THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Zeng G, Bidel Z, Yang Q, et al. Pharmacological blood-pressure lowering for the prevention of cardiovascular disease and death across the full spectrum of chronic kidney disease severity: an individual-participant data meta-analysis. *Lancet* 2026; **407:** 1626–38.

Supplementary Materials

Pharmacological blood pressure-lowering for prevention of cardiovascular disease and death across the full spectrum of chronic kidney disease severity: an individual participant data meta-analysis of 46 randomised controlled trials

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Supplementary Methods

Method S1. Estimated glomerular filtration rate calculation

The estimated glomerular filtration rate (eGFR) levels were calculated according to the 2021 race-free Chronic Kidney Disease Epidemiology Collaboration equation:

$$eGFR = 142 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012 \text{ [if female]}$$

Abbreviations/units:

- eGFR = mL/min/1.73 m²
- Scr (serum creatinine) = mg/dL
- $\kappa = 0.7$ (females) or 0.9 (males)
- $\alpha = -0.241$ (females) or -0.302 (males)
- min = indicates the minimum of Scr/κ or 1
- max = indicates the maximum of Scr/κ or 1

Method S2. Standardisation of proportional effects

Standardisation of effect sizes is appropriate when the objective is to pool results from various blood pressure (BP)-lowering trials to investigate BP-lowering treatment effect per se on risk of outcomes and to express the relative treatment effect for a fixed level of BP reduction.[1] This is necessary because the magnitude of BP reduction often varies across trials. The established linear association between the magnitude of BP reduction and the relative risk reduction for major cardiovascular outcomes underpins this approach.[2,3]

A key advantage of standardisation is its ability to include a wide range of trials without setting arbitrary exclusion thresholds for the achieved BP reduction. For instance, head-to-head trials comparing different drugs may yield only modest BP differences (e.g., 1–2 mmHg). Rather than excluding these valuable data, standardisation permits their inclusion, thereby enhancing the overall statistical power of the meta-analysis. In practical terms, this method adjusts for heterogeneity by assigning proportionally greater weight to trials that achieve larger BP reductions, reflecting their greater contribution to understanding the BP-mediated effect. Without such standardisation, a pooled effect size (e.g., a hazard ratio) would lack a clear scale, rendering clinical interpretation difficult.[1]

To implement this approach, effect sizes are standardised to a clinically meaningful level, such as a 5 mmHg reduction in systolic BP and a 3 mmHg reduction in diastolic BP. In a one-stage individual participant data meta-analysis, this is typically achieved by incorporating the average BP reduction for each trial (Δ) as a continuous variable in a Cox proportional hazards model. The model includes terms for the treatment group, Δ, and, crucially, an interaction term between treatment and Δ (treatment $\times$ Δ). This interaction term allows the treatment effect to be scaled by the magnitude of BP reduction in each trial. The model can be further expanded to explore effect modification by including additional interaction terms with baseline characteristics, such as chronic kidney disease status or baseline systolic BP category.[1,4-7]

Method S3. Mathematical framework of the stratified Cox proportional hazards models and test for interaction

1. General stratified Cox model structure

1.1 Base model

The partial likelihood for a stratified Cox model across multiple trials is:

$$L = \prod_{k=1}^{K} \prod_{j:Y_j=1 \text{ in trial } k} \frac{\exp(\mathrm{X}_j\beta)}{\sum_{i \in R_{k,j}} \exp(\mathrm{X}_i\beta)}$$

Where:

- K = number of trials (strata)
- $Y_j = 1$ if event occurred for individual j
- X_j = covariate vector for individual j
- β = vector of regression coefficients (estimated on a common scale across all trials)
- $R_{k,j}$ = risk set at time t_j within trial k

1.2 Instantaneous hazard function

Each trial has its own baseline hazard $h_{0,k}(t)$, but treatment effects and covariate effects are estimated as common across trials.

For an individual i in trial k:

$$h_i(t \mid \text{trial } k) = h_{0,k}(t)\exp(\mathrm{X}_i\beta)$$

The hazard ratio (HR) comparing two individuals, i and j, is:

$$HR_{ij} = \frac{h_i(t)}{h_j(t)} = \frac{\exp(\mathrm{X}_i\beta)}{\exp(\mathrm{X}_j\beta)} = \exp\left[(\mathrm{X}_i - \mathrm{X}_j)\beta\right]$$

2. Full model with achieved systolic blood pressure (SBP) reduction parameterisation

2.1 Model for all participants (without subgroup analysis)

$$\log h_i(t) = \log h_{0,k}(t) + \beta_{\text{Treat}} \cdot \mathbb{I}_{\text{Treat}} + \beta_{\Delta\text{SBP}} \cdot \Delta\text{SBP}_i + \beta_{\text{Treat}\times\Delta\text{SBP}} \cdot \mathbb{I}_{\text{Treat}} \times \Delta\text{SBP}_i$$

Component definitions:

- $\mathbb{I}_{\text{Treat}}$ = treatment arm indicator (1 if treatment, 0 if comparator)
- ΔSBP_i = Mean systolic blood pressure change for trial i (mmHg)
- β_{Treat} = Treatment effect
- $\beta_{\Delta\text{SBP}}$ = SBP change effect across all participants

- $\beta_{\text{Treat}\times\Delta\text{SBP}}$ = interaction term: how much the treatment effect changes per unit SBP difference

Interpretation:

- The treatment effect is log-linear in SBP change
- At any fixed SBP reduction Δ, the log-HR = $\beta_{\text{Treat}} + \beta_{\text{Treat}\times\Delta\text{SBP}} \times \Delta$
- The model evaluates this at $\Delta = 5$ mmHg to report "HR per 5 mmHg SBP reduction." (See below section 6.2 for logic behind using 5 mmHg).

2.2 Standardised HR calculation at $\Delta = 5$ mmHg

Log-HR for total population:

$$\log\ HR_{\text{total}}(\Delta = 5) = \hat{\beta}_{\text{Treat}} + 5 \cdot \hat{\beta}_{\text{Treat}\times\Delta\text{SBP}}$$

HR:

$$HR_{\text{total}}(5) = \exp\left[\hat{\beta}_{\text{Treat}} + 5 \cdot \hat{\beta}_{\text{Treat}\times\Delta\text{SBP}}\right]$$

Variance (using the delta method):

$$\text{Var}(\log\ HR) = \text{Var}(\hat{\beta}_{\text{Treat}}) + 25 \cdot \text{Var}(\hat{\beta}_{\text{Treat}\times\Delta\text{SBP}}) + 2 \times 5 \times \text{Cov}(\hat{\beta}_{\text{Treat}}, \hat{\beta}_{\text{Treat}\times\Delta\text{SBP}})$$

The key insight: variances are multiplied by Δ or Δ^2 to account for the evaluation at a specific SBP reduction value.

95% Confidence interval:

$$95\%\ \text{CI} = \exp\left[\log\ HR \pm 1.96 \times \sqrt{\text{Var}(\log\ HR)}\right]$$

3. Model stratified by CKD status

3.1 Extended model including CKD interactions

The model is extended to allow different treatment effects in CKD and non-CKD subgroups:

$$\log\ h_i(t) = \log\ h_{0,k}(t) + \beta_{\text{Treat}} \cdot \mathbb{I}_{\text{Treat}} + \beta_{\Delta\text{SBP}} \cdot \Delta\text{SBP}_i$$
$$+\beta_{\text{Treat}\times\Delta\text{SBP}} \cdot \mathbb{I}_{\text{Treat}} \times \Delta\text{SBP}_i + \beta_{\text{Treat}\times\text{CKD}} \cdot \mathbb{I}_{\text{Treat}} \times \mathbb{I}_{\text{CKD}}$$
$$+\beta_{\text{Treat}\times\Delta\text{SBP}\times\text{CKD}} \cdot \mathbb{I}_{\text{Treat}} \times \Delta\text{SBP}_i \times \mathbb{I}_{\text{CKD}}$$

Plus corresponding terms for the comparator arm interactions with CKD:

$$+\beta_{\text{Comp}\times\text{CKD}} \cdot \mathbb{I}_{\text{Comp}} \times \mathbb{I}_{\text{CKD}} + \beta_{\text{Comp}\times\Delta\text{SBP}\times\text{CKD}} \cdot \mathbb{I}_{\text{Comp}} \times \Delta\text{SBP}_i \times \mathbb{I}_{\text{CKD}}$$

Where $\mathbb{I}_{\text{CKD}} = 1$ if CKD status is 1, else 0 (non-CKD).

3.2 Log-HR expressions for CKD and non-CKD groups

For non-CKD (simple case, no additional CKD terms):

$$\log HR_{\text{non-CKD}}(\Delta = 5) = \hat{\beta}_{\text{Treat}} + 5 \cdot \hat{\beta}_{\text{Treat}\times\Delta\text{SBP}}$$

For CKD (must account for treatment–CKD interactions in both arms):

$$\log HR_{\text{CKD}}(\Delta = 5) = \left[\hat{\beta}_{\text{Treat}} + \hat{\beta}_{\text{Treat}\times\text{CKD}} + 5 \cdot (\hat{\beta}_{\text{Treat}\times\Delta\text{SBP}} + \hat{\beta}_{\text{Treat}\times\Delta\text{SBP}\times\text{CKD}})\right] - \left[\hat{\beta}_{\text{Comp}\times\text{CKD}} + 5 \cdot \hat{\beta}_{\text{Comp}\times\Delta\text{SBP}\times\text{CKD}}\right]$$

Rationale for subtraction: The Cox model baseline is the comparator arm. To isolate the treatment vs comparator contrast within CKD, we subtract the comparator's CKD effects.

3.3 Variance for CKD log-HR

This stage involves a variance–covariance calculation. The 6 key coefficients:

$$P : \hat{\beta}_{\text{Treat}} \quad (1)$$
$$Q : \hat{\beta}_{\text{Treat}\times\Delta\text{SBP}} \quad (2)$$
$$R : \hat{\beta}_{\text{Comp}\times\text{CKD}} \quad (3)$$
$$S : \hat{\beta}_{\text{Treat}\times\text{CKD}} \quad (4)$$
$$T : \hat{\beta}_{\text{Comp}\times\Delta\text{SBP}\times\text{CKD}} \quad (5)$$
$$U : \hat{\beta}_{\text{Treat}\times\Delta\text{SBP}\times\text{CKD}} \quad (6)$$

Then the log-HR is a linear combination:

$$\log HR_{\text{CKD}} = P + 5Q + S - R - 5T + 5U$$

Variance**:**

$$\text{Var}(\log HR_{\text{CKD}}) = \text{Var}(P + 5Q + S - R - 5T + 5U)$$

Expanded:

$$= \text{Var}(P) + 25 \cdot \text{Var}(Q) + \text{Var}(R) + \text{Var}(S) + 25 \cdot \text{Var}(T) + 25 \cdot \text{Var}(U)$$
$$+10 \cdot \text{Cov}(P,Q) - 2 \cdot \text{Cov}(P,R) + 2 \cdot \text{Cov}(P,S) - 10 \cdot \text{Cov}(P,T) + 10 \cdot \text{Cov}(P,U)$$
$$+10 \cdot \text{Cov}(Q,S) - 10 \cdot \text{Cov}(Q,R) + \cdots \text{(many more terms)}$$

In the R code: Each variance and covariance component is pre-computed (labelled P–AJ), then summed with appropriate signs (+ or −) to get the final variance.

4. Subgroup-specific models

4.1 CKD stage stratification (stages 1, 2, 3a, 3b, 4-5)

The model is further extended to allow five different CKD stage levels, each with its own treatment and SBP-interaction terms:

$$\log\, h_i(t) = \log\, h_{0,k}(t) + \text{(base terms as before)}$$

$$+\sum_{s=1}^{4}\left[\beta_{\text{Treat}\times\text{Stage}_s}\cdot \mathbb{I}_{\text{Treat}} \times \mathbb{I}_{\text{Stage}_s} + \beta_{\text{Treat}\times\Delta\text{SBP}\times\text{Stage}_s}\cdot \mathbb{I}_{\text{Treat}} \times \Delta\text{SBP} \times \mathbb{I}_{\text{Stage}_s}\right]$$

Plus corresponding comparator terms (subtracted to get treatment contrast).

For stage 1:

$$\log\, HR_{\text{Stage }0}(\Delta = 5) = \hat{\beta}_{\text{Treat}} + 5\cdot\hat{\beta}_{\text{Treat}\times\Delta\text{SBP}}$$

For stages 2, 3a, 3b, 4-5:

$$\log\, HR_{\text{Stage }s}(\Delta = 5) = \hat{\beta}_{\text{Treat}} + \hat{\beta}_{\text{Treat}\times\text{Stage}_s} + 5(\hat{\beta}_{\text{Treat}\times\Delta\text{SBP}} + \hat{\beta}_{\text{Treat}\times\Delta\text{SBP}\times\text{Stage}_s})$$

$$-\hat{\beta}_{\text{Comp}\times\text{Stage}_s} - 5\cdot\hat{\beta}_{\text{Comp}\times\Delta\text{SBP}\times\text{Stage}_s}$$

4.2 SBP and DBP categories

Similar logic applies for stratification by categories of SBP and DBP at baseline:

- Each baseline BP category has its own interaction with treatment and with SBP/DBP change
- HRs are computed at fixed SBP reduction ($\Delta = 5$ mmHg) or DBP reduction ($\Delta = 3$ mmHg)
- Variance calculations follow the same pattern: identify all relevant coefficients and their covariances, then apply the delta method.

5. Delta method for standard error calculation

5.1 General form

If $Y = g(\boldsymbol{\theta})$ and $\hat{\boldsymbol{\theta}}$ is the MLE with variance–covariance matrix Σ, then:

$$\text{Var}(Y) \approx \nabla g(\hat{\boldsymbol{\theta}})^T \Sigma \nabla g(\hat{\boldsymbol{\theta}})$$

Where ∇g is the gradient vector.

5.2 Application to our setting

Let $L = \hat{\beta}_1 + \Delta\cdot\hat{\beta}_2 + \cdots$ be the log-HR as a linear combination of $\hat{\beta}_j$ at a chosen Δ.

Then:

$$\text{Var}(L) = \sum_{i,j} c_i c_j \text{Cov}(\hat{\beta}_i, \hat{\beta}_j)$$

where $c_i = \partial L/\partial\hat{\beta}_i$ includes factors of Δ or Δ^2 as appropriate.

For example:

- If $L = \hat{\beta}_1 + \Delta\cdot\hat{\beta}_2$, then $c_1 = 1$ and $c_2 = \Delta$
- $\text{Var}(L) = \text{Var}(\hat{\beta}_1) + \Delta^2\cdot\text{Var}(\hat{\beta}_2) + 2\Delta\cdot\text{Cov}(\hat{\beta}_1, \hat{\beta}_2)$

Each variance and covariance term is multiplied by the appropriate power of Δ (or other interaction coefficients), then summed.

The same framework extends to all other subgroups, including proteinuria (present/absent) and diabetes (yes/no).

6. Interpretation and logic

6.1 Standardised HR per 5 mmHg SBP reduction

For example, if $HR = 0.90$, it means that over the study follow-up period, a 5 mm Hg reduction in SBP lowers the relative risk of major cardiovascular events by 10%.

6.2 Why standardisation to 5 mmHg?

- **Across trials variation and increased power:** Trials with different designs achieve different mean reductions in SBP.[6] Standardisation to a fixed SBP difference enables meta-analytic comparison on a common scale, allowing pooling of estimates from trials with varying BP reductions (including those with low achieved BP reductions, e.g., head-to-head trials), thereby increasing power while assigning lower weight to trials with smaller BP reductions

- **Interpretability:** Provides an effect size per clinically meaningful BP reduction, enhancing clinical interpretability.

- **Linear assumption:** Based on previous evidence, the model assumes a linear relationship between logHR and ΔSBP;[4] therefore, any fixed contrast could, in principle, be chosen. We selected 5 and 3 mmHg because the average between-group reductions (treatment versus comparator) in SBP and DBP, excluding the first 12 months, were approximately 5 mmHg and 3 mmHg, respectively (the closest round numbers).[6]

6.3 Heterogeneity by subgroup

If $HR_{\text{CKD}}(5) \neq HR_{\text{non-CKD}}(5)$, there is effect modification by CKD status. Statistical testing uses likelihood-ratio tests to compare nested models.

All other details, including the rationale, underlying logic, and methodological aspects, have been published previously.[1]

7. Adjustment for multiple comparisons in assessing heterogeneity in subgroup analysis

When testing hypotheses across several subgroups simultaneously, the probability of making at least one Type I error (false positive) increases substantially. For example, if testing a hypothesis across 7 subgroups at α = 0.05, the probability of at least one false positive is approximately 1 - (0.95)^7 ≈ 30%, far exceeding the nominal 5% level.[8-10]

Hommel's method is a stepwise multiple testing procedure that controls the family-wise error rate (FWER), the probability of making at least one Type I error across all tests.[9] It builds upon Simes' (1986) global test by

applying a closed testing framework, allowing inference on individual hypotheses while maintaining strict error control.

For m ordered p-values $p_{(1)} \leq ... \leq p_{(m)}$: find the largest integer j such that $p_{(m-j+k)} > k\alpha/j$ for all $k = 1,...,j$. If no such j exists, reject all hypotheses; otherwise reject all hypotheses with $p_i \leq \alpha/j$.[9]

Hommel's method is one of the most powerful FWER-controlling procedures, producing smaller adjusted p-values while maintaining strict error control (Power hierarchy: Bonferroni < Holm < Hochberg < Hommel). In this study, we used this method to adjust interaction P-values across multiple subgroup comparisons (CKD status, CKD stages, diabetes, proteinuria, BP categories). This maximised power to detect true treatment effect modifications while controlling false-positive discovery at $\alpha = 0.05$. This approach was more appropriate than the conservative Bonferroni correction because: 1) It provides greater statistical power for detecting true treatment effect modifications, 2)The subgroup comparisons are likely positively correlated (not negatively dependent), and 3) It maintains rigorous FWER control at $\alpha = 0.05$.

A non-significant interaction P-value ($P > 0.05$ while adjusted for multiple comparisons) indicates no evidence of treatment effect modification across subgroup categories; in such cases, the overall effect estimate was considered the most valid estimate of the treatment effect, with observed subgroup variation attributed to chance. Conversely, a significant interaction P-value suggested potential differences in treatment effect, which were interpreted cautiously in light of the magnitude and direction of the effect, biological plausibility, clinical relevance, and implications for practice.

8. Computational workflow in R

1. Fit stratified Cox model using `coxph(Surv(time, event) ~ RAND_ARM + sbp_delta + RAND_ARM:sbp_delta + ... + strata(TRIAL), data=...)`
2. Extract coefficients and covariance matrix: `coef(model)` and `vcov(model)`
3. Construct log-HR at $\Delta = 5$: Plug in 5 for all instances of `sbp_delta` in the linear predictor
4. Apply the delta method: Sum the variance and covariance components, scaled by powers of 5
5. Exponentiate and compute CI: $HR = e^{\log HR}$ and CI $= e^{\log HR \pm 1.96\sqrt{\mathrm{Var}(\log HR)}}$
6. Repeat for all subgroups (CKD stages, BP categories, proteinuria status, diabetes status, outcomes)

9. Cox proportional hazards model assumptions

Conventional Cox model diagnostics, such as Schoenfeld residual analysis,[11] are not appropriate for this analysis for three reasons. First, apart from the treatment arm, which is the main independent variable, the only covariate included in the model is achieved blood pressure reduction at the trial level (ΔSBP), a trial-level ecological exposure with only k discrete values (one per trial), rendering residual-based diagnostics designed for individual-level continuous covariates uninformative.[12] Second, with approximately 285,000 participants across 46 trials, statistical tests for proportional hazards are overly powered and will detect trivial deviations that lack clinical significance.[13,14] Third, the analytical objective is interaction testing (heterogeneity of treatment effect by CKD status), not individual-level survival prediction; the likelihood ratio test for interaction remains robust to violations of the proportional hazards assumption.[15]

Additionally, we have provided a detailed explanation below as to why the model results are valid and robust:

9.1 Assumptions by study design

Between-trial heterogeneity. The strata(TRIAL) specification permits unrestricted baseline hazard functions h0t(t) for each trial, thereby eliminating the requirement for proportional hazards assumptions across trials. This stratified approach is methodologically appropriate given the inherent heterogeneity in multi-trial consortia data regarding patient populations, trial protocols, follow-up durations, and enrolment calendar periods.[16]
Randomisation. Within-trial randomisation ensures exchangeability of treatment arms with respect to measured and unmeasured confounders. Hazard ratios for treatment assignment are therefore causally interpretable under standard randomised trial assumptions, independent of proportional hazards verification.[17]
Ecological exposure. The trial-level blood pressure reduction coefficient represents meta-regression across discrete trial-level values.[18] Linearity is a reasonable parametric assumption given the biological plausibility of dose-response relationships in blood pressure lowering and previous evidence.[6,19,20]

9.2 Proportional hazards assumption for treatment effects

Several factors mitigate potential non-proportionality. Randomisation precludes time-varying selection bias.[21] Our study of meta-analyses of blood pressure-lowering trials demonstrates consistent relative risk reductions across follow-up. Non-proportionality, if present, would typically bias toward the null in randomised trials with symmetric crossover or discontinuation.[22,23] Importantly, when proportional hazards is violated, the hazard ratio converges to a weighted average of time-dependent effects—an accepted summary measure in randomised trial meta-analyses.[24] Since the analytical goal is to determine whether treatment efficacy differs by CKD status (qualitative interaction), this summary estimate is sufficient to establish evidence of differential efficacy. Additionally, the primary analytical objective was to test for heterogeneity of treatment effect by chronic kidney disease status (interaction testing) rather than to derive a precise predictive model for individual patient survival. The statistical test for interaction (the likelihood ratio test) remains robust to violations of the proportional hazards assumption. Even when hazard ratios for the treatment arm vary over time, the difference in these effects between subgroups—the parameter of interest—is unlikely to be systematically biased by time-dependencies in the baseline hazard function. The interaction term captures relative modification of the treatment effect, which is structurally distinct from the shape of the baseline hazard.[10]

9.3 Independence of censoring

Standard assumptions regarding non-informative censoring apply. In this framework, censoring predominantly reflects administrative end-of-trial constraints rather than informative dropout, supporting the validity of the primary analysis.[25] Because administrative censoring is determined by the staggered entry of participants and a fixed study termination date, the 'censoring mechanism' is stochastically independent of the hazard of the primary outcome. This independence ensures that the observed event rates provide an unbiased estimate of the true survival function, as the censored individuals remain representative of those still at risk.

9.4 Summary

Standard diagnostics for the Cox model, such as Schoenfeld residuals, are poorly suited to one-stage IPD meta-analyses that utilise stratified baseline hazards.[26] Our approach addresses design-based differences in blood

pressure reduction through trial-level adjustment. This stratification complicates the interpretation of traditional residuals, which are not designed to evaluate treatment-by-time interactions across heterogeneous, multi-centre datasets. The study design—trial stratification, within-trial randomisation, and a focus on interaction testing—addresses the primary concerns while maintaining scientific rigour.

All statistical code, analysis scripts, and accompanying documentation used for this study are available in an open-access repository at the DeepMedicine research group GitHub page.

Method S4. R packages used for statistical analysis

R package	Version	Analysis
survival	3.5-7	Defining survival data (Surv), fitting Cox proportional hazards models (coxph)
gemtc	1.0-2	Defining the network model (mtc.model) and running the MCMC simulations for Bayesian network meta-analysis
meta	8.0-2	Performing fixed- and random-effects meta-analysis on aggregated HRs (metagen), calculating subgroup interaction tests, and creating forest plots
dplyr	1.1.2	Efficient data filtering and general data wrangling
forestplot	3.1.6	Creation of high-quality, customisable forest plots
ggplot2	3.4.3	High-quality, customised graphics and plots (e.g., Kaplan-Meier curves)
metafor	4.8-0	Meta regression

Supplementary Tables

Table S1. Risk of bias assessment of each trial.

Trial	Randomisation	Assignment to intervention	Missing outcome	Outcome measurement	Reporting of results	Overall risk of bias
AASK	Low	Low	Low	Low	Low	Low
ABCD	Low	Low	Low	Low	Low	Low
ACCORD BP	Low	Some	Low	Low	Low	Low
ACTIVE I	Low	Low	Low	Low	Low	Low
ADVANCE	Low	Low	Low	Low	Low	Low
ALLHAT	Low	Low	Low	Low	Low	Low
ANBP2	Low	Some	Low	Low	Low	Low
ASCOT-BPLA	Low	Some	Low	Low	Low	Low
BENEDICT	Low	Low	Low	Low	Low	Low
CAMELOT	Low	Low	Low	Low	Low	Low
CAPPP	Low	Some	Low	Low	Low	Some
CARDIO-SIS	Low	Some	Some	Low	Low	Some
CASE-J	Low	Some	Low	Low	Low	Low
COLM	Low	Some	Low	Low	Low	Low
COPE	Low	Some	Low	Low	Low	Low
DIABHYCAR	Low	Low	Low	Low	Low	Low
Dutch TIA	Low	Low	Low	Low	Low	Low
ELSA	Low	Low	Low	Low	Low	Low
EUROPA	Low	Low	Low	Low	Low	Low
EWPHE	Low	Some	Low	Low	Low	Some
HDFP	Low	Low	Low	Low	Low	Low
HIJ-CREATE	Low	Some	Low	Low	Low	Low
HOMED-BP	Low	Some	Low	Low	Low	Low
HOPE	Low	Some	Low	Low	Low	Low
HYVET	Low	Low	Low	Low	Low	Low
IDNT	Low	Low	Low	Low	Low	Low
INSIGHT	Low	Low	Low	Low	Low	Low
JMIC-B	Low	Some	Low	Low	Low	Low
LIFE	Low	Low	Low	Low	Low	Low
NICS-EH	Low	Some	Low	Low	Low	Some
NORDIL	Low	Some	Low	Low	Low	Low
ONTARGET	Low	Some	Low	Low	Low	Low
PART 2	Low	Low	Low	Low	Low	Low
PREVEND IT	Low	Low	Low	Low	Low	Low
PREVENT	Low	Low	Low	Low	Low	Low
PROFESS	Low	Low	Low	Low	Low	Low
PROGRESS	Low	Low	Low	Low	Low	Low
SHEP	Low	Low	Low	Low	Low	Low
SPRINT	Low	Some	Low	Low	Low	Low
STOP-2	Low	Some	Low	Low	Low	Low
SYST-EUR	Low	Some	Low	Low	Low	Low
TRANSCEND	Low	Low	Low	Low	Low	Low
UKPDS	Low	Some	Low	Low	Low	Low
VALISH	Low	Low	Low	Low	Low	Low
VALUE	Low	Low	Low	Low	Low	Low
VHAS	Low	Low	Low	Low	Low	Low

Risk of bias assessed using the revised Cochrane risk-of-bias tool(RoB 2 tool).[27] The table was extracted from a previous BPLTTC publication[6] and subsequently updated for the present study.
In trials comparing different blood pressure treatment goals, blinding the intervention is not feasible.

Table S2. General characteristics of included trials

Trial name	Trial design	Inclusion criteria	Exclusion criteria	Mean age (SD)	Mean follow-up (year)	Study arms		Achieved SBP reduction	Achieved DBP reduction	n of CKD/ without CKD at baseline	Mean eGFR at baseline	Proteinuria definition at baseline	Diabetes definition at baseline
						Intervention (n)	Comparator (n)						
AASK[28]	Intensive	Age 18-70 years, African American, hypertension, renal disease (GFR=20-65 ml/min per 1.73m^2)	DBP <95 mmHg, diabetes, urine protein:creatinine ratio >25, recent malignant hypertension, secondary hypertension, non-blood pressure-related CKD, serious systemic disease, HF	54 (11)	4.8	More intensive (540)	Less intensive (554)	13.0	7.9	1,043/1,094	38.9	Urinary protein-to-creatinine ratio >0.22	Fasting glucose level ≥140 mg/dl (7.8 mmol/L), a random glucose level ≥200 mg/dl (11.1 mmol/L), or pharmacological glucose-lowering therapy
ABCD[29]	Intensive	Age 40-74 years, type 2 diabetes mellitus, DBP ≥80 mmHg, not on antihypertensive treatment	Recent CAD or CeVD, heart failure, renal disease	58 (8)	4.7	More intensive (474)	Less intensive (476)	7.7	6.9	224/725	72.4	Urinary albumin excretion >200µg/min	Diagnosis/history of type 2 diabetes mellitus
ACCORD BP[30]	Intensive	Age ≥40 years with CVD or ≥50 years with substantial atherosclerosis, diagnosis/history of type 2 diabetes mellitus, HbA1c ≥7.5%, albuminuria, LVH or ≥2 CVD risk factors (dyslipidaemia, hypertension, smoking, obesity); SBP 130-180 mmHg and taking ≤3 antihypertensive drugs, 24-hour protein excretion rate <1g	Body mass index ≥45 kg/m2, serum creatinine ≥132.6 µmol/l and other serious illness	63 (7)	4.7	More intensive (2362)	Less intensive (2371)	13.9	1.8	476/4,238	85.5	Urinary albumin to creatinine ratio >300 mg/g	Diagnosis/history of type 2 diabetes mellitus, or HbA1c ≥7.5%
ACTIVE I[31]	Placebo-controlled	Atrial fibrillation, ≥1 risk factor (age ≥75 years, on antihypertensive treatment, history of stroke, TIA or non-central nervous system embolism, LVEF <45%, PVD, or age 55-74 years with either CAD or diabetes)	Use of anticoagulant, peptic ulcer disease in past 6 months, history of intracerebral haemorrhage, thrombocytopaenia or mitral stenosis	70 (10)	4.1	ARB (3058)	Placebo (3076)	2.6	1.4	1,454/3,648	71.0	/	Diagnosis/history of type 2 diabetes mellitus, or pharmacological glucose-lowering therapy
ADVANCE[32]	Placebo-controlled	Age ≥55 years, type 2 diabetes mellitus (diagnosed aged ≥30 years), ≥1 major CVD or ≥1 CVD risk factor (microvascular disease, smoking, dyslipidaemia, microalbuminuria, Diagnosis of type 2 diabetes mellitus for ≥10 years, age ≥65 years)	Definite indication for, or contraindication to, any of the study treatments or the HbA1c target ≤6·5%, indication for long-term insulin therapy at baseline	66 (6)	4.2	ACEI and Diuretic (5569)	Placebo (5571)	5.4	2.1	1,781/9,309	78.5	/	Diagnosis of type 2 diabetes mellitus at ≥30 years old, or previous diagnosis of type 2 diabetes mellitus for ≥10 years
ALLHAT[33]	Drug classes comparison	Age ≥55 years, stage 1 or 2 hypertension plus ≥1 risk factor (MI or stroke >6 months, LVH, diagnosis/history of type 2	Symptomatic or hospitalisation for HF, LVEF <35%	67 (8)	4.8	Diuretic (15255)	ACEI, CCB and Alpha-blockers (27163)	2.0	0.1	7,162/28,412	75.0	/	Diagnosis/history of type 2 diabetes mellitus, or baseline fasting glucose level of ≥126 mg/dL (7 mmol/L)

Trial name	Trial design	Inclusion criteria	Exclusion criteria	Mean age (SD)	Mean follow-up (year)	Study arms		Achieved SBP reduction	Achieved DBP reduction	n of CKD/ without CKD at baseline	Mean eGFR at baseline	Proteinuria definition at baseline	Diabetes definition at baseline
						Intervention (n)	Comparator (n)						
		diabetes mellitus, smoking, HDL <0.91 mmol/l), other atherosclerotic CVD											
ANBP2[34]	Drug classes comparison	Age 65-84 years, SBP ≥160 mmHg or DBP ≥90 mmHg (if SBP ≥140 mmHg), no recent CVD	Serious illness, plasma creatinine >221 μmol/l, malignant hypertension, dementia	73 (5)	4.1	Diuretic (3039)	ACEI (3044)	0.9	0	1,732/4,351	68.6	/	Diagnosis/history of type 2 diabetes mellitus
ASCOT-BPLA[35]	Drug classes comparison	Age 40-79 years, untreated (SBP ≥160 or DBP ≥100 mmHg) or treated hypertension (SBP ≥140 or DBP ≥90 mmHg), ≥3 CVD risk factors (documented LVH, abnormal ECG, type 2 diabetes mellitus, PAD, previous stroke or TIA, male sex, age ≥55 years, microalbuminuria or proteinuria, smoking, TC:HDL ≥6, family history of premature coronary heart disease	Previous MI, current treatment for angina, recent CeVD, fasting triglycerides >4.5 mmol/l, heart failure, arrhythmia, haematological or biochemical abnormality at screening	63 (9)	5.3	CCB-based (9639)	Beta-blocker based (9618)	2.2	2.0	2,483/10,637	71.7	/	Fasting glucose level ≥ 126 mg/dL (7 mmol/L), or a 2-h post-load plasma of 199.8 mg/dL (11.1 mmol/l), or pharmacological and non-pharmacological glucose-lowering therapy, or diagnosis/history of type 2 diabetes mellitus
BENEDICT[36]	Placebo-controlled	Age ≥40 years, untreated SBP ≥130 / DBP ≥85 mmHg or needing treatment to attain below these levels, type 2 diabetes mellitus for <25 years, urinary albumin excretion rate <20 mcg/min, serum creatinine ≤133 μmol/l	HbA1c ≥11%, nondiabetic renal disease	62 (8)	3.1	ACEI, CCB and ACEI/CCB (907)	Placebo (302)	2.0	1.3	55/1,138	84.6	Urinary albumin excretion >200 μg/min	History of type 2 diabetes mellitus not exceeding 25 years
CAMELOT[37]	Placebo-controlled	Age 30-79 years, coronary artery stenosis >20% by angiography, DBP <100 mmHg	Left middle coronary artery obstruction >50%, LVEF <40%, heart failure	58 (10)	1.6	CCB and ACEI (1340)	Placebo (657)	5.3	3.3	195/1,788	80.6	/	Diagnosis/history of type 2 diabetes mellitus, or fasting glucose level ≥ 126 mg/dL (7 mmol/L)
CAPPP[38]	Drug classes comparison	Age 25-66 years, DBP ≥100 mmHg on two occasions	Secondary hypertension, serum creatinine >150 μmol/l, condition requiring beta-blocker treatment	52 (8)	5.8	Beta-blocker and/or Diuretic (5493)	ACEI (5492)	2.2	1.3	554/10,202	83.5	A urinary protein dipstick test result of 1+ or greater	At least two abnormal fasting glucose values that were unequivocal (i.e., between 99 mg/dL [5.5 mmol/L] and 120.6 mg/dL [6.7 mmol/L]). If they were not unequivocal, diagnosis was confirmed by an oral glucose tolerance test.
CARDIO-SIS[39]	Intensive	Age ≥55 years, SBP ≥150 mmHg, taking antihypertensive drug ≥12 weeks, ≥1 CVD risk factor (smoking, dyslipidaemia, family history of premature CVD, prior TIA or stroke, established CAD or PAD	Fasting blood glucose ≥126 mg/dL, known diabetes, serious conditions, renal disease, valvular heart disease, left ventricular hypertrophy, atrial ibrillation, substance misuse	67 (7)	4.7	More intensive (558)	Less intensive (553)	3.8	1.5	174/931	77.1	Not mentioned	Fasting blood glucose ≥126 mg/dL (≥7 mmol/l), diagnosis/history of diabetes

Trial name	Trial design	Inclusion criteria	Exclusion criteria	Mean age (SD)	Mean follow-up (year)	Study arms		Achieved SBP reduction	Achieved DBP reduction	n of CKD/ without CKD at baseline	Mean eGFR at baseline	Proteinuria definition at baseline	Diabetes definition at baseline
						Intervention (n)	Comparator (n)						
CASE-J[40]	Drug classes comparison	Age 20-85 years, ≥1 high-risk factor: SBP ≥180 or DBP ≥110 mmHg, type 2 diabetes mellitus, history of angina pectoris, MI, stroke, TIA >6 months	BP ≥200/120 mmHg, type 1 diabetes, HF, LEF <40%, atrial fibrillation, cancer	64 (11)	3.1	CCB (2349)	ARB (2354)	1.7	0.9	486/4,217	85.6	Not mentioned	Fasting blood glucose ≥126 mg/dL [7 mmol/l], casual blood glucose ≥200 mg/dL [11.1 mmol/l], haemoglobin A1c ≥ 6.5%, 2-h blood glucose on 75 g oral glucose tolerance test ≥200 mg/dL [11.1 mmol/l], or pharmacological glucose-lowering therapy
COLM[41]	Drug classes comparison	Age 65-84 years, hypertension (treated: blood pressure ≥140/90 mmHg; untreated: blood pressure ≥160/100 mmHg), CVD history or CVD risk factors including diabetes and dyslipidaemia	Secondary/malignant hypertension, recent major CVD, revascularisation, angina pectoris hospitalisation or severe heart failure, atrial fibrillation, hepatic or renal dysfunction	74 (5)	3	ARB and Diuretic (2573)	ARB and CCB (2568)	0.3	0.4	322/3,932	86.1	/	Diagnosis/history of type 2 diabetes mellitus, fasting blood glucose ≥110 mg/dL [6.1 mmol/l] or postprandial blood glucose≥140 mg/dL [7.8 mmol/l]
COPE[42]	Drug classes comparison	Age 40-85 years, blood pressure ≥140/90 mmHg	SBP ≥200 or DBP ≥120 mmHg, secondary hypertension, type 1 diabetes or type 2 diabetes requiring insulin treatment, recent CVD or revascularisation, heart failure, atrial fibrillation/flutter, hepatic or renal dysfunction, congenital or rheumatic heart disease, cancer	64 (11)	3.6	CCB/Diuretic and CCB/ Beta-blocker (2183)	CCB and ARB (1110)	0.4	0.4	71/3,219	95.6	Refer to the value in the record	Diagnosis/history of type 2 diabetes mellitus (excluding patients required insulin treatment)
DIABHYCAR[43]	Placebo-controlled	Age ≥50 years, type 2 diabetes mellitus, urinary albumin excretion ≥20 mg/l in two consecutive urine samples	Serum creatinine >150 micro mol/l, use of insulin, ACEI or ARB, heart failure, recent MI, urinary tract infection	65 (8)	3.9	ACEI (2443)	Placebo (2469)	0.9	0.4	833/4,072	78.3	urinary albumin excretion > 200 mg/l	Treatment with at least one oral antidiabetic agent
Dutch TIA[44]	Placebo-controlled	TIA or non-disabling ischaemic stroke (Rankin Scale ≤3) in past 3 months	Cerebral ischaemia from identifiable causes other than arterial thrombosis or embolism	64 (10)	2.3	Beta-blocker (732)	Placebo (741)	3.1	2.0	235/1,235	75.5	/	Diagnosis/history of diabetes, the use of oral antidiabetic drugs or insulin, or a nonfasting plasma glucose level of ≥ 199.8 mg/dl [11.1 mmol/l]
ELSA[45]	Drug classes comparison	Age 45-79 years, blood pressure 150-210/95-115 mmHg	Recent MI or stroke, and type 2 diabetes mellitus	57 (7)	3.4	CCB (1177)	Beta-blocker (1157)	0.8	0.4	131/2,169	83.5	Urinary albumin excretion >0.5g/l	Fasting plasma glucose ≥126 mg/dl [7 mmol/l], or report of current drug treatment for diabetes
EUROPA[46]	Placebo-controlled	Age ≥18 years, documented MI >3 months before screening, revascularisation >6 months before screening, >70% coronary obstruction	HF, hypotension, uncontrolled hypertension, renal insufficiency, serum potassium >5.5 mmol/L	61 (9)	4.2	ACEI (6110)	Placebo (6108)	4.6	2.2	1,545/10,570	78.5	/	Diagnosis/history of diabetes, or taking antidiabetic agents

Trial name	Trial design	Inclusion criteria	Exclusion criteria	Mean age (SD)	Mean follow-up (year)	Study arms		Achieved SBP reduction	Achieved DBP reduction	n of CKD/ without CKD at baseline	Mean eGFR at baseline	Proteinuria definition at baseline	Diabetes definition at baseline
						Intervention (n)	Comparator (n)						
EWPHE[47]	Placebo-controlled	Age ≥60 years, blood pressure 160-239/90-119 mmHg	Curable causes of high BP, retinopathy, heart failure, stroke history, hepatitis/cirrhosis, gout, malignancy, diabetes requiring insulin treatment	71 (8)	4.6	Diuretic (416)	Placebo (424)	22.4	9.5	264/563	68.8	/	Fasting plasma glucose ≥126 mg/dl [7 mmol/l], or diagnosis/history of type 2 diabetes mellitus
HIJ-CREATE[48]	Drug classes comparison	Age 20-80 years, CAD hospitalisation and hypertension (blood pressure ≥140/90 mmHg or antihypertensive treatment use)	Secondary hypertension, recent AMI or CeVD, severe aortic valve stenosis, cardiomyopathy, serum creatinine >2 mg/dl, serum potassium >5 mmol/l, hepatic dysfunction, malignancy	65 (9)	4	ARB (1024)	non-ARB (1025)	0.4	0.5	148/1,895	88.0	/	Fasting blood glucose ≥126 mg/dL [7 mmol/l] or treatment with hypoglycaemic agents at the time of enrolment.
HOMED-BP[49]	Intensive	Self-measured SBP 135-179 mmHg or DBP 85-119 mmHg, but not if DBP <65 mmHg or SBP <110 mmHg (clinic SBP <220 mmHg and DBP <125 mmHg)	None specified	60 (10)	4.9	More intensive (1759)	Less intensive (1759)	2.0	0.9	48/3,281	96.0	A urinary protein dipstick test result of 1+ or greater	Fasting blood glucose ≥126 mg/dL [7 mmol/l], or an HbA1c ≥ 6.5%, or treatment with oral antidiabetic drugs or insulin
HOPE[50]	Placebo-controlled	Age ≥55 years, CAD, stroke, PVD or diabetes, plus ≥1 risk factor (hypertension, dyslipidaemia, smoking, or documented microalbuminuria)	HF, LEF <40%, using ACEI or vitamin E, uncontrolled hypertension, nephropathy, or recent MI or stroke	66 (7)	4.5	ACEI (4645)	Placebo (4652)	3.0	1.4	2,307/6,979	71.8	Dipstick-positive proteinuria is excluded	Diagnosis/history of type 2 diabetes mellitus
HYVET[51]	Placebo-controlled	Age ≥80y years, sustained SBP ≥160 mmHg	Accelerated or secondary hypertension, recent haemorrhagic stroke, HF, serum creatinine >150 micro mol/l, serum potassium <3.5 or >5.5 mmol/l, gout, and dementia	84 (3)	2.1	Diuretic (1933)	Placebo (1912)	13.1	5.1	1,629/2,214	64.6	Not mentioned	Diagnosis/history of type 2 diabetes mellitus, the receipt of antidiabetic treatment, or a random blood glucose > 200 mg/dl [11.1 mmol/l]
IDNT[52]	Placebo-controlled	Age 30-70 years, type 2 diabetes, hypertension (blood pressure ≥135/85 mmHg or taking anti-hypertensive drug), proteinuria, serum creatinine (μmol/l): 88 to 265 (women) or 106 to 265 (men)	Type 2 diabetes mellitus onset <20 years; type 1 diabetes mellitus; absolute requirement for ACE inhibitor, ARB, or CCB; recent/unstable cardiovascular disease (unstable angina, MI, CABG, or PTCA within 3 months; NYHA class III–IV heart failure; TIA within 6 months; stroke within 3 months); and serum potassium outside the normal range	59 (8)	2.6	ARB and CCB (1143)	Placebo (568)	2.8	2.8	1,116/464	49.5	Urinary albumin to creatinine ratio >300 mg/g	Diagnosis/history of type 2 diabetes mellitus
INSIGHT[53]	Drug classes comparison	Age 55-80 years, hypertensive (SBP ≥150 or DBP ≥95 mmHg, or SBP	None specified	65 (6)	2.8	Diuretic (3164)	CCB (3157)	1.1	0.9	1,596/4,721	71.8	Urinary protein excretion >0·5g/24h	Diagnosis/history of diabetes mellitus

Trial name	Trial design	Inclusion criteria	Exclusion criteria	Mean age (SD)	Mean follow-up (year)	Study arms		Achieved SBP reduction	Achieved DBP reduction	n of CKD/ without CKD at baseline	Mean eGFR at baseline	Proteinuria definition at baseline	Diabetes definition at baseline
						Intervention (n)	Comparator (n)						
		≥160 mmHg), ≥1 other risk factor (TC ≥6.43 mmol/l, smoking, family history of premature MI, CAD, other CVD											
JMIC-B[54]	Drug classes comparison	Age <75 years, hypertension (blood pressure ≥160/≥95 mmHg or both SBP ≥150 and DBP ≥90 mmHg, or antihypertensive treatment), CAD or meeting both criteria: history of >2 anginal attacks per week with stable frequency and ST-segment depression of ≥1 mm on stress test (or detection of MI with myocardial scintigraphy)	MI, unstable angina, DBP ≥120 mmHg, secondary hypertension, symptomatic CeVD, HF, atrial fibrillation/arrhythmias, renal or hepatic dysfunction, uncontrollable diabetes and familial hypercholesterolaemia	65 (85)	2.3	CCB (828)	ACEI (822)	2.0	1.5	144/1,197	85.9	/	Diagnosis/history of diabetes mellitus
LIFE[55]	Drug classes comparison	Age 55-80 years, hypertension (SBP 160-200 mmHg; DBP 95-115 mmHg), electrocardiogram signs of LVH	Secondary hypertension, recent MI or stroke, angina pectoris requiring treatment, HF or LVEF ≤40%	67 (7)	4.9	ARB (4605)	Beta-blocker (4588)	1.2	0.5	1,597/7,181	75.0	Urinary albumin to creatinine ratio >300 mg/g	Diagnosis/history of diabetes mellitus
NICS-EH[56]	Drug classes comparison	Age ≥60 years, SBP 160-220 mmHg and DBP <115 mmHg and no cardiovascular complications	None specified	70 (7)	3.2	Diuretic (214)	CCB (215)	0.3	0.7	37/379	85.3	/	Diagnosis/history of diabetes mellitus
NORDIL[57]	Drug classes comparison	Age 50-74 years, untreated hypertension (DBP ≥100 mmHg on two occasions); if previously treated, DBP ≥100 mmHg on two consecutive visits at one week apart during run-in period and no treatment was given	Age <50 or ≥70y, bradycardia, secondary hypertension, atrial fibrillation, recent CeVD or MI, HF	60 (7)	4.2	Beta-blocker and/or Diuretic (5471)	CCB (5410)	3.3	0.1	1,032/9,719	78.3	/	Diagnosis/history of type 2 (non-insulin dependent) diabetes mellitus
ONTARGET[58]	Drug classes comparison	CAD, PAD, CeVD or diabetes with end-organ damage	HF, pericarditis, CHD, unexplained syncope, planned revascularisation <3 months of consent, uncontrolled hypertension, heart transplant, subarachnoid haemorrhage, renal artery disease, hepatic dysfunction, volume or sodium depletion, primary hyper-aldosteronism, hereditary fructose intolerance, other serious conditions	67 (7)	4.8	ARB/ACEI (8502)	ACEI and ARB (17118)	1.9	1.0	6,425/18,538	72.2	A urinary protein dipstick test result of 1+ or greater	Diagnosis/history of type 2 diabetes mellitus with end-organ damage

Trial name	Trial design	Inclusion criteria	Exclusion criteria	Mean age (SD)	Mean follow-up (year)	Study arms		Achieved SBP reduction	Achieved DBP reduction	n of CKD/ without CKD at baseline	Mean eGFR at baseline	Proteinuria definition at baseline	Diabetes definition at baseline
						Intervention (n)	Comparator (n)						
PART 2[59]	Placebo-controlled	Age ≤75 years, diagnosis (in past 5 year) of MI, documented CAD, TIA or intermittent claudication	HF, serious nonvascular disease, SBP >160 mmHg, DBP >100 mm Hg, DBP <100 mmHg during pre-randomization run-in period	60 (8)	4.6	ACEI (308)	Placebo (309)	6.5	3.6	97/520	76.1	A urinary protein dipstick test result of 1+ or greater	Diagnosis/history of diabetes mellitus
PREVEND IT[60]	Placebo-controlled	Microalbuminuria, SBP <160/100 mmHg (no previous antihypertension treatment)	Creatinine clearance <60% of normal age-adjusted value	51 (12)	3.8	ACEI (431)	Placebo (433)	5.6	2.8	23/840	88.5	urinary albumin excretion rate >300mg/24h	Diagnosis/history of diabetes mellitus, or fasting blood glucose ≥126 mg/dL [7 mmol/l]
PREVENT[61]	Placebo-controlled	Age 30-80 years, documented CAD, DBP <95 mmHg, cholesterol <325 mg/dl, fasting blood glucose <200 mg/dl	Contraindication for dihydropyridines, uncontrolled hypertension, diabetes and other major illness	57 (10)	3	CCB (417)	Placebo (408)	6.1	3.3	180/641	70.7	Not mentioned	Diagnosis/history of diabetes mellitus
PROFESS[62]	Placebo-controlled	Age ≥55 years with ischaemic stroke <90 days before randomization (later modified to include age 50 to 54 years or had stroke 90 to 120 days before randomisation if with ≥2 additional risk factors: diabetes, hypertension, smoker, obesity previous CVD, end-organ damage or hyperlipidaemia) and remained stable[a]	Haemorrhagic stroke, severe disability after the qualifying stroke, contraindication to treatments	66 (8)	2.5	ARB (9873)	Placebo (9925)	3.4	3.4	2,977/13,640	78.2	/	Diagnosis/history of diabetes mellitus
PROGRESS[63]	Placebo-controlled	Stroke or TIA in past 5 years	Indication or contraindication for ACEI	64 (10)	3.9	ACEI and/or Diuretic (3051)	Placebo (3054)	9.2	4.0	932/5,072	79.9	/	Diagnosis/history of diabetes mellitus
SHEP[64]	Placebo-controlled	Age ≥60 years, isolated systolic hypertension (BP 160-219/<90 mmHg, not on treatment)	Major CVD, cancer, alcoholic liver disease, renal dysfunction, competing risk of SHEP primary endpoint or presence of medical management exclusions	72 (7)	5	Beta-blocker and Diuretic (2365)	Placebo (2371)	12.8	4.2	1,590/3,214	66.4	/	Diagnosis/history of type 2 diabetes mellitus
SPRINT[65]	Intensive	Age ≥50 y years, SBP 130-180 mmHg, increased CVD risk (clinical/subclinical CVD other than stroke, CKD excluding polycystic kidney disease and with eGFR of 20-60 ml/min/1.73m^2 body surface area, 10-year Framingham CVD risk ≥15%, age ≥75y)	Prior stroke	68 (9)	3	More intensive (4678)	Less intensive (4683)	14.9	7.7	2,332/6,976	73.2	Urinary albumin to creatinine ratio >300 mg/g	Diagnosis/history of diabetes mellitus, fasting glucose at randomization ≥126 mg/dL (7 mmol/L), treatment with hypoglycaemic agents
STOP Hypertension-2[66]	Drug classes comparison	Aged 70-84 years, SBP ≥180 mmHg and/or DBP ≥105 mmHg	Not specified	76 (4)	4.5	Beta-blocker and/or Diuretic (2213)	ACEI and CCB (4401)	2.1	0.3	2,121/4,450	67.0	/	Diagnosis/history of diabetes mellitus
SYST-EUR[67]	Placebo-	Age ≥60 years, sitting SBP	Secondary hypertension,	70 (7)	2.6	CCB	Placebo	10.1	4.0	1,299/3,389	70.1	A urinary protein	Diagnosis/history of

Trial name	Trial design	Inclusion criteria	Exclusion criteria	Mean age (SD)	Mean follow-up (year)	Study arms		Achieved SBP reduction	Achieved DBP reduction	n of CKD/ without CKD at baseline	Mean eGFR at baseline	Proteinuria definition at baseline	Diabetes definition at baseline
						Intervention (n)	Comparator (n)						
	controlled	160-219 mmHg, sitting DBP <95 mmHg, and standing SBP ≥140 mmHg	retinal haemorrhage/papilloedema, HF, dissecting aortic aneurysm, serum creatinine ≥180 micro mol/l, recent severe nosebleeds, stroke or MI, dementia, disorders prohibiting standing position, severe CVD/non-CVD			(2398)	(2297)					dipstick test result of 1+ or greater	diabetes mellitus, or fasting glucose at randomization ≥ 126 mg/dL (7 mmol/L)
TRANSCEND[68]	Placebo-controlled	Intolerant to ACEI and with established CAD, PVD, CeVD or diabetes with end-organ damage	HF, valvular/cardiac outflow tract obstruction, pericarditis, congenital heart disease, unexplained syncope, recent revascularisation, SBP >160 mmHg, heart transplantation, subarachnoid haemorrhage, significant renal stenosis, proteinuria, renal or hepatic dysfunction	68 (7)	4.9	ARB (2954)	Placebo (2972)	4.5	2.2	1,574/4,213	71.7	A urinary protein dipstick test result of 1+ or greater	Diagnosis/history of diabetes mellitus, or fasting glucose at randomization ≥ 126 mg/dL (7 mmol/l)
UKPDS[69]	Intensive	Age 25-65 years, newly-diagnosed diabetes, and hypertension (untreated: SBP ≥160 mmHg and/or DBP ≥90 mmHg; treated: SBP ≥150 mmHg and/or DBP ≥85 mmHg)	Ketonuria, recent MI, angina, HF, >1 major vascular episode, serum creatinine >15 micro mol/, retinopathy, malignant hypertension, uncorrected endocrine abnormality, severe concurrent illness	56 (8)	7.9	More intensive (758)	Less intensive (390)	11.2	1.2	77/1,043	85.1	/	Fasting plasma glucose concentration > 108 mg/dl (6 mmol/l) on two mornings
VALISH[70]	Intensive	Age ≥70 to <85 years, isolated hypertension (SBP >160 mmHg and DBP <90 mmHg)	Secondary or malignant hypertension, BP ≥200/≥90 mmHg, recent CeVD or MI, recent/planned revascularisation, HF, aortic stenosis, valvular heart disease, atrial fibrillation/flutter, serious arrhythmia, renal/liver dysfunction	76 (4)	2.6	More intensive (1545)	Less intensive (1534)	5.0	1.8	177/2,120	84.6	/	Diagnosis/history of diabetes mellitus, or fasting glucose at randomization ≥126 mg/dL (7 mmol/L)
VALUE[71]	Drug classes comparison	Age ≥50 years, hypertension, CVD, CVD risk factors (male sex, age >50 years, diabetes, current smoking, high cholesterol, LVH, proteinuria, serum creatinine 150 to 265 micro mol/l)	Renal artery stenosis, recent CAD or CeVD, severe hepatic disease or chronic renal failure, HF, on monotherapy with beta-blocker for CAD and hypertension	67 (8)	4.2	CCB-based (7596)	ARB-based (7649)	1.6	1.3	5,280/9,965	65.7	A urinary protein dipstick test result of 1+ or greater	Diagnosis/history of diabetes mellitus, or fasting glucose at randomization ≥126 mg/dl (7 mmol/L)
VHAS[72]	Drug classes	Age 40-65 years, BP ≥160/95 mmHg	Secondary hypertension, recent stroke or TIA, CAD,	54 (7)	1.7	Diuretic (707)	CCB (707)	1.7	1.3	79/1,321	86.1	/	Diagnosis/history of diabetes mellitus

Trial name	Trial design	Inclusion criteria	Exclusion criteria	Mean age (SD)	Mean follow-up (year)	Study arms		Achieved SBP reduction	Achieved DBP reduction	n of CKD/ without CKD at baseline	Mean eGFR at baseline	Proteinuria definition at baseline	Diabetes definition at baseline
						Intervention (n)	Comparator (n)						
	comparison		PAD, bradycardia, arrhythmias, HF, renal or hepatic dysfunction, hyperuricaemia, hypokalemia, type 1 diabetes mellitus, familial dyslipidemia, serious concomitant disease										
HDFP[73]	Intensive	Ages 30-69 years, hypertension, DBP home readings and clinic readings ≥ 95 mmHg and 90 mmHg, respectively	Bedfast or institutionalized persons	50.8	7.2	More intensive (5553)	Less intensive (5387)	9.9	4.9	3,148/6,652	68.0	/	Diagnosis/history of diabetes mellitus, or random blood glucose > 200 mg/dl (11.1 mmol/L)

Continuous variables are presented as mean (SD) unless otherwise stated; follow-up is reported in years. n denotes the number randomised per arm. "More intensive" versus "less intensive" indicates the randomised blood-pressure target/strategy (or, for drug-class/placebo trials, the randomised treatment comparison). Achieved SBP reduction and Achieved DBP reduction denote the between-arm difference in achieved systolic and diastolic blood pressure during follow-up (mmHg), and were estimated using linear mixed models applied to each trial separately, and the values were used as delta for standardisation of blood pressure reduction across trials in the Cox proportional hazard model for assessing treatment effect per fixed amount of systolic blood pressure reduction on risk of cardiovascular diseases. The "n of CKD/without CKD at baseline" column provides the number of participants with and without chronic kidney disease at baseline using trial-specific definitions; baseline renal function is summarised as mean eGFR where available (mL/min/1.73 m²). Proteinuria and diabetes definitions are reproduced verbatim from the original trial reports; units are as reported (with SI conversions shown in parentheses where available). "/" indicates not reported or not applicable. Superscript numerals after trial names correspond to the reference list beneath the table.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CeVD, cerebrovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; CCB, calcium-channel blocker; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein (cholesterol); HF, heart failure; (L)VEF, (left) ventricular ejection fraction; LVH, left ventricular hypertrophy; MI, myocardial infarction; NYHA, New York Heart Association; PAD/PVD, peripheral arterial/vascular disease; SBP, systolic blood pressure; SD, standard deviation; TC:HDL, total cholesterol:HDL cholesterol ratio; TIA, transient ischaemic attack.

Table S3. Number at risk per year for Kaplan-Meier curves of major cardiovascular events, stratified by treatment allocation and chronic kidney disease stage

Subgroup	Arms	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
CKD stage 1	Treatment	31625	29761	27002	23156	16230	6658
	Comparator	34869	32869	30037	25879	18768	7400
CKD stage 2	Treatment	74107	69506	63121	55723	43443	19470
	Comparator	84531	79161	72233	63717	49956	21858
CKD stage 3a	Treatment	21068	19249	17043	14857	11594	5021
	Comparator	23834	21670	19260	16726	13133	5589
CKD stage 3b	Treatment	5643	5050	4334	3554	2660	1093
	Comparator	6350	5603	4898	4038	3052	1231
CKD stage 4–5	Treatment	1015	896	760	594	391	162
	Comparator	1092	918	790	612	422	163

Table S4. Effects of blood pressure-lowering treatment on primary and secondary outcomes, stratified by a composite of chronic kidney disease and proteinuria status at baseline

Outcome	Subgroup	Events Trt	Events Cmp	Total Trt	Total Cmp	HR (95% CI)
Major cardiovascular events	CKD + proteinuria	584	618	2962	3005	0.89 (0.78–1.01)
	CKD + no proteinuria	1309	1652	11022	12081	0.87 (0.80–0.93)
	No CKD + proteinuria	666	791	5383	6104	0.94 (0.83–1.07)
	No CKD + no proteinuria	2975	3991	41219	45757	0.87 (0.83–0.91)
						P interaction >0.99
Stroke	CKD + proteinuria	150	178	2962	3014	0.80 (0.61–1.04)
	CKD + no proteinuria	430	609	11041	12107	0.78 (0.69–0.88)
	No CKD + proteinuria	248	285	5387	6106	1.02 (0.80–1.30)
	No CKD + no proteinuria	1028	1490	41279	45806	0.77 (0.70–0.84)
						P interaction = 0.21
Ischaemic heart disease	CKD + proteinuria	188	205	2962	3008	0.84 (0.67–1.05)
	CKD + no proteinuria	577	688	11038	12103	0.92 (0.82–1.03)
	No CKD + proteinuria	197	252	5386	6099	0.89 (0.72–1.09)
	No CKD + no proteinuria	1541	1961	41271	45798	0.91 (0.85–0.97)
						P interaction >0.99
Cardiovascular death	CKD + proteinuria	187	2957	202	3006	0.82 (0.65-1.03)
	CKD + no proteinuria	375	10971	479	12030	0.85 (0.74-0.97)
	No CKD + proteinuria	215	5368	235	6077	0.98 (0.78-1.25)
	No CKD + no proteinuria	610	40872	789	45411	0.89 (0.80-0.99)
						P interaction>0.99
All-cause death	CKD + proteinuria	508	2963	605	3013	0.87 (0.76-1.00)
	CKD + no proteinuria	1269	11042	1561	12108	0.90 (0.83-0.97)
	No CKD + proteinuria	549	5389	642	6104	0.98 (0.84-1.14)
	No CKD + no proteinuria	2299	41275	2890	45802	0.96 (0.91-1.02)
						P interaction=0.84

Trt = treatment; Cmp = comparator. Subgroup: a four-level categorical variable was defined based on CKD and proteinuria status. The P-value for interaction was derived using a likelihood-ratio test comparing models with and without an interaction term (treatment arm × CKD/proteinuria composite status).

Table S5. Comparison of treatment effects estimated by the Cox model versus the Fine-Gray model for competing risk adjustment of all-cause death.

Outcome	Subgroup	Cox model HR (95% CI)	Fine & Gray SHR (95% CI)
Major CVD	CKD	0.91 (0.87–0.94)	0.90 (0.87–0.94)
	No CKD	0.90 (0.88–0.93)	0.90 (0.88–0.93)
Stroke	CKD	0.90 (0.84–0.96)	0.89 (0.84–0.95)
	No CKD	0.86 (0.83–0.90)	0.86 (0.83–0.90)
Ischaemic heart disease	CKD	0.92 (0.87–0.97)	0.92 (0.87–0.98)
	No CKD	0.93 (0.89–0.96)	0.93 (0.89–0.96)
Heart failure	CKD	0.85 (0.78–0.92)	0.86 (0.79–0.93)
	No CKD	0.87 (0.81–0.93)	0.87 (0.81–0.93)

HR = hazard ratio; SHR = subdistribution hazard ratio; CI = confidence interval.

Table S6. Two-stage random-effects meta-analysis of the effects of blood pressure lowering on the risk of major cardiovascular disease outcomes, stratified by chronic kidney disease status

Trial	CKD			Non CKD	
	HR (95% CI) per 5 mmHg SBP reduction	W%		HR (95% CI) per 5 mmHg SBP reduction	W%
AASK	1.02 [0.89, 1.16]	5.9		0.75 [0.38, 1.49]	0.3
ABCD	1.00 [0.69, 1.45]	0.7		0.98 [0.77, 1.24]	2.1
ACCORD	0.95 [0.83, 1.09]	5.3		0.96 [0.91, 1.02]	8
ACTIVE	0.89 [0.62, 1.27]	0.8		1.13 [0.85, 1.50]	1.5
ADVANCE	1.02 [0.86, 1.21]	3.6		0.96 [0.88, 1.05]	6.4
ALLHAT	0.77 [0.62, 0.96]	2.1		0.93 [0.81, 1.06]	4.5
ANBP2	3.11 [0.58, 16.76]	0		0.93 [0.28, 3.11]	0.1
ASCOT-BPLA	0.83 [0.54, 1.28]	0.5		0.74 [0.57, 0.96]	1.8
BENEDICT	—	0		0.33 [0.00, 42.23]	0
CAMELOT	4.60 [0.66, 32.30]	0		0.54 [0.34, 0.86]	0.6
CAPPP	1.24 [0.35, 4.36]	0.1		0.76 [0.54, 1.09]	1
CARDIOSIS	0.70 [0.10, 5.04]	0		0.36 [0.12, 1.07]	0.1
CASEJ	0.72 [0.09, 5.77]	0		0.62 [0.23, 1.65]	0.1
COLM	Exc	0		4.49 [0.01, 1557.02]	0
COPE	Exc	0		Exc	0
DIABHYCAR	0.74 [0.15, 3.54]	0		0.99 [0.38, 2.53]	0.2
Dutch TIA	1.18 [0.46, 3.07]	0.1		1.02 [0.61, 1.72]	0.5
ELSA	Exc	0		0.33 [0.01, 9.47]	0
EUROPA	0.87 [0.63, 1.20]	1		0.73 [0.63, 0.84]	4
EWPHE	0.91 [0.83, 1.01]	11.1		0.97 [0.89, 1.04]	7
HDFP	0.92 [0.87, 0.99]	23.9		0.95 [0.90, 1.01]	8.1
HIJCREATE	Exc	0		2.06 [0.06, 66.96]	0
HOPE	0.58 [0.42, 0.80]	1		0.68 [0.55, 0.85]	2.4
HYVET	0.85 [0.75, 0.96]	6.4		0.86 [0.77, 0.96]	5.3
IDNT	0.81 [0.52, 1.24]	0.5		1.44 [0.68, 3.06]	0.3
INSIGHT	1.87 [0.38, 9.22]	0		0.28 [0.08, 0.91]	0.1
JMIC-B	2.69 [0.25, 29.39]	0		0.77 [0.21, 2.78]	0.1
LIFE	0.95 [0.31, 2.97]	0.1		0.52 [0.28, 1.00]	0.3
NICSEH	Exc	0		Exc	0
NORDIL	1.32 [0.73, 2.37]	0.3		0.93 [0.75, 1.17]	2.2
ONTARGET	0.71 [0.51, 0.99]	0.9		0.99 [0.77, 1.26]	1.9
PART2	1.29 [0.52, 3.20]	0.1		0.87 [0.60, 1.25]	1
PREVENDIT	0.91 [0.12, 6.90]	0		0.73 [0.47, 1.13]	0.7
PREVENT	0.67 [0.31, 1.43]	0.2		0.94 [0.55, 1.63]	0.5
PROGRESS	0.89 [0.77, 1.02]	5.4		0.84 [0.78, 0.90]	7.2
PROFESS	0.99 [0.77, 1.28]	1.6		0.94 [0.81, 1.09]	4.1
SHEP	0.94 [0.85, 1.04]	9.5		0.97 [0.88, 1.07]	6.2
SPRINT	0.93 [0.85, 1.02]	12.6		0.89 [0.83, 0.96]	7.3
STOP2	1.13 [0.74, 1.74]	0.6		1.00 [0.71, 1.42]	1.1
SYSTEUR	0.87 [0.72, 1.05]	3		0.84 [0.73, 0.98]	4
TRANSCEND	0.88 [0.66, 1.16]	1.3		0.84 [0.68, 1.03]	2.5
UKPDS	1.14 [0.72, 1.80]	0.5		0.84 [0.74, 0.95]	4.9
VALISH	1.39 [0.45, 4.24]	0.1		0.70 [0.38, 1.28]	0.4
VALUE	0.78 [0.50, 1.20]	0.5		0.87 [0.59, 1.29]	0.9
VHAS	Exc	0		2.09 [0.18, 23.57]	0
HOMEDBP	0.00 [0.00, Inf]	0		1.29 [0.34, 4.86]	0.1
Fixed Effects Model (Overall)	0.92 [0.89, 0.95]			0.91 [0.89, 0.93]	
Random Effects Model (Overall)	0.92 [0.89, 0.95]			0.89 [0.86, 0.93]	
I^2 (Percentage of Total Variability)	0			37%	
τ (Between-Study Standard Deviation)	0			0.0627	
Tau-square	0			0.0039	
Q Test p-value	0.8288			0.0071	

W: Weight. Dash (–): Data not available for the BENEDICT trial. Exc: Excluded from the two-stage meta-analysis due to extremely wide confidence intervals, SBP: systolic blood pressure.

Table S7. Unstandardised treatment effects

	Events Int	Events Cmp	Total Int	Total Cmp	HR (95% CI)
Major cardiovascular events					
CKD	4777	6022	27726	31276	0.91 (0.88–0.95)
No CKD	11153	14521	105732	119400	0.92 (0.89–0.94)
Overall	15930	20543	133458	150676	0.92 (0.90–0.94)
					P interaction >0.99
Stroke					
CKD	1665	2112	27753	31319	0.90 (0.85–0.96)
No CKD	3922	5096	105819	119459	0.88 (0.85–0.92)
Overall	5587	7208	133572	150778	0.89 (0.86–0.92)
					P interaction >0.99
Ischemic heart disease					
CKD	2124	27751	2760	31312	0.92 (0.87-0.98)
No CKD	5555	105812	7378	119458	0.94 (0.90-0.97)
Overall	7679	133563	10138	150770	0.93 (0.91-0.96)
					P interaction>0.99
Heart failure					
CKD	1169	24710	1572	28512	0.86 (0.80-0.93)
No CKD	1695	89609	2439	103371	0.89 (0.83-0.95)
Overall	2864	114319	4011	131883	0.89 (0.84-0.93)
					P interaction>0.99
Cardiovascular death					
CKD	1656	27627	2104	31215	0.93 (0.87-0.99)
No CKD	2767	104699	3517	118681	0.95 (0.91-1.00)
Overall	4423	132326	5621	149896	0.95 (0.91-0.99)
					P interaction=0.97
All-cause death					
CKD	3958	27756	4926	31332	0.95 (0.91-0.99)
No CKD	7357	105828	8956	119459	0.99 (0.96-1.03)
Overall	11315	133584	13882	150781	0.98 (0.96-1.01)
					P interaction=0.15

Int = intervention; Cmp = comparator.

Table S8. Sensitivity analysis excluding head-to-head trials

Subgroups by outcomes	Events Trt	Events Cmp	Total Trt	Total Cmp	HR (95% CI)
Major cardiovascular events					
CKD	2469	2637	14211	13490	0.90 (0.84–0.95)
No CKD	5453	6095	50301	48749	0.89 (0.86–0.93)
Overall	7922	8732	64512	62239	0.89 (0.87–0.92)
					P interaction >0.99
Stroke					
CKD	894	14217	1020	13497	0.89 (0.80-0.98)
No CKD	2042	50319	2413	48757	0.86 (0.81-0.91)
Overall	2936	64536	3433	62254	0.87 (0.82-0.91)
					P interaction>0.99
Ischemic heart disease					
CKD	967	14214	1042	13494	0.82 (0.74-0.91)
No CKD	2250	50318	2496	48764	0.86 (0.81-0.92)
Overall	3217	64532	3538	62258	0.86 (0.81-0.90)
					P interaction>0.99
Heart failure					
CKD	521	12014	557	11500	0.84 (0.74-0.95)
No CKD	753	44086	823	42654	0.94 (0.84-1.04)
Overall	1274	56100	1380	54154	0.90 (0.83-0.97)
					P interaction=0.55
Cardiovascular death					
CKD	909	14086	990	13390	0.90 (0.81-0.99)
No CKD	1437	49195	1543	47972	0.96 (0.89-1.03)
Overall	2346	63281	2533	61362	0.94 (0.88-1.00)
					P interaction=0.71
All-cause death					
CKD	1878	14218	2026	13498	0.89 (0.83-0.95)
No CKD	3480	50330	3610	48760	0.97 (0.92-1.02)
Overall	5358	64548	5636	62258	0.94 (0.91-0.98)
					P interaction=0.29

Trt = treatment; Cmp = comparator.

Table S9. Absolute risk reduction (ARR) and number needed to treat (NNT) for the effect of blood pressure-lowering treatment on primary and secondary outcomes, by chronic kidney disease status and stage.

Outcome	Subgroup	Absolute risk %		ARR % (95% CI)	NNT (95% CI)
		Intervention	Comparator		
Major cardiovascular events	CKD	17.23	19.25	2.03 (1.40 to 2.65)	49 (38 to 71)
	No CKD	10.55	12.16	1.61 (1.35 to 1.88)	62 (53 to 74)
	Overall	11.94	13.63	1.70 (1.45 to 1.94)	59 (51 to 69)
Stroke	CKD	6.00	6.74	0.74 (0.35 to 1.14)	134 (88 to 286)
	No CKD	3.71	4.27	0.56 (0.40 to 0.72)	179 (139 to 251)
	Overall	4.18	4.78	0.60 (0.45 to 0.75)	167 (133 to 224)
Ischemic heart disease	CKD	7.65	8.81	1.16 (0.72 to 1.60)	86 (62 to 139)
	No CKD	5.25	6.18	0.93 (0.73 to 1.12)	108 (89 to 136)
	Overall	5.75	6.72	0.97 (0.80 to 1.15)	103 (87 to 125)
Heart failure	CKD	4.73	5.51	0.78 (0.41 to 1.16)	128 (86 to 245)
	No CKD	1.89	2.36	0.47 (0.34 to 0.60)	214 (168 to 295)
	Overall	2.51	3.04	0.54 (0.41 to 0.67)	187 (150 to 246)
Cardiovascular death	CKD	5.99	6.74	0.75 (0.35 to 1.14)	134 (88 to 284)
	No CKD	2.64	2.96	0.32 (0.18 to 0.46)	312 (219 to 544)
	Overall	3.34	3.75	0.41 (0.27 to 0.54)	245 (184 to 369)
All-cause death	CKD	14.26	15.72	1.46 (0.89 to 2.04)	68 (49 to 113)
	No CKD	6.95	7.50	0.55 (0.33 to 0.76)	183 (132 to 302)
	Overall	8.47	9.21	0.74 (0.53 to 0.95)	136 (106 to 190)
Major cardiovascular events	1	8.83	10.17	1.35 (0.90 to 1.79)	74 (56 to 111)
	2	11.28	12.98	1.70 (1.38 to 2.02)	59 (50 to 73)
	3a	15.69	17.57	1.88 (1.19 to 2.57)	53 (39 to 84)
	3b	21.23	23.81	2.58 (1.09 to 4.08)	39 (25 to 92)
	4-5	26.90	29.49	2.59 (-1.25 to 6.43)	39 (16 to ∞)
Stroke	1	3.08	3.37	0.29 (0.02 to 0.56)	346 (179 to 4928)
	2	3.97	4.64	0.66 (0.46 to 0.86)	151 (116 to 216)
	3a	5.68	6.33	0.65 (0.22 to 1.09)	153 (91 to 464)
	3b	6.98	7.82	0.84 (−0.10 to 1.78)	119 (56 to ∞)
	4-5	7.19	9.42	2.23 (−0.12 to 4.58)	45 (22 to ∞)
Ischemic heart disease	1	4.34	5.26	0.91 (0.59 to 1.24)	110 (81 to 170)
	2	5.64	6.56	0.92 (0.68 to 1.15)	109 (87 to 146)
	3a	7.19	8.23	1.04 (0.54 to 1.53)	96 (65 to 184)
	3b	8.83	10.49	1.66 (0.60 to 2.71)	60 (37 to 166)
	4-5	10.72	11.88	1.17 (−1.54 to 3.87)	86 (26 to ∞)
Heart failure	1	1.43	1.87	0.44 (0.23 to 0.65)	228 (155 to 432)
	2	2.09	2.56	0.47 (0.31 to 0.63)	212 (158 to 322)
	3a	3.88	4.58	0.70 (0.30 to 1.09)	143 (92 to 330)
	3b	6.63	7.82	1.19 (0.23 to 2.15)	84 (46 to 436)
	4-5	10.79	11.64	0.85 (−1.90 to 3.59)	118 (28 to ∞)
Cardiovascular death	1	2.03	2.14	0.10 (−0.12 to 0.32)	986 (313 to ∞)
	2	2.90	3.30	0.40 (0.23 to 0.57)	248 (174 to 432)
	3a	4.95	5.79	0.84 (0.42 to 1.25)	120 (80 to 239)
	3b	8.76	9.28	0.53 (−0.50 to 1.55)	190 (64 to ∞)
	4-5	12.25	12.71	0.45 (−2.37 to 3.28)	221 (31 to ∞)
All-cause death	1	5.50	5.96	0.47 (0.11 to 0.82)	214 (122 to 882)
	2	7.57	8.13	0.56 (0.29 to 0.82)	180 (122 to 343)
	3a	12.02	13.57	1.54 (0.93 to 2.16)	65 (46 to 108)
	3b	19.92	20.90	0.98 (−0.47 to 2.42)	102 (41 to ∞)
	4-5	29.23	32.79	3.55 (−0.39 to 7.50)	28 (13 to ∞)

ARR unit is the percentage of absolute risk difference between the treatment and comparator groups over follow-up time and reflects the mean blood pressure reduction in BPLTTC. ∞ Indicates that the 95% CI crosses zero, resulting in an undefined upper bound for NNT.

Table S10. Trials included in the network meta-analysis stratified by chronic kidney disease status, stage, and proteinuria.

Trial	Comparison	No CKD					CKD					No proteinuria					Proteinuria				
		Treatment		Comparator		OR (95% CI)	Treatment		Comparator		OR (95% CI)	Treatment		Comparator		OR (95% CI)	Treatment		Comparator		OR (95% CI)
		E	N	E	N		E	N	E	N		E	N	E	N		E	N	E	N	
ACTIVE	Placebo vs ARB	361	1,821	341	1,827	1.08 (0.91–1.27)	217	726	227	728	0.94 (0.75–1.18)	—	—	—	—	—	—	—	—	—	—
ALLHAT	ACE vs CCB	1,340	6,062	1,331	6,034	1.00 (0.92–1.09)	485	1,507	480	1,565	1.07 (0.92–1.25)	—	—	—	—	—	—	—	—	—	—
ALLHAT	ACE vs DIURET	2,158	10,219	1,331	6,034	0.95 (0.88–1.02)	764	2,597	480	1,565	0.94 (0.82–1.08)	—	—	—	—	—	—	—	—	—	—
ANBP2	ACE vs DIURET	160	2,163	164	2,188	0.99 (0.79–1.24)	93	876	76	856	1.22 (0.89–1.68)	—	—	—	—	—	—	—	—	—	—
ASCOT-BPLA	BETA vs CCB	561	5,327	632	5,310	0.87 (0.77–0.98)	203	1,230	223	1,253	0.91 (0.74–1.13)	—	—	—	—	—	—	—	—	—	—
BENEDICT	Placebo vs ACE	6	288	7	282	0.84 (0.28–2.52)	0	9	0	16	—	0	9	0	16	—	—	—	—	—	—
BENEDICT	Placebo vs CCB	6	286	7	282	0.84 (0.28–2.54)	0	14	0	16	—	0	14	0	16	—	—	—	—	—	—
CAMELOT	Placebo vs ACE	17	603	31	580	0.51 (0.28–0.94)	8	67	1	72	9.63 (1.17–79.20)	—	—	—	—	—	—	—	—	—	—
CAMELOT	Placebo vs CCB	21	605	31	580	0.64 (0.36–1.12)	1	56	1	72	1.29 (0.08–21.10)	—	—	—	—	—	—	—	—	—	—
CASEJ	ARB vs CCB	64	2,118	74	2,099	0.85 (0.61–1.20)	14	231	17	255	0.90 (0.43–1.88)	6	142	11	160	0.60 (0.22–1.66)	8	89	6	95	1.47 (0.49–4.40)
DIABHYCAR	Placebo vs ACE	265	2,023	269	2,049	1.00 (0.83–1.20)	94	417	100	416	0.92 (0.67–1.27)	0	4	1	6	—	94	413	99	410	0.93 (0.67–1.28)
Dutch TIA	Placebo vs BETA	74	613	74	622	1.02 (0.72–1.43)	23	118	21	117	1.11 (0.57–2.13)	—	—	—	—	—	—	—	—	—	—
ELSA	BETA vs CCB	27	1,087	32	1,082	0.84 (0.50–1.40)	1	71	2	60	0.41 (0.04–4.68)	1	64	2	55	0.42 (0.04–4.77)	0	3	—	—	—
EUROPA	Placebo vs ACE	369	5,281	490	5,289	0.74 (0.64–0.85)	81	772	92	773	0.87 (0.63–1.19)	—	—	—	—	—	—	—	—	—	—
EWPHE	Placebo vs DIURET	59	279	69	284	0.84 (0.56–1.24)	35	128	52	136	0.61 (0.36–1.02)	—	—	—	—	—	—	—	—	—	—
HOPE	Placebo vs ACE	423	3,454	534	3,525	0.78 (0.68–0.90)	187	1,187	236	1,120	0.70 (0.57–0.87)	187	1,187	236	1,120	0.70 (0.57–0.87)	—	—	—	—	—
HYVET	Placebo vs DIURET	78	1,135	103	1,079	0.70 (0.51–0.95)	58	798	90	831	0.65 (0.46–0.91)	49	670	74	701	0.67 (0.46–0.98)	9	128	16	130	0.54 (0.23–1.27)
IDNT	Placebo vs ARB	34	145	31	160	1.27 (0.74–2.21)	102	389	100	368	0.95 (0.69–1.31)	3	8	3	16	2.60 (0.39–17.45)	95	370	95	344	0.91 (0.65–1.26)
IDNT	Placebo vs CCB	36	159	31	160	1.22 (0.71–2.09)	91	359	100	368	0.91 (0.65–1.27)	4	14	3	16	1.73 (0.31–9.57)	83	332	95	344	0.87 (0.62–1.23)
INSIGHT	CCB vs DIURET	102	2,351	124	2,370	0.82 (0.63–1.07)	70	811	56	785	1.23 (0.85–1.77)	65	780	47	738	1.34 (0.91–1.97)	5	31	9	47	0.81 (0.24–2.70)
JMIC-B	ACE vs CCB	28	589	30	608	0.96 (0.57–1.63)	14	82	6	62	1.92 (0.69–5.33)	—	—	—	—	—	—	—	—	—	—
LIFE	BETA vs ARB	368	3,585	402	3,596	0.91 (0.78–1.06)	131	809	138	788	0.91 (0.70–1.18)	95	665	98	621	0.89 (0.65–1.21)	23	75	25	87	1.10 (0.56–2.16)
NICSEH	CCB vs DIURET	12	193	7	186	1.70 (0.65–4.40)	1	17	2	20	0.56 (0.05–6.81)	—	—	—	—	—	—	—	—	—	—
ONTARGET	ACE vs ARB	694	6,280	699	6,361	1.01 (0.90–1.12)	361	2,072	341	2,007	1.03 (0.88–1.21)	252	1,622	253	1,583	0.97 (0.80–1.17)	105	434	88	417	1.19 (0.86–1.65)
PART2	Placebo vs ACE	32	263	37	257	0.82 (0.50–1.37)	6	45	5	52	1.45 (0.41–5.10)	6	42	2	46	3.67 (0.70–19.28)	0	3	3	6	—
PREVENDIT	Placebo vs ACE	28	413	40	427	0.70 (0.43–1.16)	3	18	1	5	0.80 (0.06–9.92)	3	18	1	5	0.80 (0.06–9.92)	—	—	—	—	—
PREVENT	Placebo vs CCB	17	324	18	317	0.92 (0.47–1.82)	7	89	12	91	0.56 (0.21–1.50)	6	78	7	78	0.85 (0.27–2.64)	1	11	4	12	0.20 (0.02–2.16)
PROFESS	Placebo vs ARB	800	6,803	840	6,837	0.95 (0.86–1.05)	253	1,465	262	1,512	1.00 (0.82–1.20)	—	—	—	—	—	—	—	—	—	—
STOP2	ACE vs CCB	283	1,506	256	1,447	1.08 (0.89–1.30)	165	676	181	746	1.01 (0.79–1.28)	—	—	—	—	—	—	—	—	—	—
SYSTEUR	Placebo vs CCB	76	1,721	101	1,668	0.72 (0.53–0.97)	51	671	61	628	0.76 (0.52–1.13)	49	649	54	603	0.83 (0.55–1.24)	1	12	6	21	0.23 (0.02–2.17)
TRANSCEND	Placebo vs ARB	197	2,066	239	2,147	0.84 (0.69–1.03)	121	827	123	747	0.87 (0.66–1.14)	121	821	121	744	0.89 (0.68–1.17)	0	5	1	2	—
VALUE	ARB vs CCB	486	4,956	510	5,009	0.96 (0.84–1.09)	385	2,640	407	2,640	0.94 (0.81–1.09)	269	1,963	295	1,965	0.90 (0.75–1.07)	116	677	112	675	1.04 (0.78–1.38)
VHAS	CCB vs DIURET	12	662	13	659	0.91 (0.41–2.04)	0	40	1	39	—	—	—	—	—	—	—	—	—	—	—

CKD: eGFR <60 ml/min/1.73m² (CKD-EPI 2021). Proteinuria: UACR ≥30 mg/g, UPCR ≥150 mg/g, or dipstick ≥1+. Proteinuria analysis is restricted to participants with CKD. E: events. N: participants. OR: odds ratio. CI: confidence interval. '—': not available/estimable.

Trial	Comparison	Stage 1 (≥90)					Stage 2 (60–89)					Stage 3a (45–59)					Stage 3b (30–44)					Stage 4–5 (<30)				
		Trt		Cmp		OR (95% CI)	Trt		Cmp		OR (95% CI)	Trt		Cmp		OR (95% CI)	Trt		Cmp		OR (95% CI)	Trt		Cmp		OR (95% CI)
		E	N	E	N		E	N	E	N		E	N	E	N		E	N	E	N		E	N	E	N	
ACTIVE	Placebo vs ARB	60	437	62	424	0.93 (0.63–1.36)	301	1,384	279	1,403	1.12 (0.93–1.34)	152	537	155	544	0.99 (0.76–1.29)	51	164	57	154	0.77 (0.48–1.22)	14	25	15	30	1.27 (0.44–3.69)
ALLHAT	ACE vs CCB	353	1,742	364	1,741	0.96 (0.82–1.13)	987	4,320	967	4,293	1.02 (0.92–1.13)	349	1,118	329	1,127	1.10 (0.92–1.32)	114	337	125	380	1.04 (0.76–1.42)	22	52	26	58	0.90 (0.42–1.92)
ALLHAT	ACE vs DIURET	575	2,931	364	1,741	0.92 (0.80–1.07)	1,583	7,288	967	4,293	0.95 (0.87–1.04)	507	1,889	329	1,127	0.89 (0.76–1.05)	214	601	125	380	1.13 (0.86–1.48)	43	107	26	58	0.83 (0.43–1.58)
ANBP2	ACE vs DIURET	17	267	20	286	0.90 (0.46–1.77)	143	1,896	144	1,902	1.00 (0.78–1.27)	74	723	61	721	1.23 (0.86–1.76)	18	144	13	129	1.27 (0.60–2.72)	1	9	2	6	0.25 (0.02–3.66)
ASCOT-BPLA	BETA vs CCB	63	593	61	603	1.06 (0.73–1.53)	498	4,734	571	4,707	0.85 (0.75–0.97)	170	1,073	182	1,074	0.92 (0.73–1.16)	31	150	39	172	0.89 (0.52–1.51)	2	7	2	7	1.00 (0.10–10.17)
BENEDICT	Placebo vs ACE	0	110	1	109	—	6	178	6	173	0.97 (0.31–3.07)	0	9	0	15	—	—	—	—	—	—	—	—	—	—	—
BENEDICT	Placebo vs CCB	2	118	1	109	1.86 (0.17–20.83)	4	168	6	173	0.68 (0.19–2.45)	0	11	0	15	—	0	3	0	1	—	—	—	—	—	—
CAMELOT	Placebo vs ACE	7	218	8	186	0.74 (0.26–2.08)	10	385	23	394	0.43 (0.20–0.92)	7	55	1	62	8.90 (1.06–74.76)	1	12	0	8	—	—	—	—	—	—
CAMELOT	Placebo vs CCB	3	201	8	186	0.34 (0.09–1.29)	18	404	23	394	0.75 (0.40–1.42)	1	47	1	62	1.33 (0.08–21.76)	0	8	0	8	—	0	1	0	2	—
CASEJ	ARB vs CCB	23	1,152	38	1,147	0.59 (0.35–1.00)	41	966	36	952	1.13 (0.71–1.78)	10	163	12	184	0.94 (0.39–2.23)	4	52	3	60	1.58 (0.34–7.43)	0	16	2	11	—
DIABHYCAR	Placebo vs ACE	77	750	79	750	0.97 (0.70–1.35)	188	1,273	190	1,299	1.01 (0.81–1.26)	78	361	78	347	0.95 (0.67–1.36)	16	55	21	68	0.92 (0.42–2.00)	0	1	1	1	—
Dutch TIA	Placebo vs BETA	16	144	16	139	0.96 (0.46–2.01)	58	469	58	483	1.03 (0.70–1.52)	17	92	19	100	0.97 (0.47–2.00)	6	25	2	16	2.21 (0.39–12.63)	0	1	0	1	—
ELSA	BETA vs CCB	10	413	9	386	1.04 (0.42–2.59)	17	674	23	696	0.76 (0.40–1.43)	1	67	2	55	0.40 (0.04–4.55)	0	4	0	5	—	—	—	—	—	—
EUROPA	Placebo vs ACE	84	1,507	120	1,558	0.71 (0.53–0.94)	285	3,774	370	3,731	0.74 (0.63–0.87)	71	692	76	690	0.92 (0.66–1.30)	10	80	15	81	0.63 (0.26–1.50)	0	0	1	2	—
EWPHE	Placebo vs DIURET	13	60	11	62	1.28 (0.52–3.14)	46	219	58	222	0.75 (0.48–1.17)	24	93	32	99	0.73 (0.39–1.36)	10	31	17	32	0.42 (0.15–1.17)	1	4	3	5	0.22 (0.01–3.98)
HOPE	Placebo vs ACE	88	732	124	782	0.73 (0.54–0.97)	335	2,722	410	2,743	0.80 (0.68–0.93)	141	963	171	906	0.74 (0.58–0.94)	40	212	58	191	0.53 (0.34–0.85)	6	12	7	23	2.29 (0.54–9.63)
HYVET	Placebo vs DIURET	8	98	7	99	1.17 (0.41–3.36)	70	1,037	96	980	0.67 (0.48–0.92)	39	588	65	624	0.61 (0.40–0.92)	19	210	25	205	0.72 (0.38–1.35)	0	0	0	2	—
IDNT	Placebo vs ARB	3	18	3	21	1.20 (0.21–6.84)	31	127	28	139	1.28 (0.72–2.29)	47	150	36	132	1.22 (0.73–2.04)	30	152	34	142	0.78 (0.45–1.36)	25	87	30	94	0.86 (0.46–1.62)
IDNT	Placebo vs CCB	0	9	3	21	—	36	150	28	139	1.25 (0.72–2.19)	31	126	36	132	0.87 (0.50–1.52)	38	150	34	142	1.08 (0.63–1.84)	22	83	30	94	0.77 (0.40–1.48)
INSIGHT	CCB vs DIURET	19	478	25	505	0.79 (0.43–1.46)	83	1,873	99	1,865	0.83 (0.61–1.12)	57	694	41	646	1.32 (0.87–2.00)	13	114	15	132	1.00 (0.46–2.21)	0	3	0	7	—
JMIC-B	ACE vs CCB	12	341	15	343	0.80 (0.37–1.73)	16	248	15	265	1.15 (0.56–2.38)	8	61	4	53	1.85 (0.52–6.53)	5	18	2	8	1.15 (0.17–7.74)	1	3	0	1	—
LIFE	BETA vs ARB	84	833	77	907	1.21 (0.87–1.67)	284	2,752	325	2,689	0.84 (0.71–0.99)	95	666	107	660	0.86 (0.64–1.16)	28	128	28	121	0.93 (0.51–1.69)	8	15	3	7	1.52 (0.25–9.29)
NICSEH	CCB vs DIURET	9	105	7	113	1.42 (0.51–3.96)	3	88	0	73	—	0	14	1	16	—	1	3	1	4	1.50 (0.06–40.63)	—	—	—	—	—
ONTARGET	ACE vs ARB	143	1,640	158	1,734	0.95 (0.75–1.21)	551	4,640	541	4,627	1.02 (0.90–1.15)	206	1,460	212	1,448	0.96 (0.78–1.18)	132	537	105	487	1.19 (0.89–1.59)	23	75	24	72	0.88 (0.44–1.77)
PART2	Placebo vs ACE	6	59	7	61	0.87 (0.28–2.77)	26	204	30	196	0.80 (0.46–1.42)	6	40	5	49	1.55 (0.44–5.52)	0	5	0	3	—	—	—	—	—	—
PREVENDIT	Placebo vs ACE	11	187	16	212	0.77 (0.35–1.69)	17	226	24	215	0.65 (0.34–1.24)	3	15	0	4	—	0	3	1	1	—	—	—	—	—	—
PREVENT	Placebo vs CCB	2	35	2	41	1.18 (0.16–8.86)	15	289	16	276	0.89 (0.43–1.84)	5	78	9	78	0.53 (0.17–1.64)	2	11	3	12	0.67 (0.09–4.99)	0	0	0	1	—
PROFESS	Placebo vs ARB	284	2,580	294	2,612	0.98 (0.82–1.16)	516	4,223	546	4,225	0.94 (0.82–1.07)	179	1,090	178	1,139	1.06 (0.85–1.33)	58	326	69	316	0.77 (0.52–1.14)	16	49	15	57	1.36 (0.59–3.14)
STOP2	ACE vs CCB	23	138	20	133	1.13 (0.59–2.17)	260	1,368	236	1,314	1.07 (0.88–1.30)	130	562	142	630	1.03 (0.79–1.36)	33	107	37	109	0.87 (0.49–1.54)	2	7	2	7	—
SYSTEUR	Placebo vs CCB	8	330	14	302	0.51 (0.21–1.24)	68	1,391	87	1,366	0.76 (0.55–1.05)	38	561	48	534	0.74 (0.47–1.15)	12	106	11	88	0.89 (0.37–2.14)	1	4	2	6	0.67 (0.04–11.29)
TRANSCEND	Placebo vs ARB	50	486	60	546	0.93 (0.62–1.38)	147	1,580	179	1,601	0.81 (0.65–1.03)	85	611	83	562	0.93 (0.67–1.29)	30	180	30	159	0.86 (0.49–1.50)	6	36	10	26	0.32 (0.10–1.04)
VALUE	ARB vs CCB	39	424	41	434	0.97 (0.61–1.54)	447	4,532	469	4,575	0.96 (0.84–1.10)	264	2,039	276	1,993	0.93 (0.77–1.11)	95	510	109	541	0.91 (0.67–1.23)	26	91	22	106	1.53 (0.79–2.94)
VHAS	CCB vs DIURET	8	287	6	300	1.41 (0.48–4.10)	4	375	7	359	0.54 (0.16–1.87)	0	40	0	37	—	0	0	1	2	—	—	—	—	—	—

CKD stages are defined by eGFR (ml/min/1.73 m²) using the CKD-EPI 2021 equation. Trt: treatment arm. Cmp: comparator arm. E: events. N: participants. OR: odds ratio. CI: confidence interval. '—': not available/estimable.

Table S11. Assessment of heterogeneity and network inconsistency in network meta-analysis.

Subgroup Analysis	No. of Studies	Heterogeneity			Global Inconsistency (Design-by-Treatment interaction)					
		I^2	tau	tau^2	Q statistics (total)	P value (total)	Q statistics (Within-designs)	P value (Within-designs)	Q statistics (Between-designs)	P value (Between-designs)
CKD status										
CKD	29	0.0%	0.000	0.000	24.34	0.56	7.21	0.89	17.13	0.19
No CKD	29	0.0%	0.045	0.002	25.65	0.59	15.11	0.44	10.54	0.65
CKD stages										
Stage 1 (eGFR >=90)	29	0.0%	0.000	0.000	15.78	0.97	9.31	0.86	6.47	0.93
Stage 2 (60<=eGFR<90)	29	0.0%	0.027	0.001	24.41	0.65	15.32	0.43	9.19	0.76
Stage 3a (45<=eGFR<60)	29	6.7%	0.044	0.002	26.80	0.37	5.98	0.92	20.81	0.08
Stage 3b (30<=eGFR<45)	29	0.0%	0.000	0.000	9.82	0.98	4.26	0.94	5.57	0.90
Stage 4-5 (eGFR <30)	23	0.0%	0.000	0.000	11.69	0.63	8.37	0.14	3.32	0.95
Proteinuria status										
Proteinuria	13	0.0%	0.000	0.000	7.06	0.53	1.57	0.67	5.49	0.36
No proteinuria	16	0.0%	0.073	0.005	10.25	0.51	4.47	0.48	5.78	0.45

Supplementary Figures

Figure S1. Flow chart of trial selection for the BPLTTC systematic review and current study

The left panel shows the BPLTTC third-cycle systematic review conducted to identify eligible trials, and the right panel shows the selection process for the current study. IPD: Individual participant data, the previous aggregate data meta-analysis refers to the following publication by the same team: PMID: 26724178

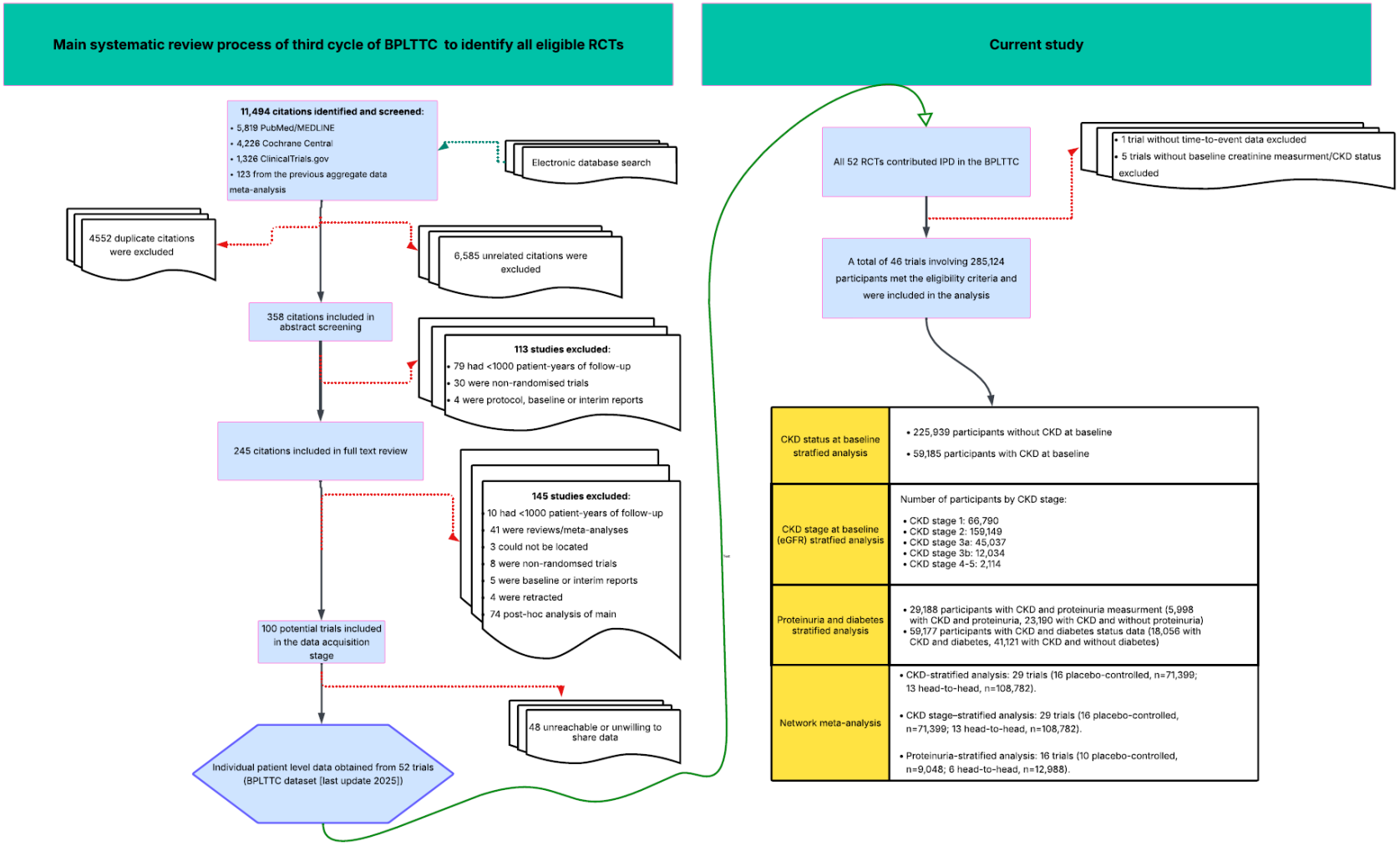


Figure S2. Distribution of estimated glomerular filtration rate (eGFR) and chronic kidney disease stage at baseline

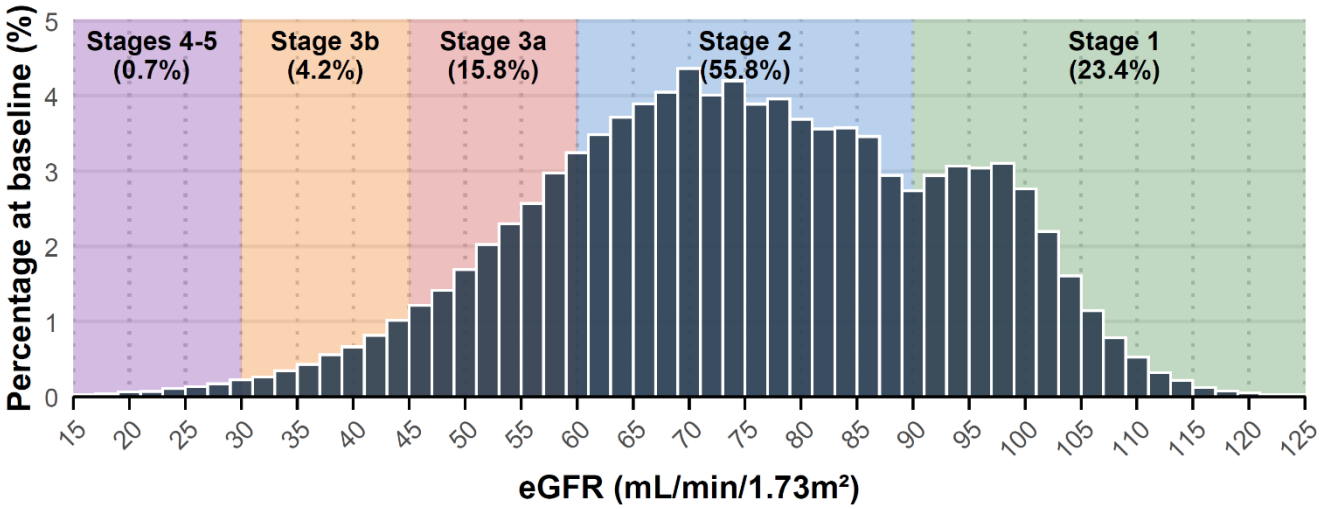


Figure S3. Cumulative probability of major cardiovascular events by treatment allocation per 5 mmHg reduction in systolic blood pressure, stratified by CKD status at baseline

CKD = chronic kidney disease. HR = hazard ratio. CI = confidence interval.

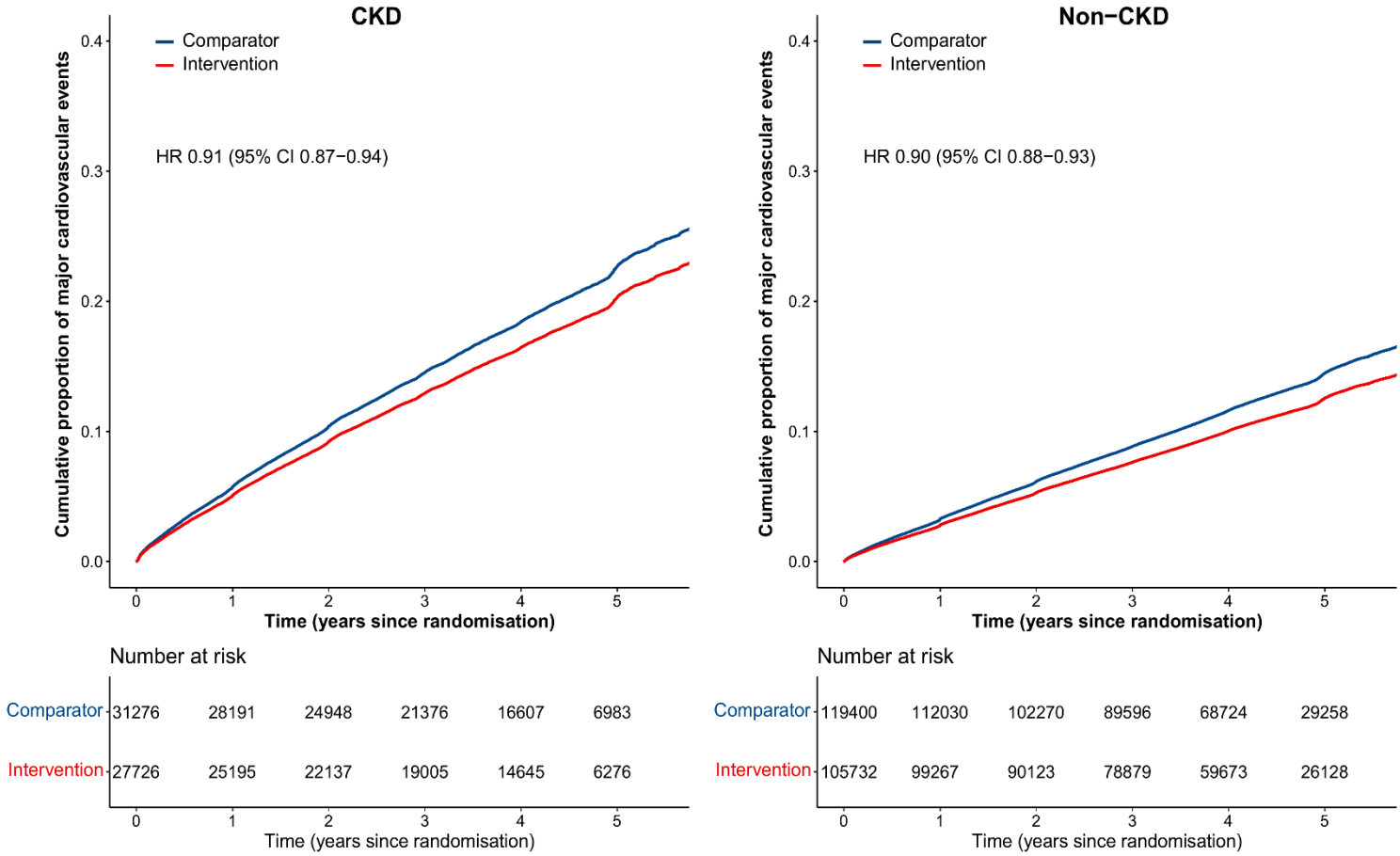


Figure S4. Effects of blood pressure-lowering treatment on primary and secondary outcomes by baseline chronic kidney disease status

The forest plot shows hazard ratios (HRs) and 95% confidence intervals (CIs) per 5 mmHg reduction in systolic blood pressure, separately for each outcome. P-values for interaction were derived from likelihood-ratio tests comparing models with and without treatment-by-CKD interaction terms and were adjusted for multiple testing using Hommel's method. 'Events' denotes the number of participants who experienced the outcome; 'Total' denotes the total number at risk. The size of each square is proportional to the inverse variance of the log HR. The vertical line indicates HR = 1.0 (no effect). CKD = chronic kidney disease.

	Intervention		Comparator		
	Events	Total	Events	Total	HR (95%CI)
Major cardiovascular events					
CKD	4777	27726	6022	31276	0.91 (0.87–0.94)
No CKD	11153	105732	14521	119400	0.90 (0.88–0.93)
Overall	15930	133458	20543	150676	0.91 (0.89–0.93)
					P interaction >0.99
Stroke					
CKD	1665	27753	2112	31319	0.90 (0.84–0.96)
No CKD	3922	105819	5096	119459	0.86 (0.83–0.90)
Overall	5587	133572	7208	150778	0.88 (0.85–0.91)
					P interaction >0.99
Ischemic heart disease					
CKD	2124	27751	2760	31312	0.92 (0.87–0.97)
No CKD	5555	105812	7378	119458	0.93 (0.89–0.96)
Overall	7679	133563	10138	150770	0.93 (0.90–0.96)
					P interaction >0.99
Heart failure					
CKD	1169	24710	1572	28512	0.85 (0.78–0.92)
No CKD	1695	89609	2439	103371	0.87 (0.81–0.93)
Overall	2864	114319	4011	131883	0.87 (0.82–0.92)
					P interaction >0.99
Cardiovascular death					
CKD	1656	27627	2104	31215	0.93 (0.87–0.99)
No CKD	2767	104699	3517	118681	0.94 (0.89–0.99)
Overall	4423	132326	5621	149896	0.94 (0.90–0.98)
					P interaction=0.97
All−cause death					
CKD	3958	27756	4926	31332	0.95 (0.91–0.99)
No CKD	7357	105828	8956	119459	0.98 (0.95–1.01)
Overall	11315	133584	13882	150781	0.97 (0.95–1.00)
					P interaction=0.15

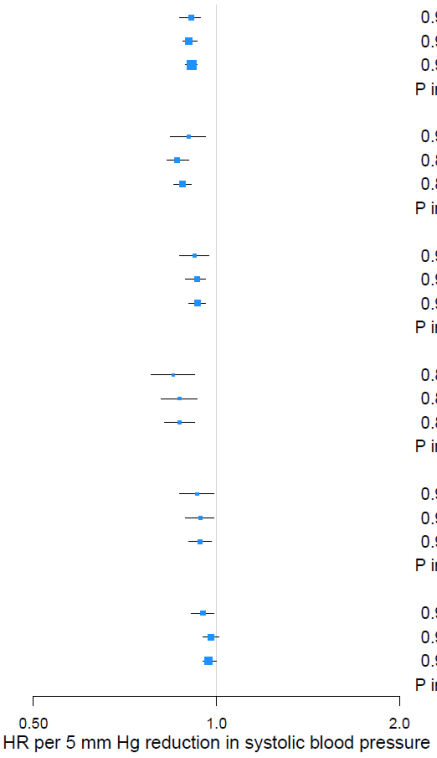


Figure S5. Effects of blood pressure-lowering treatment on primary and secondary outcomes stratified by baseline systolic blood pressure in patients with (A) and without CKD (B)

CKD = chronic kidney disease. HR = hazard ratio. CI = confidence interval. P for interaction was adjusted for multiple testing using Hommel's method.

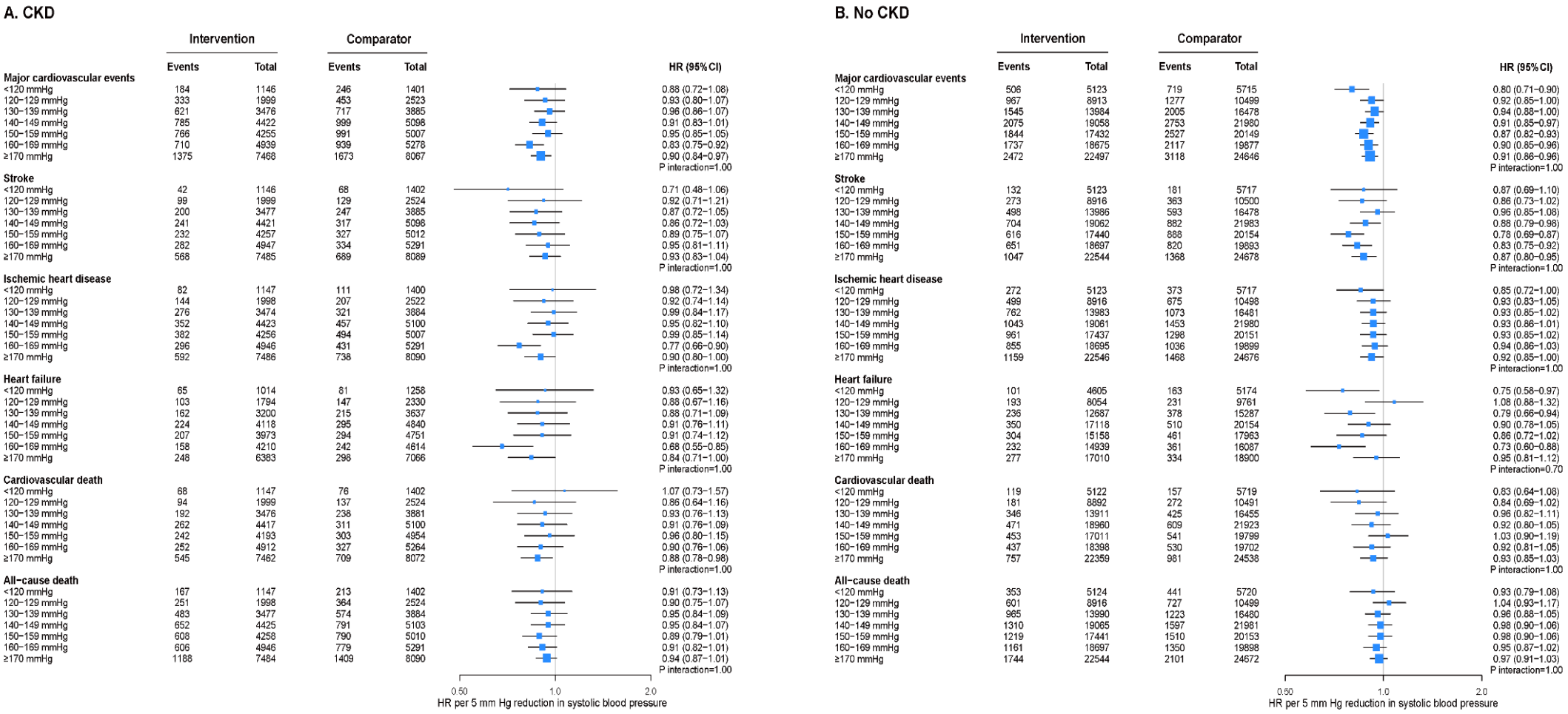


Figure S6. Effects of blood pressure-lowering treatment on primary and secondary outcomes stratified by baseline diastolic blood pressure in patients with (A) and without CKD (B)

CKD = chronic kidney disease. HR = hazard ratio. CI = confidence interval. P for interaction was adjusted for multiple testing using Hommel's method.

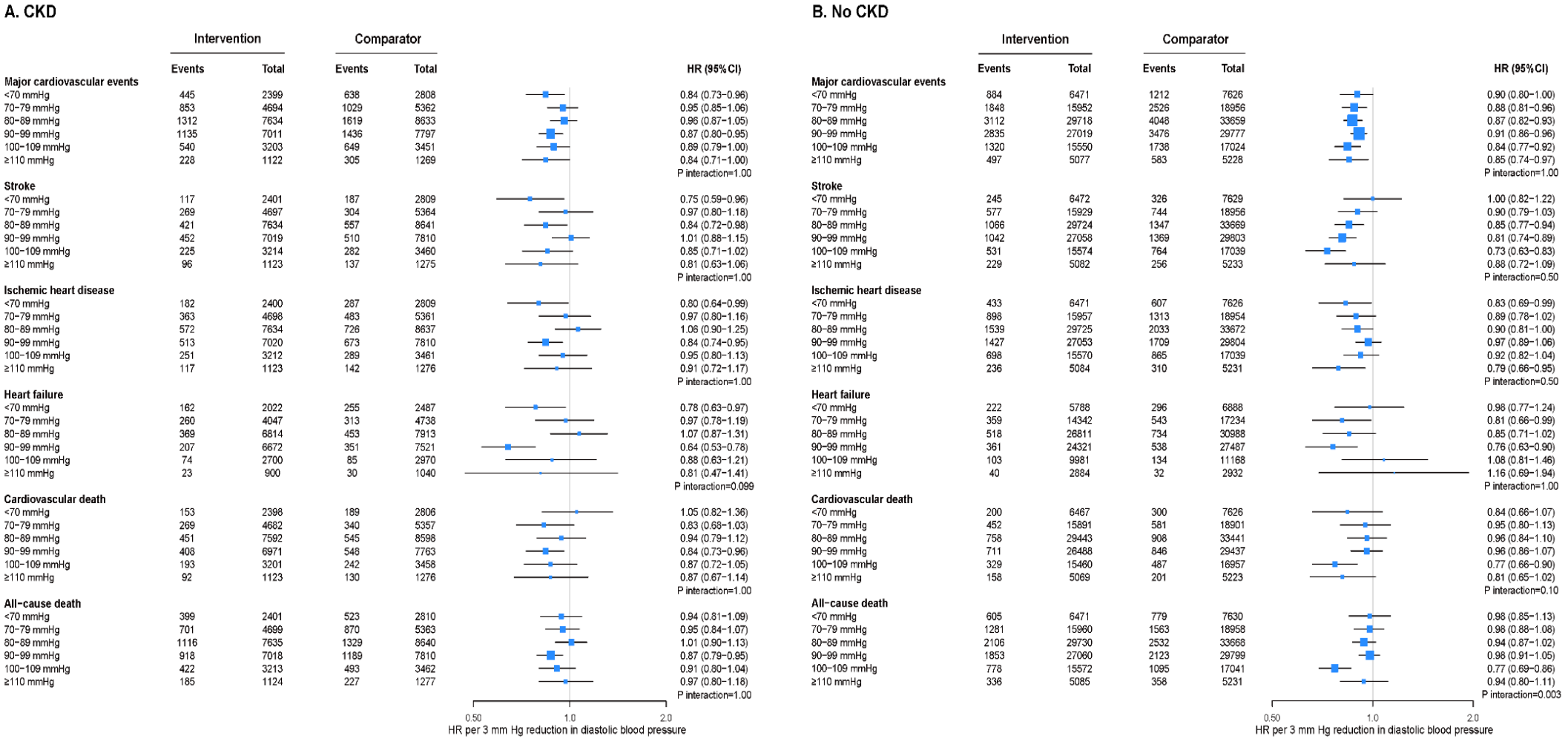


Figure S7. Effects of blood pressure-lowering treatment on primary and secondary outcomes stratified by proteinuria status in CKD patients

Proteinuria was defined as protein-to-creatinine ratio >0.22, urinary albumin excretion rates >200 µg/min or >300 mg/day, urinary albumin concentration >200 mg/L, urinary albumin creatinine ratio >300 µg/mg, or a urinary protein dipstick test result of 1+ or greater. HR = hazard ratio. CI = confidence interval. P for interaction was adjusted for multiple testing using Hommel's method.

	Intervention		Comparator		HR (95%CI)
	Events	Total	Events	Total	
Major cardiovascular events					
Proteinuria	584	2962	618	3005	0.90 (0.79−1.02)
No proteinuria	1309	11022	1652	12081	0.87 (0.80−0.93)
					P interaction>0.99
Stroke					
Proteinuria	150	2962	178	3014	0.80 (0.61−1.04)
No proteinuria	382	9854	535	10987	0.77 (0.68−0.88)
					P interaction=0.65
Ischemic heart disease					
Proteinuria	188	2962	205	3008	0.85 (0.68−1.07)
No proteinuria	577	11038	688	12103	0.91 (0.81−1.02)
					P interaction>0.99
Heart failure					
Proteinuria	272	2945	270	2976	1.00 (0.83−1.21)
No proteinuria	379	9567	496	10724	0.89 (0.78−1.02)
					P interaction>0.99
Cardiovascular death					
Proteinuria	187	2957	202	3006	0.84 (0.67−1.05)
No proteinuria	375	10971	479	12030	0.86 (0.75−0.98)
					P interaction>0.99
All−cause death					
Proteinuria	508	2963	605	3013	0.88 (0.77−1.01)
No proteinuria	1269	11042	1561	12108	0.90 (0.83−0.97)
					P interaction>0.99

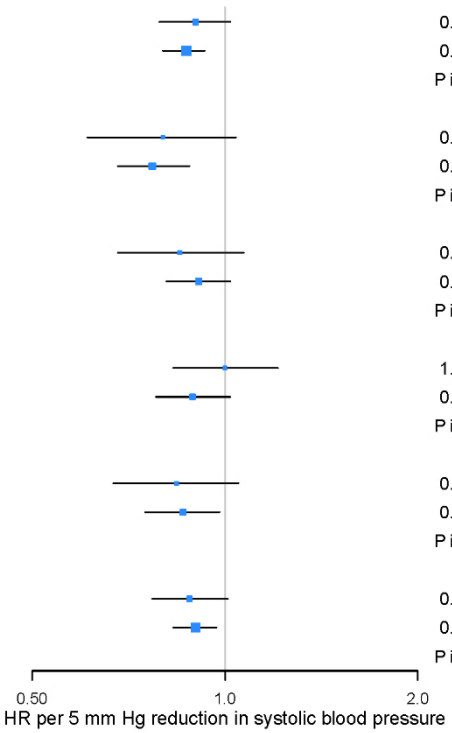


Figure S8. Effects of blood pressure-lowering treatment on primary and secondary outcomes stratified by diabetes status in CKD patients

HR = hazard ratio. CI = confidence interval. P for interaction was adjusted for multiple testing using Hommel's method.

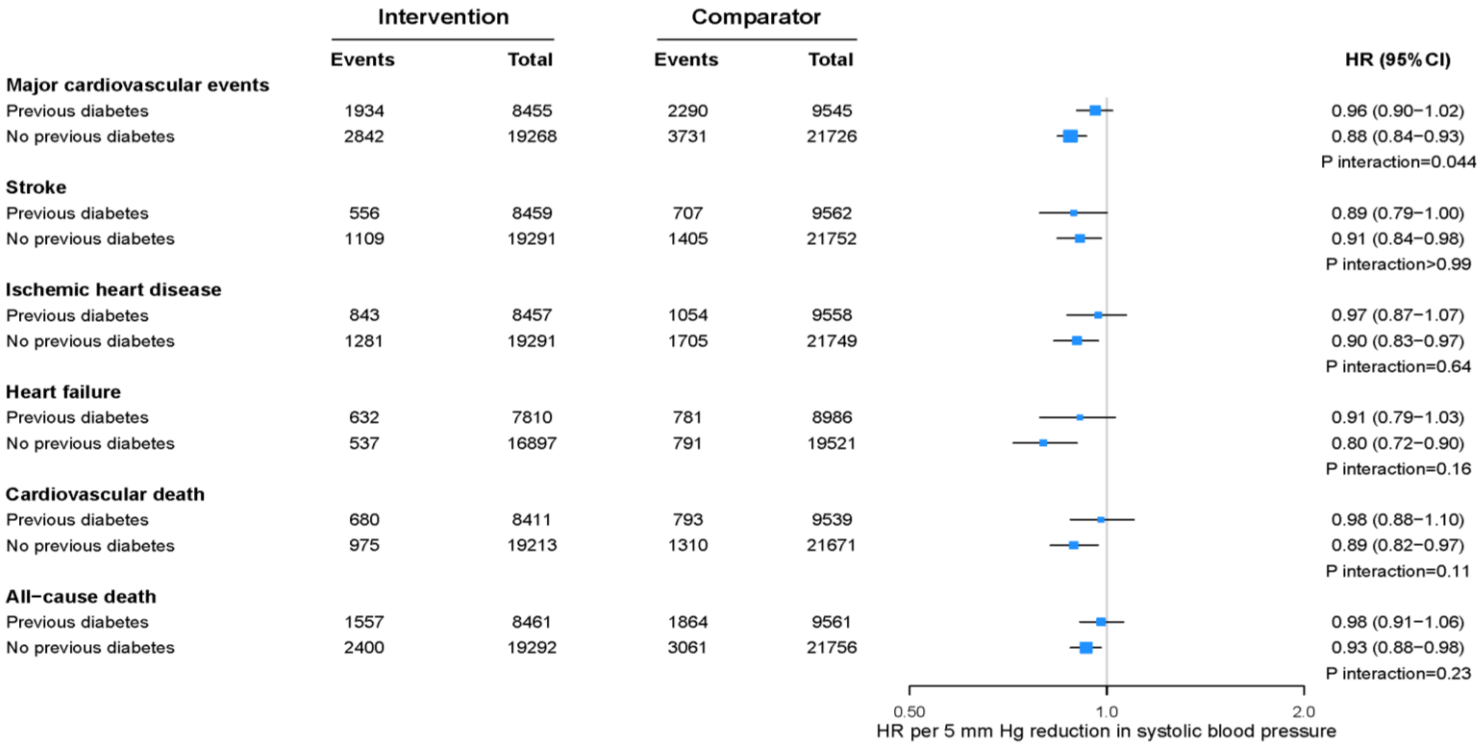
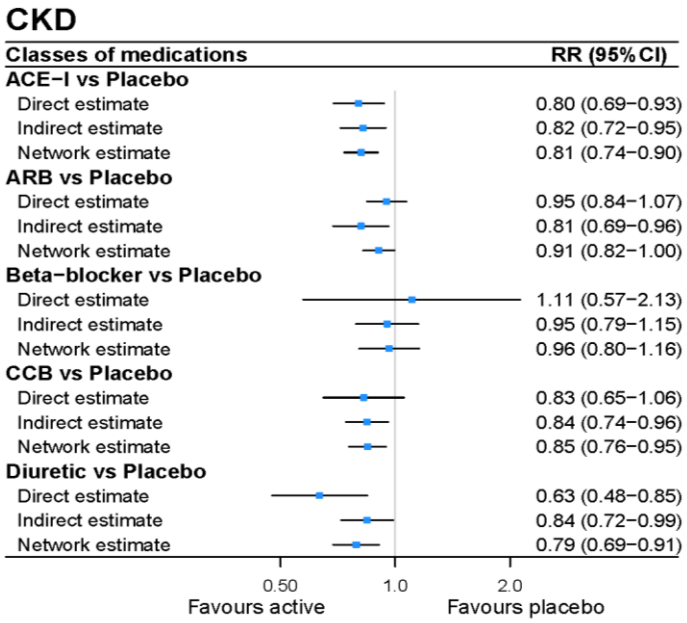


Figure S9. Direct, indirect, and network estimates of the effects of antihypertensive drug classes compared with placebo on the primary outcome, stratified by CKD status at baseline

ACE-I = angiotensin-converting enzyme inhibitors. ARB = angiotensin-receptor blockers. CCB = calcium-channel blockers. CKD = chronic kidney disease. CI = confidence interval. RR = relative treatment effect.



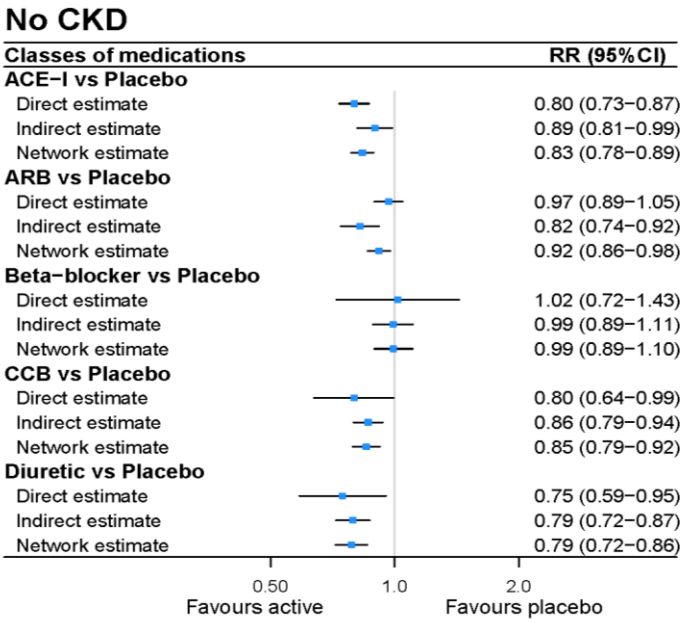


Figure S10. Direct, indirect, and network estimates of the effects of antihypertensive drug classes compared with placebo on the primary outcome, stratified by CKD stages at baseline

ACE-I = angiotensin-converting enzyme inhibitors. ARB = angiotensin-receptor blockers. CCB = calcium-channel blockers. CKD = chronic kidney disease. CI = confidence interval. eGFR = estimated glomerular filtration rate. RR = relative treatment effect.

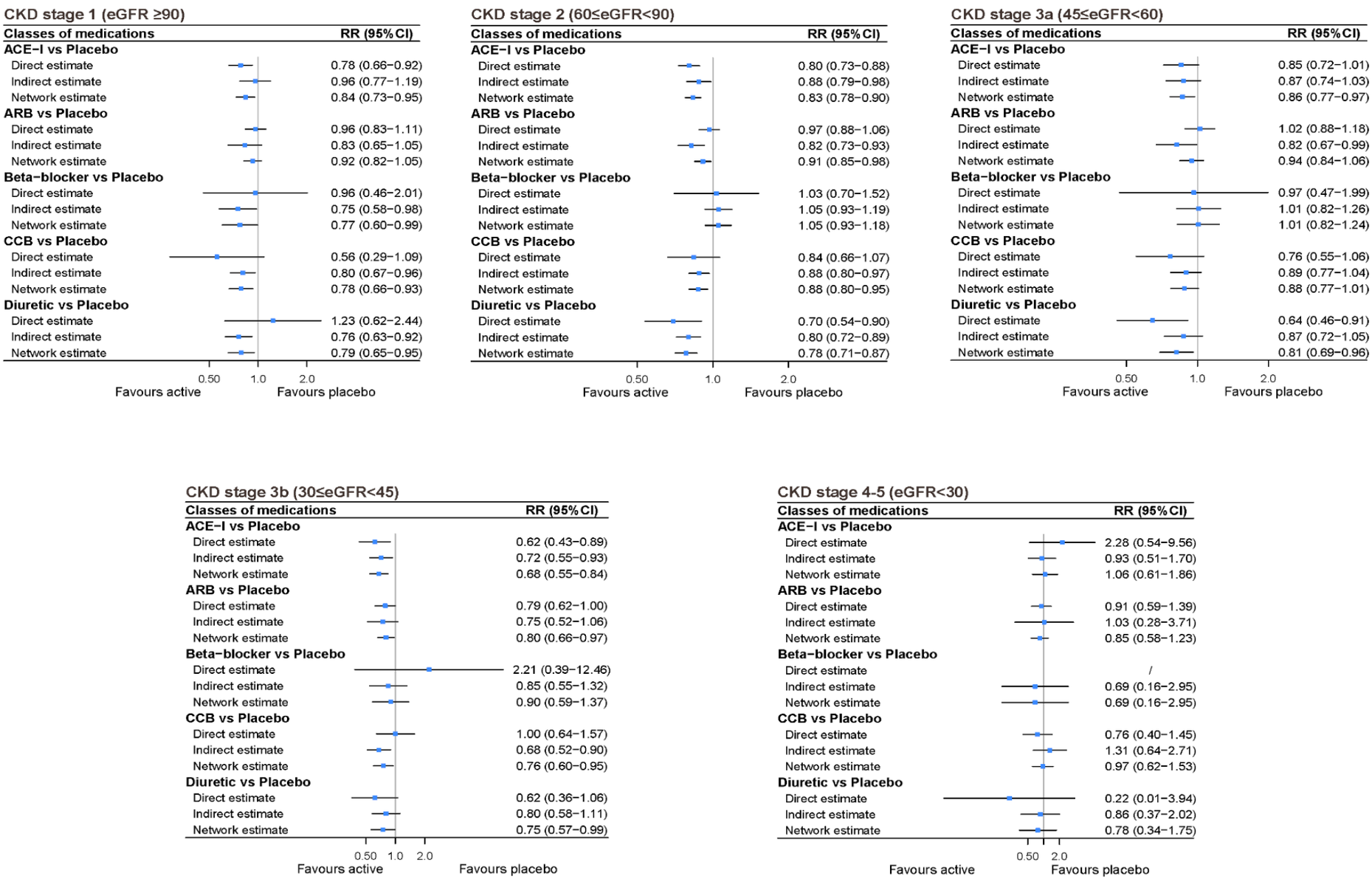
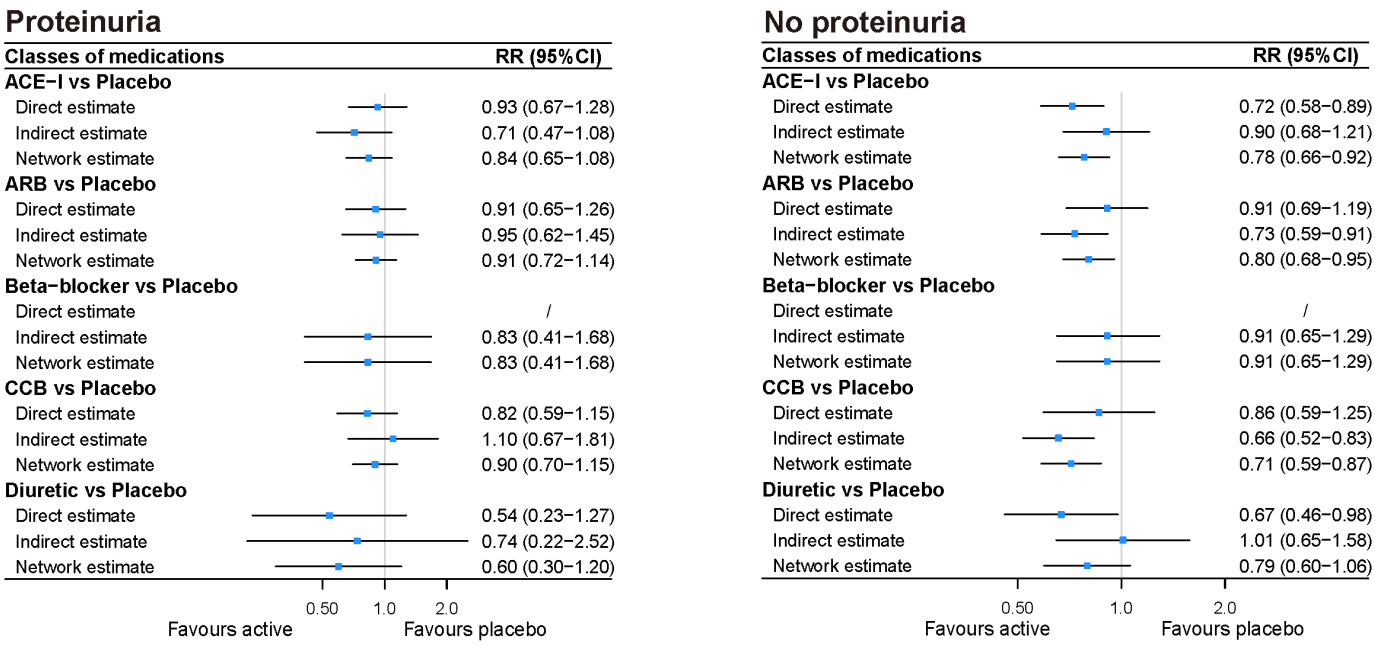


Figure S11. Direct, indirect and network estimates of the effects of antihypertensive drug classes compared with placebo on primary outcome stratified by proteinuria at baseline

ACE-I = angiotensin-converting enzyme inhibitors. ARB = angiotensin-receptor blockers. CCB = calcium-channel blockers. CKD = chronic kidney disease. CI = confidence interval. RR = relative treatment effect.



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PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)

Completed for: Pharmacological blood pressure-lowering for prevention of cardiovascular disease and death across the full spectrum of chronic kidney disease severity

PRISMA-IPD Section/topic	Item No	Checklist item	Reported section/page
TITLE AND ABSTRACT			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	Title section: The title explicitly states 'individual participant data meta-analysis of 46 randomised controlled trials'
Structured summary	2	Provide a structured summary including as applicable:	Summary/abstract section
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	Summary section
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	Summary section, Methods subsection
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes with confidence intervals and measures of statistical heterogeneity.	Summary section, Findings subsection
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	Summary section, Interpretation subsection
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	Summary section, Method section
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction section, paragraphs #1-3: • Paragraph #1: Notes cardioprotective benefits documented but efficacy in CKD underinvestigated due to underrepresentation in RCTs • Paragraph #2: Individual trials complicated evidence (SPRINT findings, post-hoc analyses) • Paragraph #3: Meta-analyses produced inconsistent findings; prior IPD meta-analysis had limited advanced CKD representation

PRISMA-IPD Section/topic	Item No	Checklist item	Reported section/page
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	Introduction section, paragraph #4: • Participants: Non-CKD and CKD patients across full spectrum of stages • Intervention: BP-lowering therapy • Comparisons: CKD vs non-CKD, across CKD stages, by drug class vs placebo • Outcomes: Major cardiovascular events, mortality • Subgroups: CKD status, CKD stage, diabetes, proteinuria, baseline BP categories
METHODS			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	Methods section, Study design and setting subsection, paragraph #2: Protocol prospectively registered in PROSPERO (CRD42018099283); references published protocols (refs 1, 15, 17)
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics. Note whether these were applied at the study or individual level.	Methods section, Study design and setting subsection, paragraph #1: RCTs comparing antihypertensive vs placebo/another agent, minimum 1000 patient-years per arm, excluded non-pharmacological/heart failure/acute settings trials Methods section, Eligibility criteria subsection, paragraph #1: Required baseline BP, creatinine, CV events with dates; excluded heart failure history, extreme creatinine (<0.2 or >5.0 mg/dL) - applied at individual level
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including databases searched with dates of coverage, hand searching, contact with experts. Give the date of last search.	Methods section, Study design and setting subsection, paragraph #1: Refers to BPLTTC third cycle which includes systematic review; details reported elsewhere (refs 1, 15, 17); central systematic review and quality assessment described in prior publications
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods section, Study design and setting subsection, paragraph #1: Full search strategy reported elsewhere (ref 15); refers to published BPLTTC systematic review protocol
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	Methods section, Study design and setting subsection, paragraph #1: BPLTTC eligibility criteria described; Results section, paragraph #1: 52 trials → 46 included after excluding 1 without time-to-event data (E-COST) and 5 without baseline creatinine. Flow chart reported
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators.	Methods section, Study design and setting subsection, paragraph #2: BPLTTC operates under University of Oxford policies; Steering Committee oversees all activities; studies must be pre-specified and approved before data release Methods section, Statistical analysis subsection, paragraph #1: Core variables already harmonised in previous BPLTTC studies
		If applicable, describe how any studies for which IPD were not available were dealt with.	Not applicable - IPD obtained for all 46 included trials; 6 trials excluded for specific reasons (Results section, paragraph #1)
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought.	Methods section, Definition of pre-planned subgroups subsection: • eGFR: 2021 CKD-EPI equation (Method S1) • CKD: eGFR ≤60 ml/min/1.73m²

PRISMA-IPD Section/topic	Item No	Checklist item	Reported section/page
		Describe methods of standardising or translating variables.	• Proteinuria: Multiple definitions (PCR >0.22, UAE >200 µg/min, etc.) • CKD stages: 1 (>90), 2 (60-89), 3a (45-59), 3b (30-44), 4-5 (<30) • BP categories: SBP in 7 intervals (<120 to ≥170), DBP in 6 intervals (<70 to ≥110) • Diabetes: Per trial diagnostic information Methods section, Statistical analysis subsection, paragraph #1: Dedicated harmonisation for creatinine, eGFR, proteinuria, diabetes
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	Methods section, Statistical analysis subsection, paragraph #1: Core variables harmonised in previous BPLTTC studies; dedicated harmonisation undertaken for study-specific variables Methods section, Study design and setting subsection, paragraph #2: Risk of bias evaluation reported elsewhere (refs 1, 15, 17)
Risk of bias assessment in individual studies	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. Report if and how risk of bias assessment was used in any data synthesis.	Methods section, Study design and setting subsection, paragraph #1: Quality assessment and risk of bias evaluation reported elsewhere (refs 1, 15, 17)
Specification of outcomes and effect measures	13	State all treatment comparisons of interest. State all outcomes addressed and define them in detail. State whether they were pre-specified and whether primary/secondary.	Methods section, Eligibility criteria subsection: • Comparisons: Active vs placebo (placebo-controlled trials), higher vs lower BP reduction (head-to-head trials), intensive vs standard (intensity comparison trials) • Primary outcome: First major CV event (fatal/non-fatal stroke, IHD, heart failure hospitalisation/death) • Secondary outcomes: Individual components + CV death + all-cause death • Effect measure: Hazard ratios per 5 mmHg SBP reduction Pre-specified in BPLTTC protocol
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD: • One-stage vs two-stage approach • How effect estimates generated within/across studies • Specification of one-stage models including clustering • Fixed vs random effects and assumptions • How survival curves generated • Methods for quantifying heterogeneity • How missing data dealt with	Methods section, Statistical analysis subsection: • One-stage fixed-effects IPD meta-analysis framework (paragraph #1) • Pooled participant-level data analysed as single dataset with trials as clusters (paragraph #1) • Stratified Cox proportional hazards model allowing trial-specific baseline hazards (paragraph #2) • Effect sizes standardised per 5 mmHg SBP/3 mmHg DBP reduction (paragraph #2) • Kaplan-Meier estimates for cumulative incidence (paragraph #2) • Network meta-analysis: Bayesian MCMC (4 chains, 10,000 burn-in, 100,000 sampling) (paragraph #4)
Exploration of variation in effects	A2	Describe any methods used to explore variation in effects by study or participant level characteristics. State all participant-level characteristics analysed as potential effect modifiers, and whether these were pre-specified.	Methods section, Statistical analysis subsection, paragraphs #3-4: • Likelihood-ratio test with Hommel's correction for multiple comparisons • Pre-specified subgroups: CKD status, CKD stage (5 levels), diabetes, proteinuria, baseline BP (7 SBP and 6 DBP categories) • Stratified network meta-analysis by CKD status, CKD stage, proteinuria

PRISMA-IPD Section/topic	Item No	Checklist item	Reported section/page
			• Z-tests for interaction between subgroups; meta-regression for trend across CKD stages
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	Methods section, Study design and setting subsection, paragraph #1: assessment of risk of bias reported elsewhere (refs 1, 15, 17) Discussion section, Limitations paragraph (paragraph #5): Notes limitations, including not examining adverse events/kidney outcomes; refers to ongoing BPLTTC data acquisition for benefit-harm evaluation
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	Methods section, Statistical analysis subsection, paragraph #4: Stratified network meta-analysis of 5 drug classes (ACEi, ARBs, beta-blockers, CCBs, thiazides) vs placebo Pre-specified to assess within-class effects by CKD status, stage, and proteinuria Post-hoc sensitivity analysis during the peer review stage is specified in the method section
RESULTS			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included with reasons for exclusions. Indicate number of studies and participants for which IPD were sought and obtained. Include flow diagram.	Results section, paragraph #1 and flow chart in supplementary: • 52 trials in BPLTTC → 46 included (285,124 participants) • Excluded: 1 trial without time-to-event data (E-COST), 5 trials without baseline creatinine data • 59,185 with CKD, 225,939 without CKD • IPD obtained for all 46 included trials • Proteinuria data available in 24 trials (Table S1)
Study characteristics	18	For each study, present information on key study and participant characteristics. Provide citations for each study.	Results section, paragraph #1: Characteristics compared between CKD and non-CKD groups Table 1: Baseline characteristics by CKD status and study arms (sex, age, BP, BMI, smoking, ethnicity, comorbidities, medications, eGFR, follow-up) Table S1: Individual trial characteristics and citations
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	Methods section, Statistical analysis subsection, paragraph #1: Core variables already harmonised in previous BPLTTC studies; no issues reported; variables balanced between intervention and control arms (Results section, paragraph #1; Table 1) Statistical analysis plan
Risk of bias within studies	19	Present data on risk of bias assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	Methods section, Study design and setting subsection: Risk of bias evaluation reported elsewhere (refs 1, 15, 17); all included trials were RCTs with clearly defined randomisation processes
Results of individual studies	20	For each comparison and for each main outcome, report number of eligible participants, simple summary data, effect estimates and confidence intervals.	Results section, paragraph #2: 36,473 major CV events (17,817 IHD, 12,795 strokes, 6,875 heart failure), 10,044 CV deaths, 25,197 all-cause deaths Table S1: Characteristics of trials included in the analysis Figure S1: Incidence rates by CKD status and treatment arm Figures 1-6: Forest plots with HRs, 95% CIs, and P-interaction values Figures S2-S8: Additional outcome analyses
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and	Results section, paragraphs #3-6:

PRISMA-IPD Section/topic	Item No	Checklist item	Reported section/page
		measures of statistical heterogeneity. State whether analysis was pre-specified. When exploring variation in effects, present summary interaction estimates with confidence intervals. Provide description of direction and size of effect in terms meaningful to practice.	• Primary outcome: HR 0.91 (95% CI 0.87-0.94) for CKD vs HR 0.90 (95% CI 0.88-0.93) for non-CKD per 5 mmHg SBP reduction (P-interaction >0.99) - Figure 1 • Across CKD stages: Consistent effects including stages 4-5 (P-interaction >0.99) - Figure 2 • Secondary outcomes: All P-interaction >0.15 - Figure 1 • By baseline BP: No heterogeneity from <120 to ≥170 mmHg - Figure 4 • By proteinuria: No interaction (P >0.65) - Figure 5 • By diabetes: Significant interaction (P=0.04); HR 0.96 in CKD with diabetes vs HR 0.88 without - Figure 5 • Network meta-analysis: No drug class superiority by CKD status/stage/proteinuria - Figure 6 Pre-specified analyses; ~10% risk reduction per 5 mmHg SBP reduction
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies.	Methods section, Study design and setting subsection, paragraph #1: assessment of risk of bias had done before, and no risk of bias was observed (refs 1, 15, 17) Discussion section, Limitations paragraph (paragraph #7): • Did not examine adverse events or kidney-specific outcomes • Stratified analyses by individual clinical features • Novel phenotyping approaches may identify additional heterogeneity Results section: Wide CIs noted for advanced CKD stages due to smaller numbers
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses).	Results section, paragraph #5: Network meta-analysis results • Figure 6: Class-specific effects vs placebo by CKD status, CKD stage, proteinuria • Meta-regression: No significant stage-specific heterogeneity • Figures S6-S8: Additional network meta-analysis results All post-hoc sensitivity analyses are reported in the supplementary material and mentioned in the method section
DISCUSSION			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	Discussion section, paragraph #1: • 46 RCTs, >285,000 participants (59,185 CKD, 225,939 non-CKD) • ~10% relative risk reduction per 5 mmHg SBP reduction • Similar proportional benefits in CKD and non-CKD • Consistent across all CKD stages (eGFR ≥90 to <30) • Consistent across baseline BP (including <120/<70 mmHg) • Proteinuria did not modify effects • A reduced relative treatment effect was observed in the CKD group with diabetes • No drug class superiority in CKD
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	Discussion section, Limitations paragraph (paragraph #7): Limitations: • Only relative treatment effects examined; adverse events/kidney outcomes not assessed • Stratified by individual clinical features; multidimensional approaches needed • Limited to pharmacological BP-lowering (excludes SGLT2i/GLP-1RA)

PRISMA-IPD Section/topic	Item No	Checklist item	Reported section/page
			Strengths: • Largest randomised dataset in CKD population (Introduction paragraph #4) • 24% of CKD cohort had eGFR <45 ml/min/1.73m² • IPD allows consistent subgroup definitions and interaction testing
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	Discussion section, final paragraph (paragraph #6): • BP-lowering recommended at any CKD stage and baseline BP • Consistently reduces CV risk regardless of CKD stage/initial BP • Treatment decisions should balance benefits with potential risks • No drug class superiority in CKD • Attenuated effect in CKD with diabetes requires adapted management Summary section, Interpretation: Supports initiating BP-lowering in CKD; challenges class superiority notion; diabetes complicates CV risk reduction in CKD
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	Research in context section, Implications paragraph: • Clinicians should recommend BP-lowering in CKD at any stage/BP level • Freedom to choose from main antihypertensive classes • Balance benefits/harms and consider patient preferences • In CKD with diabetes: BP-lowering essential but may need combination with SGLT2i/GLP-1RA Discussion section, paragraph #5: Future research needs include novel phenotyping approaches, combination therapies with newer agents
FUNDING			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	Reported in the Acknowledgments section and the Declaration of Interests section Methods section, Statistical analysis subsection, final sentence: Funders had no role in study design, data collection, analysis, interpretation, or writing

A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.

BPLTTC statistical analysis plan

Project title: CKD and BP Control

Date and version: V7- 27 January 2025

Project Title

Blood pressure-lowering treatment for prevention of cardiovascular events in patients with and without chronic kidney disease: an individual participant-level data meta-analysis

CKD Working Group Members

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Background and literature review

Chronic kidney disease (CKD) affects 10-15% of the adult population worldwide and markedly increases cardiovascular risk.[1,2] Hypertension is particularly prevalent in CKD, exacerbating the progression of both CKD and cardiovascular diseases. As a result, adequate blood pressure (BP) control is crucial for risk management in this population.[3] However, there is inadequate randomized controlled trial (RCT) data to determine if the benefit of BP-lowering treatment differs by CKD status or across CKD stages. Similarly, there is uncertainty around initiating BP reduction therapy at a specific BP threshold in this patient group, particularly in people with normal or high-to-normal BP levels who have a diagnosis of CKD.

Evidence from individual RCTs has been mixed. Notably, trials such as the Modification of Diet in Renal Disease and the African American Study of Kidney Disease and Hypertension did not demonstrate a benefit of BP lowering for cardiovascular and mortality risk reduction in this group.[4,5] Although the Systolic Blood Pressure Intervention Trial (SPRINT) results showed a mortality reduction from intensive BP lowering in CKD patients, the cardiovascular risk reduction was less pronounced in the CKD subgroup compared with those without CKD in the SPRINT trial.[6,7] Furthermore, the SPRINT trial excluded diabetic patients and reported an increased risk of acute kidney injury in the intensive BP control group.[8]

Similarly, evidence from previous meta-analyses has not fully addressed the existing knowledge gap (**Table 1**). While some studies indicated that intensive BP control did not significantly influence renal outcomes or all-cause mortality in CKD patients,[9,10] others demonstrated that it reduced mortality risks in this population.[11] Furthermore, a study based on the earlier cycle of Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC) suggested similar cardiovascular benefits per 5-mmHg systolic BP reduction in those with and without CKD.[12] However, the analysis was limited by insufficient data on proteinuria and the underrepresentation of patients in severe CKD.

There is controversy over the recommended BP thresholds for CKD patients in clinical practice guidelines. The 2021 Kidney Disease Improving Global Outcome guidelines advocate a lower systolic BP target (<120 mmHg) in CKD and recommend initiating BP-lowering therapy when BP exceeds this level.[3] In contrast, other guideline committees, such as the American College of

Cardiology/American Hypertension Association, and the European Society of Cardiology/European Society of Hypertension, recommend higher BP thresholds (systolic BP ≥130 mmHg) for initiating treatment based on the same evidence.[13,14] Existing RCTs targeting systolic BP <120 mmHg in CKD, such as the SPRINT, excluded individuals with baseline systolic BP <130 mmHg, leaving a critical evidence gap.[6] Furthermore, a prior meta-analysis found no significant mortality benefit from intensive BP-lowering therapy in CKD patients with baseline systolic BP <140 mmHg, although the small sample size in this group limited the statistical power of the findings.[11] Therefore, there is limited evidence to ascertain the effect of BP-lowering treatment in individuals with CKD who exhibit "elevated BP", a new definition of BP defined recently by the 2024 ESC guideline for BP management. [14]

Recent studies indicate that the renal benefits of BP-lowering therapy vary by CKD stage, with benefits observed primarily in stages 4–5.[10] Additionally, studies suggested that diabetes or albuminuria status might interact with the mortality outcomes in CKD patients receiving BP-lowering treatment.[9,15,16] Different BP-lowering drug classes can also modify treatment effects in CKD patients, with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) demonstrating consistent benefits in reducing cardiovascular events and kidney failure in this population.[16,17] However, a meta-analysis based on the previous cycle of BPLTTC found no evidence of differential effects of drug classes on cardiovascular risks in CKD patients.[12] These conflicting findings highlight the need for a comprehensive evaluation of BP-lowering treatment in individuals with CKD, accounting for patient-specific factors such as CKD stage and comorbidities, including diabetes, to optimize cardiovascular outcomes.

The third cycle of BPLTTC, including over 350,000 participants, represents the largest dataset available for studying the effects of antihypertensive therapy. This expansive dataset enables a more detailed evaluation of BP-lowering effects in CKD patients. Based on individual participant-level data from the new cycle, this study aims to evaluate the effects of BP-lowering treatment on cardiovascular outcomes in patients with and without CKD. The analysis will further investigate the effects across subgroups defined by CKD stage, baseline BP, diabetes, and proteinuria status. Finally, it will assess the individual effects of each antihypertensive drug class by CKD status on cardiovascular risk reduction.

Objectives

- To investigate the effect of a fixed amount of BP-lowering on primary and secondary outcomes in people with and without CKD.
- To evaluate the effects of a fixed amount of BP lowering on primary and secondary outcomes stratified by CKD stages.
- To evaluate the effects of a fixed amount of BP-lowering on primary and secondary outcomes stratified by baseline systolic and diastolic BP in people with and without CKD.
- To evaluate the effects of a fixed amount of BP-lowering on primary and secondary outcomes stratified by diabetes status in CKD patients.
- To evaluate the effects of BP lowering on primary and secondary outcomes stratified by proteinuria status in CKD patients.
- To assess the effects of each drug class on the risk of the primary outcome in people with and without CKD.

Methods

Harmonisation, inclusion, and exclusion criteria

All previously harmonised BPLTTC data will be used in this study, following an additional round of quality checks. Given that CKD was not the primary focus of previous BPLTTC analyses, any new variables related to kidney function (e.g., creatinine, eGFR, baseline CKD status, proteinuria) that are of interest in this study will undergo a new round of harmonisation.

We will conduct a one-stage individual-participant-level meta-analysis of major RCTs using the most recent BPLTTC dataset. This resource comprises 52 RCTs and includes 358,636 participants. [18] RCTs were eligible for inclusion in the BPLTTC if they randomized participants to BP-lowering drugs versus placebo or alternative classes, or to regimens of varying intensity, with a minimum of 1,000 patient-years of follow-up per randomized arm. Trials conducted on people with heart failure or short-term therapies in people with acute myocardial infarction or other acute settings were excluded.

In this project, only trials that collected information on kidney function (CKD diagnosis or baseline creatinine data) at baseline will be included. We will exclude participants with a history of heart failure and those with extreme creatinine values (<0.2 mg/dL or >5.0 mg/dL). Patients with a baseline estimated glomerular filtration rate (eGFR) ≤60 ml/min/1.73 m^2 or a medical history of CKD will be defined as having baseline CKD. If data are available, eGFR will be calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration equation.[19] Proteinuria will be defined as a protein-to-creatinine ratio >0.22, urinary albumin excretion rates>200 µg/min or >300 mg/day, urinary albumin concentration >200 mg/L, urinary albumin creatinine ratio >300 µg/mg, or a urinary protein dipstick test result of 1+ or greater in line with previous studies.[12,20,21] CKD stages will be defined according to the Kidney Disease Outcomes Quality Initiative guidelines.[22] Baseline diabetes status was determined based on the diagnostic information provided by each trial.[23]

Outcome definition

The primary outcome in this study is the occurrence of major cardiovascular events, which include fatal or non-fatal stroke or cerebrovascular disease, fatal or non-fatal ischemic heart disease, or heart failure resulting in death or hospitalization. The secondary outcomes are the individual components of the major cardiovascular events, cardiovascular-related causes of mortality, and all-cause mortality.

Comparison arms

We will use the same definitions of intervention and comparator groups as in previous BPLTTC studies.[24-27]

The treatment and comparator groups in each trial will be defined according to the trial design. The active treatment group in placebo-controlled trials, the group with the greater systolic BP reduction in head-to-head trials comparing two or more classes of drugs, and the intensive group in trials investigating two BP-lowering strategies will be defined as the intervention group. For comparison group, the placebo arm in placebo-controlled trials, the group with the least systolic BP reduction in head-to-head trials, and the standard or less-intensive group in trials investigating two BP-lowering strategies are defined as the comparator groups.

Statistical analysis

The main stratified analysis: We will apply a fixed-effect, one-stage, individual-participant-level data meta-analysis that simultaneously uses individual-level data from all trials by fitting a

single statistical model. We will fit stratified Cox proportional hazards models to calculate hazard ratios (HRs) for the primary and secondary outcomes. To account for varying baseline hazards across different trial populations, each trial will be considered as a stratum in the model. Analyses will assess effects across subgroups defined by CKD status, CKD stage, BP category, proteinuria status, and diabetes status.[28] Kaplan-Meier estimates of cumulative incidence will be used to calculate event rates for the CKD and non-CKD groups, and for CKD stages at baseline. The interaction between subgroups and treatment arms will be included to assess heterogeneity in the BP-lowering effect across defined subgroups. The effect sizes will be adjusted for trial-level achieved systolic BP reduction and standardised to a 5 mmHg reduction in systolic BP, which closely approximates the mean systolic BP reduction achieved across BP-lowering intensity and placebo-controlled trials in BPLTTC.[28] The likelihood-ratio test will be used to assess for interaction between treatment arms and the stratifying factors, and p-values for interaction will be adjusted for multiple comparisons using Hommel's method.[29,30]

Network meta-analysis: The effects of each of the five major BP-lowering drug classes, including ACEIs, ARBs, β blockers, calcium channel blockers, and thiazide diuretics, will be assessed using an individual patient data network meta-analysis framework and will follow the same methodology as in previous publication.[31,32] The logistic regression model will be used to estimate the relative risk for each available comparison using individual data from each trial, separately for those with and without CKD. We will use the Markov chain Monte Carlo simulation with four chains and 100,000 iterations after a 10,000-burn-in to fit the network meta-analysis model.[31] Given that the network meta-analysis method allows for flexible selection of the comparison group and to estimate the pure effects of each drug class, the placebo will be chosen as the reference group.

Subgroups definition

The following subgroups and categories will be considered for subgroup analyses:

- **Baseline CKD status** will be defined as a binary variable (yes/no). Participants with an eGFR ≤60 mL/min/1.73 m² or with a diagnosis of CKD at baseline in the trial will be categorised as having CKD at baseline.[33,34]
- **CKD stages** will be defined according to baseline eGFR (mL/min/1.73 m²) as follows: stage 1, >90; stage 2, 60–89; stage 3a, 45–59; stage 3b, 30–44; and stages 4–5, <30.[22]

- **Baseline systolic BP** will be defined in the following categories: <120 mmHg, 120–129 mmHg, 130–139 mmHg, 140–149 mmHg, 150–159 mmHg, 160–169 mmHg, and ≥170 mmHg.
- **Baseline diastolic BP** will be defined in the following categories: <70 mmHg, 70–79 mmHg, 80–89 mmHg, 90–99 mmHg, 100–109 mmHg, and ≥110 mmHg.
- **Baseline Proteinuria status** will be defined as a binary variable according to the definition provided in the Methods section above.
- **Baseline diabetes status** will be defined as a binary variable based on the diagnostic information provided by each trial, consistent with previous BPLTTC analyses.[23]

Feasibility Check

After reviewing the currently available BPLTTC data on baseline CKD prevalence, we identified 54,857 participants with a CKD diagnosis (non-harmonised, CKD stage unknown), compared with 30,295 in the previous analysis using an earlier data cycle. [12] We anticipate that this number will increase following further harmonisation and, consequently, we are confident that there will be sufficient power for this analysis.

Planned tables and figures

Table 1. Baseline participant characteristics by CKD status.

Figure 1. Effects of blood pressure-lowering treatment on primary and secondary outcomes, by chronic kidney disease status at baseline.

Figure 2. Cumulative probability of major cardiovascular events by treatment allocation per 5 mmHg reduction in systolic blood pressure, stratified by CKD status and stages at baseline.

Figure 3. Effects of blood pressure–lowering treatment on major cardiovascular outcomes, stratified by baseline systolic blood pressure level, in people with and without chronic kidney disease.

Figure 4. Effects of blood pressure-lowering treatment on major cardiovascular outcomes in people with chronic kidney disease, stratified by baseline diabetes and proteinuria status.

Figure 5. Class-specific effects of antihypertensive drugs versus placebo on the risk of major cardiovascular disease, stratified by chronic kidney disease status

Table 1. Summary of relevant published studies.

Study Reference	Title	Year	Objectives	Sample Size	Study Design	Summary of Findings
Ku et al., 2023	Intensive BP Control in Patients with CKD and Risk for Adverse Outcomes	2023	Examine the effect of intensive BP lowering on kidney outcomes and death in CKD patients	5823 CKD participants	Participant-level meta-analysis of 7 trials	Patients with intensive BP control had a lower risk of kidney outcomes in stage 4 or 5 CKD, but not in stage 3 CKD
Cheung et al., 2017	Effects of Intensive BP Control on CKD	2017	Examine the effect of intensive BP control on CVD and kidney outcomes in the SPRINT participants with CKD at baseline	2646 CKD patients from SPRINT	Post hoc analysis of SPRINT trial	In patients with CKD and hypertension without diabetes, intensive SBP control reduced CVD and all-cause death without an effect on the kidney outcome.
Tsai et al., 2017	Association of Intensive Blood Pressure Control and Kidney Disease Progression in Nondiabetic Patients With Chronic Kidney Disease: A Systematic Review and Meta-analysis	2017	Examine the effect of intensive BP control on major renal outcomes in patients with CKD without diabetes	8127 non-diabetic CKD patients	Meta-analysis of 9 trials	Intensive BP control did not provide an additional benefit for renal outcomes in patients with CKD without diabetes
Malhotra et al., 2017	Association Between More Intensive vs Less Intensive Blood Pressure Lowering and Risk of Mortality in Chronic Kidney Disease Stages 3 to 5: A Systematic Review and Meta-analysis	2017	Investigate the effect of intensive BP control on mortality risk in persons with CKD stages 3- 5	15 924 CKD patients	Meta-analysis of 30 trials	More intensive BP control is associated with lower mortality risk among participants with hypertension and CKD
BPLTTC 2013	Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomized controlled trials	2013	Define the cardiovascular effects of lowering blood pressure in people with chronic kidney disease	152 290 participants (30 295 with eGFR <60)	Participant-level meta-analysis of 26 trials	A broad range of different BP-lowering regimens provide protection against cardiovascular complications in patients with and without CKD.

Gantt Chart

Phase	Dec 2024	Jan 2025	Feb 2025	Mar 2025	Apr 2025	May 2025	Jun 2025	Jul 2025	Aug 2025	Sep 2025	Oct 2025	Nov 2025
Proposal Development	■	■										
Data harmonization and analysis			■	■	■	■	■					
Preparing results, tables and figures						■	■	■	■			
Drafting manuscript, sharing with WG, incorporating the comments, submission							■	■	■	■	■	■

Project timeline/changes (if any)

Items	Date	Details/reasons
1) Drafting of the initial SAP	16 November 2024	
2) First draft shared with the working group (WG)	27 January 2025	
3) Incorporation of comments and finalisation	30 January 2025	
4) Share with the BPLTTC network (call for interest in collaboration)	11 February 2025	
5) SAP approval with the steering committee	19 February 2025	
6) Start of data harmonisation	19 February 2025	
7) CKD at baseline definition	26 February 2025	We originally planned to define CKD status based on both baseline diagnosis and eGFR thresholds. However, we revised this to rely exclusively on eGFR cut-points to provide a more valid definition that aligns with CKD stages stratified analysis.
8) Start of statistical analysis	27 February 2025	
9) Initial main analysis results	29 April 2025	
10) Sharing of full results with WG	30 April 2025	
11) Potential revisions/corrections	6 May 2025	
12) Finalising the analysis, tables, and figures	27 May 2025	
13) Manuscript draft and revision	4 June 2025	
14) Change in network meta-analysis	17 July 2025	We expanded the network meta-analysis to include CKD stages and proteinuria because they are critical effect modifiers. These variables are known to stratify the population's response to blood pressure-lowering medications, potentially leading to differential drug-specific effects that standard NMA would not capture.
15) Change in Table 1	13 August 2025	We expanded Table 1 to stratify baseline characteristics by CKD status within each treatment arm and subgroup, rather than by CKD status alone. This modification aimed to avoid confusion arising from collaborators' misinterpretation of Table 1 in another BPLTTC project, namely, the imbalances in baseline variables.
16) Final share with WG members/authors for approval	23 September 2025	
17) Submission	9 October 2025	

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