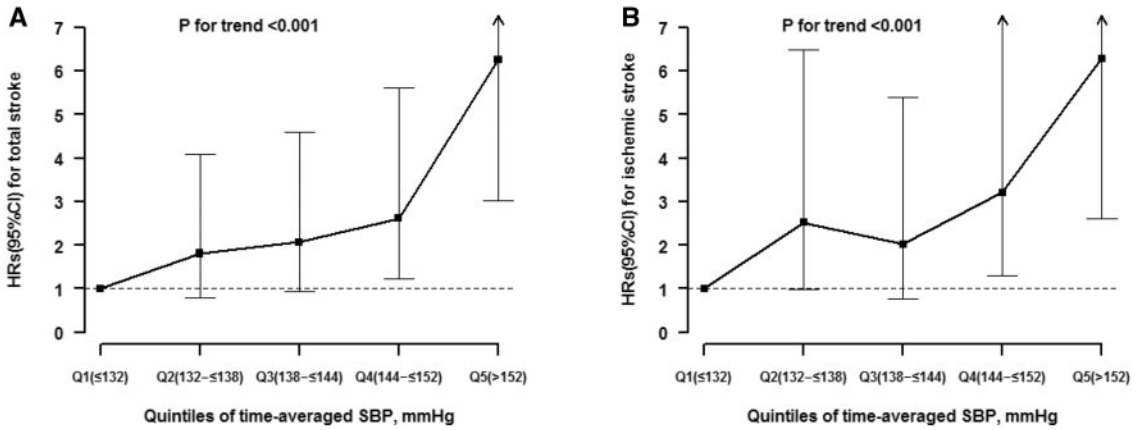


**FIGURE 1:** The association between time-averaged SBP by quintiles and risk of first stroke (**A**), and first ischemic stroke (**B**). Adjusted for age, sex, study centers, study treatment groups, MTHFR C677T polymorphisms, BMI, SBP, eGFR, fasting glucose, TC and urinary protein at baseline.

**Table 4. The associations between time-averaged on-treatment DBP and first stroke in hypertensive patients with mild or moderate CKD in the CSPPT**

| Time-averaged DBP categories (mmHg) | Time-averaged DBP, mean (SD) (mmHg) | Events (%) | Unadjusted | | Adjusted[a] | |
|---|---|---|---|---|---|---|
| | | | HR (95% CI) | P | HR (95% CI) | P |
| First stroke | | | | | | |
| Continuous measure (per 5 mmHg decrement) | 83.3 (8.5) | 135 (4.2) | 0.69 (0.63–0.75) | <0.001 | 0.67 (0.61–0.73) | <0.001 |
| Categorical measure | | | | | | |
| ≤80 | 74.9 (4.1) | 31 (2.7) | 0.82 (0.52–1.30) | 0.409 | 0.76 (0.48–1.22) | 0.261 |
| 80 to ≤90 | 84.7 (2.8) | 45 (3.2) | Ref | – | Ref | – |
| >90 | 95.7 (5.7) | 59 (9.1) | 3.03 (2.06–4.47) | <0.001 | 3.10 (2.08–4.63) | <0.001 |
| Ischemic stroke | | | | | | |
| Continuous measure (per 5 mmHg decrement) | 83.3 (8.5) | 104 (3.2) | 0.73 (0.67–0.81) | <0.001 | 0.68 (0.62–0.76) | <0.001 |
| Categorical measure | | | | | | |
| ≤80 | 74.9 (4.1) | 29 (2.5) | 1.09 (0.66–1.80) | 0.741 | 0.91 (0.54–1.52) | 0.709 |
| 80 to ≤90 | 84.7 (2.8) | 32 (2.3) | Ref | – | Ref | – |
| >90 | 95.7 (5.7) | 43 (6.6) | 3.08 (1.95–4.87) | <0.001 | 3.54 (2.20–5.69) | <0.001 |
| Hemorrhagic stroke | | | | | | |
| Continuous measure (per 5 mmHg decrement) | 83.3 (8.5) | 104 (3.2) | 0.62 (0.54–0.71) | <0.001 | 0.58 (0.48–0.69) | <0.001 |
| Categorical measure | | | | | | |
| ≤80 | 74.9 (4.1) | 2 (0.2) | 0.18 (0.04–0.81) | 0.026 | 0.18 (0.04–0.80) | 0.025 |
| 80 to ≤90 | 84.7 (2.8) | 13 (0.9) | Ref | – | Ref | – |
| >90 | 95.7 (5.7) | 16 (2.5) | 2.79 (1.34–5.81) | 0.006 | 2.75 (1.28–5.91) | 0.010 |

[a]Adjusted for age, sex, study centers, study treatment groups, MTHFR C677T polymorphisms, BMI, SBP, eGFR, fasting glucose, TC and urinary protein at baseline.

a lower rate of hemorrhagic stroke in hypertensive patients with mild-to-moderate CKD.

In fact, most previous BP-lowering trials conducted in CKD participants, including the Modification of Diet in Renal Disease (MDRD) Study [17], the African American Study of Kidney Disease and Hypertension (AASK) Study [18] and the Blood-Pressure Control for Renoprotection in Patients with Non-diabetic Chronic Renal Disease (REIN-2) study [19], failed to show any benefit in clinical outcomes for the low versus usual BP targets. However, the 2012 Kidney Disease: Improving Global Outcomes guidelines suggest a BP treatment target of <140/90 mmHg in CKD patients who have no proteinuria and a stricter target of <130/80 mmHg in CKD patients with proteinuria [11]. The recommendation was primarily based on the *post hoc* or subgroup analyses of the AASK study [low BP target, mean arterial pressure (MAP) ≤92 mmHg; usual BP target, MAP 102–107 mmHg] [18, 20] and the MDRD study (low BP target, MAP ≤92 mmHg; usual BP target, MAP ≤107 mmHg) [21], both of which showed a benefit with regard to kidney outcomes with a lower target BP in specific groups, such as patients with higher urine protein levels. More importantly, it should be noted that in both the MDRD study and the AASK study, MAP was targeted rather than SBP and DBP, and a specific MAP may translate into different SBP and DBP treatment goals, depending on the individual participant. Therefore, the 2013 European Society of Hypertension–European Society of Cardiology guidelines [22] and the 2014 JNC-8 report [23] recommend a SBP goal of <140/90 mmHg in patients with CKD. This difference in guidelines illustrates that the evidence to determine the ideal BP goal in CKD patients is scanty and confusing.

Most importantly, there have been few BP target trials involving CKD patients focused on hard CVD outcomes. The Hypertension Optimal Treatment (HOT) study included patients with DBP levels between 100 mmHg and 115 mmHg

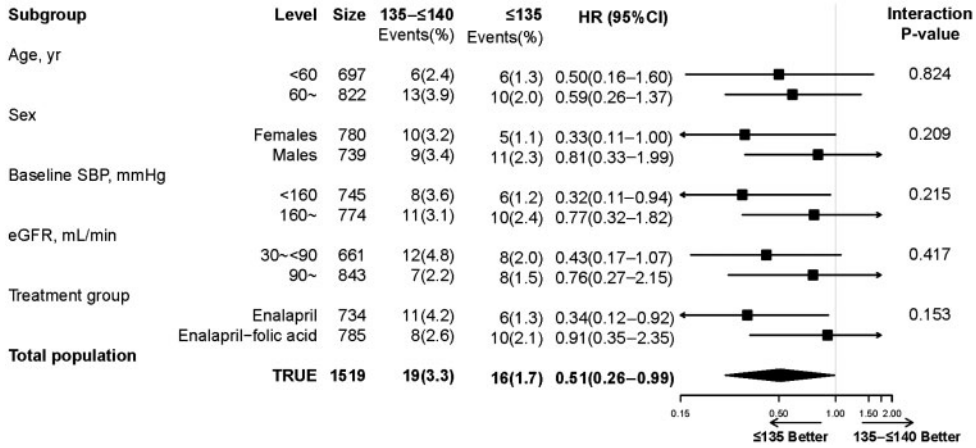


**FIGURE 2:** Stratified analysis of the association between risk of first stroke and time-averaged SBP levels of ≤135 versus 135 to ≤140 mmHg. Adjusted for age, sex, study centers, study treatment groups, MTHFR C677T polymorphisms, BMI, SBP, eGFR, fasting glucose, TC and urinary protein at baseline.

(mean 105 mmHg). Subgroup analyses from the HOT study found no benefit for CVD outcomes associated with a lower DBP target in patients with CKD [24]. It should be noted that data on proteinuria were not available in the HOT study. The Systolic Blood Pressure Intervention Trial (SPRINT) included 9361 patients with SBP ≥130 mmHg and increased cardiovascular risk, and excluded those with diabetes and a 24-h urine protein excretion of >1 g/day. It aimed to evaluate cardiovascular and kidney outcomes in patients randomized to a SBP treatment goal of <140 versus <120 mmHg. In the subgroup analysis, among participants with CKD (eGFR 20–59 mL/min/1.73 $m^2$, $n = 2646$) at baseline, there were no differences between the two groups in the primary composite outcome (MI, other acute coronary syndromes, stroke, heart failure or death from cardiovascular causes) [25]. However, a *post hoc* analysis of the Irbesartan Diabetic Nephropathy Trial, which included adults who had overt diabetic nephropathy and a baseline 24-h urine protein of >0.9 g/day, reported that progressively lower achieved SBP to 120 mmHg predicted a decrease in cardiovascular mortality and congestive heart failure (CHF). A SBP below this threshold was associated with increased risks for cardiovascular deaths and CHF events [26]. In the sub-study of the Action to Control Cardiovascular Risk in Diabetes study, among participants with type 2 diabetes and mild-to-moderate CKD (>76.8% with albuminuria) at baseline, an intensive BP treatment (SBP <120 mmHg, mean: 122 mmHg) was associated with a trend toward reduced rates for stroke (HR, 0.62; 95% CI: 0.36–1.08), when compared with a standard BP treatment (SBP <140 mmHg, mean: 134 mmHg) [27]. Consistently, our current study included participants with mild-to-moderate CKD, of which 92.8% had proteinuria at baseline. Compared with participants with a time-averaged SBP of 135 to ≤140 mmHg, the incidence of stroke decreased significantly in patients with a time-averaged SBP of ≤135 mmHg. Furthermore, a time-averaged DBP of ≤80 mmHg, compared with a DBP level of 80 to ≤90 mmHg, was significantly related to a decreased risk of hemorrhagic stroke. These results suggest that the presence of proteinuria may possibly modify the effect of intensive BP reduction on CVD outcomes in patients with CKD. These results still warrant further confirmation.

We did not observe a significant association between treated BP and renal function decline. There are several possible explanations for this outcome. First, the current study did not have enough power to test the relationship of treated BP with CKD progression. Second, most of the patients had an eGFR level of ≥60 mL/min/1.73 $m^2$. This study also had several limitations. First, this was a *post hoc* analysis of the CSPPT. Despite extensive adjustments for known factors, we could not exclude the possibility that unrecorded risk factors may explain some of our findings. Second, renin–angiotensin–system blockers (ACEIs or ARBs) have been recommended in the presence of proteinuria [28]. While proteinuria was highly prevalent in the current study, it was a *post hoc* analysis of the CSPPT, and except for a fixed dose of 10 mg/day enalapril, other ACEIs or ARBs could not be prescribed in the CSPPT. Third, a previous analysis of the CSPPT found that the association between time-averaged SBP and the risk of first stroke followed a U-shaped curve, with increased risks above and below the reference range of 120–130 mmHg in general hypertensive patients with normal renal function and without CVD or diabetes [15]. However, due to the small number of participants and events in the groups with time-averaged SBP <120 mmHg or DBP <70 mmHg, the current study could not evaluate the possible U-shaped relationship between achieved BP and the risk of stroke or all-cause death in hypertensive patients with CKD. Furthermore, although a linear association between time-averaged SBP and the risk of stroke was observed in our study, the number of events in the lower BP categories (<130 mmHg) was rather low. Most importantly, the current study included only 393 patients with eGFR <60 mL/min/1.73 $m^2$, and therefore had limited power to examine the association between achieved BP and first stroke in these patients. Due to these limitations, an adequately powered, large-scale, randomized trial in patients with CKD is essential to further explore these important issues.

In conclusion, a BP treatment level of ≤135/80 mmHg, compared with a BP treatment level of 135–140/80–90 mmHg,

could lead to a decreased risk of first stroke in hypertensive patients with mild-to-moderate CKD.

## AUTHORS' CONTRIBUTIONS

X.Q., Y.L., M.L., C.J., G.W., J.L., Y.Z., F.F., N.S., Y.C., M.H., G.T., D.Y., X.C., B.W., Y.H., Xin Xu, F.F.H. and Xiping Xu: study concept and design; X.Q., Y.L., M.L., C.J., G.W., J.L., Y.Z., F.F., N.S., Y.C., M.H., G.T., D.Y., X.C., B.W., Y.H. and F.F.H.: acquisition of data; X.Q. and Y.L.: data management and statistical analysis; X.Q. and Y.L.: drafting of the manuscript; X.Q., Y.L., M.L., C.J., G.W., J.L., Y.Z., F.F., N.S., Y.C., M.H., G.T., D.Y., X.C., B.W., Y.H., Xin Xu, F.F.H. and Xiping Xu: critical revision of the manuscript for important intellectual content; X.Q., Y.L., M.L., C.J., G.W., J.L., Y.Z., F.F., N.S., Y.C., M.H., G.T., D.Y., X.C., B.W., Y.H., Xin Xu, F.F.H. and Xiping Xu: final approval of the version to be published.

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## SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

## CONFLICT OF INTEREST STATEMENT

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(See related article by Covic and Voroneanu. Chronic kidney disease and stroke: more observations but no trials. *Nephrol Dial Transplant* 2018; 33: 367–370)

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ORIGINAL ARTICLE

# Performance of glomerular filtration rate estimating equations in a community-based sample of Blacks and Whites: the multiethnic study of atherosclerosis

Lesley A. Inker[1], Andrew S. Levey[1], Hocine Tighiouart[2,3], Tariq Shafi[4], John H. Eckfeldt[5], Craig Johnson[6], Aghogho Okparavero[1], Wendy S. Post[4], Josef Coresh[4] and Michael G. Shlipak[7]

[1]Division of Nephrology, Tufts Medical Center, Boston, MA, USA, [2]Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, USA, [3]Tufts Clinical and Translational Science Institute, Tufts University, Boston, MA, USA, [4]Johns Hopkins University, Baltimore, MD, USA, [5]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA, [6]Department of Biostatistics, School of Public Health and Community Medicine, University of Washington, Seattle, WA, USA and [7]Division of Nephrology, University of California, San Francisco, CA, USA

Correspondence and offprint requests to: Lesley A. Inker; E-mail: Linker@tuftsmedicalcenter.org

## ABSTRACT

**Background.** The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations are recommended for glomerular filtration rate (GFR) estimation in the general population. They have not been evaluated in community-based populations, including Blacks at higher levels of GFR, but are commonly applied in such populations.

**Methods.** In an ancillary study of Multi-Ethnic Study of Atherosclerosis conducted at one site, we evaluated the performance of the CKD-EPI equations for creatinine (eGFRcr), cystatin C (eGFRcys) or the combination (eGFRcr–cys) compared with GFR measured as plasma clearance of iohexol.