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

*Guyu Zeng, Zeinab Bidel, Qianqian Yang, Dexter Canoy, Mark Woodward, Julia Lewis, Sverre E Kjeldsen, William C Cushman, Jinqing Yuan, Koon Teo, Barry R Davis, John Chalmers, Carl J Pepine, Kazem Rahimi, Milad Nazarzadeh, on behalf of the Blood Pressure Lowering Treatment Trialists' Collaboration**

Lancet 2026; 407: 1626–38

See **Comment** page 1578

*Members listed in the appendix (p 4)

Deep Medicine Group, Nuffield Department of Women's and Reproductive Health, Medical Sciences Division, University of Oxford, Oxford, UK (G Zeng MD, Z Bidel MSc, Q Yang MSc, Prof M Woodward PhD, Prof K Rahimi FRCP, M Nazarzadeh DPhil); **Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Disease, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China** (G Zeng, Prof J Yuan PhD); **Population Health Sciences Institute, Newcastle University, Newcastle, UK** (D Canoy PhD); **The George Institute for Global Health, School of Public Health, Imperial College London, London, UK** (Prof M Woodward); **The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia** (Prof M Woodward, Prof J Chalmers PhD); **Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA** (Prof J Lewis MD); **Department of Cardiology, Department of Nephrology, and Institute of Clinical Medicine, University of Oslo, Ullevaal Hospital, Oslo, Norway** (Prof S E Kjeldsen MD); **Department of Preventive Medicine, The University of Tennessee Health Science Center, Memphis, TN, USA** (Prof W C Cushman MD); **Population Health Research Institute, Hamilton Health Sciences, McMaster University, Hamilton, ON, Canada** (Prof K Teo PhD); **The University of Texas School of Public Health, Houston, TX, USA**

Summary

Background Individuals with chronic kidney disease (CKD), particularly those at more advanced stages, have been systematically under-represented in randomised controlled trials (RCTs) of blood-pressure-lowering treatment due to safety concerns, leading to a persistent paucity of evidence for cardiovascular risk management in this high-risk group. We investigated the effect of blood-pressure-lowering treatment on the risk of major cardiovascular disease and death across the full spectrum of CKD stages and by key clinical subgroups.

Methods We conducted a one-stage meta-analysis of individual-participant data from RCTs in which participants were randomly assigned to a blood-pressure-lowering therapy versus a comparator. We used RCTs collated in the Blood Pressure Lowering Treatment Trialists' Collaboration dataset, published at any time in any language, which were eligible for inclusion if they had at least 1000 person-years of follow-up per arm, baseline blood-pressure and creatinine measurements, and time-to-event outcomes; those with unclear randomisation procedures or restricted to heart failure or acute care settings were excluded. Participants with a documented history of heart failure or extreme creatinine values were excluded. No age criteria were applied. The primary outcome was major cardiovascular events, defined as a composite of fatal or non-fatal stroke, ischaemic heart disease, or hospitalisation for, or death from, heart failure. Relative treatment effects were estimated with a stratified Cox proportional hazards model. Heterogeneity of treatment effects was evaluated across prespecified subgroups defined by CKD status, CKD stage (1–5), diabetes, proteinuria, and baseline blood pressure. A stratified network meta-analysis was performed to examine whether treatment effects differed by defined subgroups within each of five principal antihypertensive drug classes. The systematic review was registered in PROSPERO (CRD42018099283).

Findings From 52 RCTs (363 684 participants), a total of 285 124 participants from 46 randomised trials met the eligibility criteria; 116 145 (40·7%) were women, 168 979 (59·3%) were men, 59 185 (20·7%) had CKD at baseline, and 86 067 (30·2%) had type 2 diabetes. During a median follow-up of 4·4 years (IQR 3·2–5·1), a 5 mm Hg reduction in systolic blood pressure reduced the risk of major cardiovascular disease in individuals with CKD (hazard ratio [HR] 0·91 [95% CI 0·87–0·94]) and without CKD (0·90 [0·88–0·93]; $p_{interaction}$>0·99). Furthermore, these observed relative risk reductions were consistent across all CKD stages, including severe stages 4–5 ($p_{interaction}$>0·99). Similar treatment effects were observed by proteinuria status and across blood-pressure categories, down to <120/70 mm Hg. However, the relative treatment effect in individuals with CKD was notably attenuated among those with coexisting diabetes (HR 0·96 [95% CI 0·90–1·02]) compared with those without (0·88 [0·84–0·93]; $p_{interaction}$=0·044). The stratified analysis within each drug class showed that the class-specific effects of antihypertensive agents versus placebo on cardiovascular disease risk remained unchanged across the investigated subgroups.

Interpretation In the context of cardiovascular risk reduction, the relative benefit of blood-pressure lowering in patients with CKD is similar to that in individuals without CKD, with consistent efficacy across all CKD stages, blood-pressure thresholds, and proteinuria status. However, notably, this relative benefit is attenuated in patients with CKD and concomitant diabetes, underscoring the requirement for adapted therapeutic strategies in this high-risk subgroup. Moreover, the class-specific effects of principal antihypertensives in CKD mirror those observed in the broader population, independent of CKD stage or proteinuria status.

Funding British Heart Foundation.

Research in context

Evidence before this study

We searched PubMed and the Cochrane Library from database inception to Jan 31, 2025, using MeSH terms and keywords for "hypertension", "blood pressure", "chronic kidney disease", and "antihypertensive agents", including variant terms and relevant drug classes, without language restrictions. Existing evidence on the cardiovascular benefits of blood-pressure lowering in chronic kidney disease (CKD) is scarce, inconsistent, and often non-generalisable, deriving largely from individual trials that enrolled participants with mildly reduced kidney function or were underpowered to examine treatment effects across the full spectrum of disease severity. No previous meta-analysis has comprehensively assessed treatment effects across all CKD stages—particularly stages 4–5—or examined effect modification by diabetes and proteinuria within a unified individual-participant data framework. Studies of class-specific antihypertensive effects have predominantly focused on kidney outcomes, leaving uncertainty about whether the cardiovascular efficacy of individual drug classes observed in the general population is maintained in people with CKD, and whether any class confers differential cardiovascular benefit across disease stages or by proteinuria status.

Added value of this study

This one-stage, individual-participant data meta-analysis, pooling data from 46 large-scale trials involving 285 124 participants (20·7% with CKD at baseline), represents the largest randomised dataset to date in this population. Importantly, 14 148 (23·9%) of the CKD subgroup had stage 3b or higher disease progression, allowing for a comprehensive assessment across the entire spectrum of CKD. We found that a 5 mm Hg reduction in systolic blood pressure is associated with a relative risk reduction in major cardiovascular disease in both CKD and non-CKD participants, with consistent treatment effects across all CKD stages and baseline blood-pressure values, and by proteinuria status. We found that the relative treatment effect is attenuated in participants with coexisting diabetes, highlighting a crucial subgroup of patients with CKD for targeted treatment strategies. Furthermore, the class-specific effect of antihypertensives versus placebo was similar in those with CKD compared with those without CKD, with similar effects across all stages and by proteinuria status.

Implications of all the available evidence

When the main therapeutic goal is cardiovascular risk management, clinicians can recommend blood-pressure-lowering treatment to individuals at all stages of CKD progression, regardless of blood-pressure values, provided the balance of benefits and harms is favourable and patient preferences are considered. This recommendation can be done with the expectation that the class-specific effects of different antihypertensive drugs mirror those observed in the broader population. In individuals with CKD and coexisting diabetes, blood-pressure-lowering treatment is essential due to their notably elevated absolute risk and the well documented beneficial effects of treatment in patients with diabetes. However, the attenuated relative risk reduction associated with diabetes highlights the need for adapted strategies to enhance cardiovascular risk management in this population at high risk.

(Prof B R Davis PhD); **College of Medicine, University of Florida, Gainesville, FL, USA**
(Prof C J Pepine MD)

Correspondence to:
Dr Milad Nazarzadeh, Deep Medicine Group, Nuffield Department of Women's and Reproductive Health, Medical Sciences Division, University of Oxford, Oxford OX2 0EW, UK
milad.nazarzadeh@wrh.ox.ac.uk

See **Online** for appendix

Introduction

The cardioprotective benefits of blood-pressure-lowering therapy are well documented across diverse populations with varied clinical backgrounds.[1–3] However, the efficacy and optimal application of blood-pressure-lowering therapy in people with chronic kidney disease (CKD) remain insufficiently investigated. This evidence gap arises primarily from the under-representation of patients with CKD in randomised controlled trials (RCTs) due to concerns about kidney-related harm that have led to their frequent exclusion from blood-pressure-lowering trials.[4] As CKD severity increases, evidence becomes increasingly scarce, especially in later stages of the disease, leaving clinicians dependent on data from non-CKD or lower-risk populations.[5] Despite widespread recognition of this evidence gap, progress over the past two decades has been slow[6] and several crucial questions remain: (1) whether blood-pressure-lowering efficacy varies by CKD status, stage, or baseline blood pressure; (2) whether blood-pressure-lowering treatment influences the risk of cardiovascular disease or death in patients with advanced CKD, potentially conferring either benefit or harm; (3) whether diabetes and proteinuria modify treatment effects; and (4) and whether specific classes of antihypertensive drugs differ in their ability to reduce cardiovascular risk in CKD, depending on disease stage or the presence or absence of proteinuria.[7]

Individual blood-pressure-lowering RCTs have not succeeded in bridging this gap and, in some cases, have further complicated the evidence base, thereby making clinical interpretation more challenging. For example, although earlier trials did not report a cardiovascular benefit of blood-pressure lowering in individuals with CKD,[8] the Systolic Blood Pressure Intervention Trial (SPRINT)[9,10] showed a transparent and similar reduction in risk with intensive blood-pressure lowering in both CKD and non-CKD participants. However, a post-hoc analysis of SPRINT[10] suggested a decreasing trend in the relative reduction of risk with progression to more advanced CKD stages. Moreover, trials published in 2025 explicitly conducted in patients with advanced CKD have not shown an apparent reduction in cardiovascular risk with antihypertensive treatment.[11,12]

Similarly, meta-analyses of RCTs have produced inconsistent findings. An aggregate data meta-analysis of 18 RCTs showed that a 10 mm Hg reduction in blood

pressure decreased major cardiovascular events in both the CKD and non-CKD groups; however, the benefit was smaller in the CKD group.[13] An individual-participant data meta-analysis of 23 RCTs with 152 290 participants indicated that blood-pressure lowering reduced cardiovascular risk in both groups, with no advantage related to specific drug classes.[14] However, most participants with CKD (76%) had estimated glomerular filtration rate (eGFR) values of 45–60 mL/min per 1·73 m² and only 0·4% had eGFRs lower than 30 mL/min per 1·73 m². Limitations of this meta-analysis, such as varying treatment definitions, the absence of a direct interaction assessment, the absence of standardisation for blood-pressure reduction, and the small number of trials included, hampered definitive conclusions.[14]

We aimed to address these gaps by pooling individual-participant data from large-scale RCTs representing the largest known randomised dataset for this population that included, importantly, participants with eGFR below 45 mL/min per 1·73 m² and 30 mL/min per 1·73 m² or lower.

Methods

Study design and procedures

In this individual-participant data meta-analysis, we used RCTs from the third cycle of the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC).[15] The BPLTTC, with the first cycle established in 1995, is an international collaboration of investigators from major RCTs of pharmacological blood-pressure-lowering therapies, dedicated to assessing their effects across diverse populations and clinical subgroups.[16] The general eligibility criteria for inclusion in the BPLTTC dataset were RCTs, published at any time and in any language, that compared an antihypertensive drug versus placebo or another antihypertensive, or investigated different blood-pressure-lowering intensities, with a minimum of 1000 patient-years of follow-up in each randomised arm. There were no age criteria for participant inclusion. Trials without a clearly defined randomisation process, those evaluating non-pharmacological interventions, and those conducted exclusively in patients with heart failure or in short-term acute settings (such as acute myocardial infarction) were excluded.[1,15] Further methodological details, including the central systematic review, quality and risk-of-bias assessments, characteristics of the included trials, and estimated achieved blood-pressure reductions, have been reported previously[1,15,17] and are available in the appendix (pp 16–17, 52).

The BPLTTC operates in accordance with the University of Oxford's policies on research integrity, codes of practice, and the management of research data and records. The systematic review protocol underpinning the third cycle of BPLTTC, specifying eligibility criteria, search strategy, and analytical methods, was prospectively registered in PROSPERO (CRD42018099283). The Steering Committee oversees all scientific activities, requiring that all studies are prespecified and approved before data are released for analysis. The study obtained ethics approval from the Oxford Tropical Research Ethics Committee (reference 545–14), and each contributing trial secured informed consent from its participants.[15]

For our meta-analysis, we included BPLTTC trials that provided data on baseline blood pressure, baseline creatinine values, major cardiovascular events, cause-specific cardiovascular and all-cause death, and the corresponding dates of occurrence. We excluded participants with a history of heart failure and those with extreme creatinine values (ie, <0·2 mg/dL or >5·0 mg/dL).

Treatment and comparator groups were defined according to the original trial design. In placebo-controlled trials, the active treatment arm was considered the intervention and the placebo arm was considered the comparator. In head-to-head trials comparing drug classes, the arm with the greater reduction in systolic blood pressure was designated the intervention, and the arm with the lesser reduction was designated the comparator. In trials with different treatment intensities, the intensive arm was the intervention and the standard arm was the comparator.

We estimated eGFR using the CKD Epidemiology Collaboration 2021 race-free equations (appendix p 5).[18] For subgroup analyses by baseline CKD status, participants with an eGFR less than 60 mL/min per 1·73 m² were categorised as having CKD at baseline.[7,19] The presence of proteinuria was defined as a protein-to-creatinine ratio of 0·22 or higher, urinary albumin excretion 200 µg/min or higher (>300 mg/day), urinary albumin concentration of 200 mg/L or higher, urinary albumin-to-creatinine ratio of 30 mg/g or higher, or a urinary protein dipstick result of 1 or higher.[20,21] To assess the effects of blood-pressure-lowering treatment across the spectrum of CKD severity, five stages were defined according to baseline eGFR: stage 1 (≥90 mL/min per 1·73 m²); stage 2 (60–89 mL/min per 1·73 m²); stage 3a (45–59 mL/min per 1·73 m²); stage 3b (30–44 mL/min per 1·73 m²); and stages 4–5 (<30 mL/min per 1·73 m²).[22]

Baseline systolic and diastolic blood pressure measurements were categorised by 10 mm Hg intervals, resulting in seven categories for systolic blood pressure (ranging from <120 mm Hg to ≥170 mm Hg) and six for diastolic blood pressure (ranging from <70 mm Hg to ≥110 mm Hg). Baseline diabetes status was established based on the diagnostic information provided by each trial.[3]

Artificial intelligence (AI) was not used in the design, conduct, analysis, or interpretation of this study. However, AI-assisted tools were used for language editing, proofreading, and R code debugging.

Data analysis

The primary outcome was the first occurrence of a major cardiovascular disease, defined as a composite of fatal or non-fatal stroke or other cerebrovascular disease, fatal or non-fatal ischaemic heart disease, or heart failure leading

to death or hospitalisation. Secondary outcomes included the individual components of the primary outcome as well as cardiovascular and all-cause death. We defined and ascertained outcomes based on the diagnostic definitions and endpoint adjudication criteria applied in each contributing trial, using the adjudicated event data supplied in the individual-participant datasets.

All core variables, including comparison arms, blood-pressure measurements after treatment, trial endpoints, general baseline characteristics including sex, and diabetes status, had already been harmonised in previous BPLTTC studies and were used in this analysis.[1–3,17,23,24] In parallel, a dedicated harmonisation process was done for variables specific to this study: baseline creatinine, eGFR, and presence or absence of proteinuria. We applied a fixed-effects, one-stage, individual-participant data meta-analysis framework, pooling participant-level data from all eligible trials and analysing them as a single, large-scale dataset, with each trial as a cluster.

We fitted Cox proportional hazards models, stratified by trial, to allow trial-specific baseline hazards and to control for between-trial differences in baseline risk.[25] Given the design of the included trials, the main source of heterogeneity was the variation in blood-pressure reduction after treatment, driven primarily by differences in comparison arms and treatment types.[17] To account for this heterogeneity, the models were standardised for the blood-pressure reduction after treatment at the trial level, and hazard ratios (HRs) were rescaled to express the relative treatment effect per 5 mm Hg reduction in systolic blood pressure and 3 mm Hg reduction in diastolic blood pressure (ie, values representing the mean reductions reached in all BPLTTC trials, excluding head-to-head RCTs; appendix p 6).[1,2,17] This parametrisation implicitly scales each trial's contribution by the blood-pressure reduction after treatment such that trials with larger reductions contribute more information to the standardised effect estimate, whereas trials with smaller reductions are retained but contribute correspondingly less. This approach prevents the arbitrary exclusion of trials with small blood-pressure reductions after treatment, maximises statistical power for subgroup analyses, and yields effect estimates with clear clinical interpretation (appendix pp 7–12).[26] The cumulative probability of major cardiovascular disease was estimated in each treatment arm using the Kaplan–Meier method and plotted separately for subgroups with and without CKD and by CKD stage.

In subgroup analyses, the likelihood-ratio test was used to assess interactions between treatment and subgroups, with p values for interaction corrected for multiple comparisons by use of Hommel's method (appendix pp 11–12).[27] Results from subgroup analyses were reported and interpreted in accordance with established principles for clinical trial interpretation.[28,29] When the statistical test for interaction was non-significant, the overall effect was considered the most valid estimate of the treatment effect. A significant interaction was interpreted in the context of effect magnitude and direction, previous literature, biological plausibility, and clinical relevance.

In addition to the main analysis, we conducted an individual-participant data network meta-analysis to estimate stratified, class-specific treatment effects for the five principal antihypertensive drug classes: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β blockers, calcium channel blockers, and thiazide diuretics.[3,23] This analysis was designed to assess whether effects within drug classes varied by CKD status, CKD stage, or presence of proteinuria, which is a research question that is not feasible to investigate with a conventional network meta-analysis. The comparison or ranking of drug classes was not the objective of this study because this question has been investigated previously in several aggregate-data meta-analyses.[13,30,31] Logistic regression models were applied to individual-level data from each trial to estimate the odds ratio as the relative treatment effect for each available comparison, stratified by CKD status, CKD stage, and proteinuria status. Finally, the estimated effects were pooled with a fixed-effect Bayesian network meta-analysis based on Markov Chain Monte Carlo methods (four chains, 10 000 burn-in iterations, and 100 000 sampling iterations), with the placebo arm serving as the network reference.[32] To assess whether drug-class-specific effects varied by subgroups, Wald-type Z tests were used to compare subgroup-specific log-odds ratios.[33] For each drug class, the linear trend across CKD stages was assessed with meta-regression with CKD stage as an ordinal covariate, deriving the p value for trend from the test of moderators.[34]

All analyses in this study were conducted according to the intention-to-treat principle. We performed statistical analyses using R (version 4.2.0). Details of packages used for analysis are reported in the appendix (p 15).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The current third cycle of BPLTTC included individual-level data from 52 RCTs, encompassing 363 684 participants.[15] From these RCTs, we excluded one trial due to the absence of time-to-event data[35] and five trials for not having baseline creatinine measurements.[36–40] Consequently, 46 trials comprising 285 124 participants (59 185 with CKD and 225 939 without) met the eligibility criteria and were included in the analysis (appendix pp 17–24). A detailed flow chart showing the study selection is available in the appendix (p 35). Baseline diabetes status was available for all

	Individuals with CKD at baseline (n=59 185)			Individuals without CKD at baseline (n=225 939)		
	Intervention	Comparator	Total	Intervention	Comparator	Total
Sex						
Female	14 340/27 804 (51·6%)	16 201/31 381 (51·6%)	30 541/59 185 (51·6%)	40 474/106 149 (38·1%)	45 130/119 790 (37·7%)	85 604/225 939 (37·9%)
Male	13 464/27 804 (48·4%)	15 180/31 381 (48·4%)	28 644/59 185 (48·4%)	65 675/106 149 (61·9%)	74 660/119 790 (62·3%)	140 335/225 939 (62·1%)
Age, years	69·5 (9·4)	70·0 (9·2)	69·8 (9·3)	63·6 (9·6)	64·1 (9·3)	63·9 (9·5)
Systolic blood pressure, mm Hg	156 (23)	155 (23)	156 (23)	153 (21)	152 (21)	152 (21)
Diastolic blood pressure, mm Hg	86 (13)	86 (13)	86 (13)	88 (13)	88 (12)	88 (13)
BMI, kg/m²	28·1 (5·2)	28·1 (5·6)	28·1 (5·4)	27·8 (5·0)	28·0 (9·9)	27·9 (8·0)
Smoking status						
Never	10 082/20 001 (50·4%)	11 366/23 019 (49·4%)	21 448/43 020 (49·9%)	33 991/74 382 (45·7%)	37 972/86 375 (44·0%)	71 963/160 757 (44·8%)
Past	7108/20 001 (35·5%)	8416/23 019 (36·6%)	15 524/43 020 (36·1%)	25 526/74 382 (34·3%)	31 463/86 375 (36·4%)	56 989/160 757 (35·5%)
Current	2811/20 001 (14·1%)	3237/23 019 (14·1%)	6048/43 020 (14·1%)	14 865/74 382 (20·0%)	16 940/86 375 (19·6%)	31 805/160 757 (19·8%)
Ethnicity						
White, Caucasian, or European	13 837/21 202 (65·3%)	15 472/24 590 (62·9%)	29 309/45 792 (64·0%)	52 596/80 312 (65·5%)	60 554/92 425 (65·5%)	113 150/172 737 (65·5%)
Black	2893/21 202 (13·6%)	3856/24 590 (15·7%)	6749/45 792 (14·7%)	4852/80 312 (6·0%)	7241/92 425 (7·8%)	12 093/17 737 (68·2%)
Hispanic	965/21 202 (4·6%)	1386/24 590 (5·6%)	2351/45 792 (5·1%)	3751/80 312 (4·7%)	5644/92 425 (6·1%)	9395/17 737 (53·0%)
Asian	2484/21 202 (11·7%)	2792/24 590 (11·4%)	5276/45 792 (11·5%)	16 670/80 312 (20·8%)	16 452/92 425 (17·8%)	33 122/17 737 (186·7%)
Other	1023/21 202 (4·8%)	1084/24 590 (4·4%)	2107/45 792 (4·6%)	2443/80 312 (3·0%)	2534/92 425 (2·7%)	4977/17 737 (28·1%)
Comorbidity						
Peripheral vascular disease	1510/11 314 (13·3%)	1451/11 038 (13·1%)	2961/22 352 (13·2%)	3415/41 368 (8·3%)	3540/39 850 (8·9%)	6955/81 218 (8·6%)
Atrial fibrillation	1300/14 345 (9·1%)	1404/16 519 (8·5%)	2704/30 864 (8·8%)	3124/55 179 (5·7%)	3373/63 051 (5·3%)	6497/118 230 (5·5%)
Cerebrovascular disease	4466/22 080 (20·2%)	4879/23 813 (20·5%)	9345/45 893 (20·4%)	15 702/85 469 (18·4%)	17 132/91 583 (18·7%)	32 834/177 052 (18·5%)
Ischaemic heart disease	8191/25 157 (32·6%)	9333/26 788 (34·8%)	17 524/51 945 (33·7%)	27 243/94 999 (28·7%)	31 934/101 237 (31·5%)	59 177/196 236 (30·2%)
Type 2 diabetes	8474/27 801 (30·5%)	9582/31 377 (30·5%)	18 056/59 178 (30·5%)	31 824/106 109 (30·0%)	36 187/119 741 (30·2%)	68 011/225 850 (30·1%)
Previous use of non-trial medications						
Diuretics	5210/15 556 (33·5%)	5967/16 673 (35·8%)	11 177/32 229 (34·7%)	9492/56 753 (16·7%)	11 054/61 340 (18·0%)	20 546/118 093 (17·4%)
α blockers	833/12 126 (6·9%)	898/13 323 (6·7%)	1731/25 449 (6·8%)	1379/40 945 (3·4%)	1633/46 040 (3·5%)	3012/86 985 (3·5%)
β blockers	5734/16 365 (35·0%)	6637/17 461 (38·0%)	12 371/33 826 (36·6%)	18 464/60 339 (30·6%)	21 748/64 936 (33·5%)	40 212/125 275 (32·1%)
Angiotensin-converting enzyme inhibitors	5780/14 954 (38·7%)	6699/16 105 (41·6%)	12 479/31 059 (40·2%)	14 827/53 623 (27·7%)	18 617/58 153 (32·0%)	33 444/111 776 (29·9%)
Angiotensin-receptor blockers	748/9193 (8·1%)	746/8726 (8·5%)	1494/17 919 (8·3%)	3198/39 354 (8·1%)	3195/37 053 (8·6%)	6393/76 407 (8·4%)
Calcium-channel blockers	5977/16 377 (36·5%)	6360/17 475 (36·4%)	12 337/33 852 (36·4%)	18 634/60 342 (30·9%)	19 961/64 936 (30·7%)	38 595/125 278 (30·8%)
Antiplatelets	4825/12 353 (39·1%)	6088/13 556 (44·9%)	10 913/25 909 (42·1%)	16 138/41 257 (39·1%)	21 601/46 943 (46·0%)	37 739/88 200 (42·8%)
Anticoagulants	765/8027 (9·5%)	878/9188 (9·6%)	1643/17 215 (9·5%)	1804/26 857 (6·7%)	2221/32 457 (6·8%)	4025/59 314 (6·8%)
Lipid-lowering treatments	4159/12 528 (33·2%)	5065/12 991 (39·0%)	9224/25 519 (36·1%)	16 540/50 834 (32·5%)	20 677/53 476 (38·7%)	37 217/104 310 (35·7%)
eGFR, mL/min per 1·73m²	49·8 (8·6)	49·9 (8·6)	49·9 (8·6)	81·8 (13·5)	81·6 (13·3)	81·7 (13·4)
Proteinuria	2975/14 036 (21·2%)	3023/15 152 (20·0%)	5998/29 188 (20·5%)	5434/46 821 (11·6%)	6146/52 076 (11·8%)	11 580/98 897 (11·7%)
Follow-up, years	4·3 (3·0–5·0)	4·4 (3·0–5·0)	4·4 (3·0–5·0)	4·4 (3·2–5·1)	4·4 (3·3–5·1)	4·4 (3·3–5·1)

Data are n/N (%), mean (SD), or median (IQR). Sex refers to biological sex as recorded by trial investigators at enrolment and harmonised across trials. Data on gender identity and psychosocial or cultural gender constructs were not available in the Blood Pressure Lowering Treatment Trialists' Collaboration database and therefore could not be analysed. CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate.

Table: **Baseline characteristics of participants by CKD status and study arm**

included trials and proteinuria measurements were obtained from 24 trials (appendix pp 17–24). Compared with those without CKD, patients with CKD were more likely to be female and older, had higher baseline systolic blood pressure, were less likely to be smokers, and had a greater prevalence of cardiovascular comorbidities (table). The distribution of eGFR and corresponding CKD stages at baseline for all included participants are presented in the appendix (p 36).

During a median follow-up of 4·4 years (IQR 3·2–5·1), the primary composite outcome occurred in 36 473 (12·8%) of 284 134 participants, with individual event counts of ischaemic heart disease (17 817 [6·3%] of 284 333), stroke (12 795 [4·5%] of 284 350), heart failure (6875 [2·8%] of

246 202), cardiovascular death (10 044 [3·6%] of 282 222), and all-cause death (25 197 [8·9%] of 284 365). In participants with CKD, the incidence rate of the primary outcome was 51·6 per 1000 person-years (95% CI 50·3–52·9) in the comparator arm versus 45·8 (44·6–47·2) in the treatment arm. Among those without CKD, the corresponding rates were 30·4 (29·9–30·9) and 26·4 (25·9–26·9), respectively.

A 5 mm Hg reduction in systolic blood pressure was associated with a reduced risk of major cardiovascular disease among participants with CKD (HR 0·91 [95% CI 0·87–0·94]) and participants without CKD (0·90 [0·88–0·93]), with no evidence of heterogeneity ($p_{interaction}$>0·99; appendix p 37). Similar results were observed for all secondary outcomes (all $p_{interaction}$>0·15; appendix p 38). In the analysis stratified by CKD stage, relative treatment effects on risk of major cardiovascular disease were consistent across all stages, with clear sustained benefits in advanced CKD stages 4–5 (mean eGFR 25 mL/min per 1·73 m²) and no evidence of effect modification ($p_{interaction}$>0·99; figure 1). For secondary outcomes, although some variation in effect sizes was observed among subgroups, there was no strong statistical evidence of effect modification, suggesting these variations were likely due to chance (all $p_{interaction}$>0·74; figure 2). Likewise, analyses stratified by baseline blood pressure showed consistent treatment effects across systolic and diastolic blood-pressure categories for either the primary (figure 3) or secondary outcomes, in participants with or without CKD (appendix pp 39–40).

Baseline proteinuria status did not modify relative treatment effects, suggesting similar benefits in CKD patients with and without proteinuria (figure 4; appendix p 41). In contrast, diabetes status modified treatment effects, with attenuated relative risk reductions for major cardiovascular events in patients with CKD and coexisting diabetes compared with those without ($p_{interaction}$=0·044; figure 4). No such effect modification was observed for secondary outcomes (appendix p 42).

We performed several post-hoc analyses. A complementary analysis with four subgroups based on CKD and proteinuria status yielded results similar to the main analysis (appendix p 26). Sensitivity analyses—including Fine–Gray competing risk models (appendix p 27), a two-stage random-effects individual-participant data meta-analysis (appendix p 28), unstandardised treatment effects (appendix p 29), and exclusion of head-to-head trials (appendix p 30)—supported the robustness of our primary findings. Absolute treatment effects were also estimated (appendix p 31).

The network meta-analysis stratified by CKD status and stage included 29 trials: 16 placebo-controlled (n=71 399 participants) and 13 head-to-head comparisons (n=108 782). For the analysis stratified by proteinuria, 16 trials with available data were included: ten placebo-controlled (n=9048) and six head-to-head comparisons (n=12 988; appendix pp 32–35). The analysis comparing individual drug classes with placebo showed that class-specific antihypertensive effects did not differ by CKD status (figure 5; appendix p 43). Similarly, across CKD stages, no drug class showed a stage-related gradient of effect compared with placebo; estimates were directionally consistent and of similar magnitude in both early and advanced CKD (figure 5; appendix p 44). Furthermore, we found no evidence that class-specific effects varied by the proteinuria status (figure 5; appendix p 45).

Discussion

This individual-participant data meta-analysis, pooling 46 RCTs and comprising 59 185 participants with CKD and 225 939 without CKD, provides the most comprehensive randomised evidence on cardiovascular benefits of blood-pressure lowering across the full spectrum of CKD, including subgroups with key clinical features such as diabetes and proteinuria, and across a granular range of blood-pressure thresholds at treatment initiation. Each 5 mm Hg reduction in systolic blood pressure was associated with a lowering of the risk of major cardiovascular events, regardless of CKD status. This beneficial treatment effect extended across the full spectrum of CKD severity, including advanced CKD stages 4–5 (mean eGFR 25 mL/min per 1·73 m²), across categories of baseline blood pressure

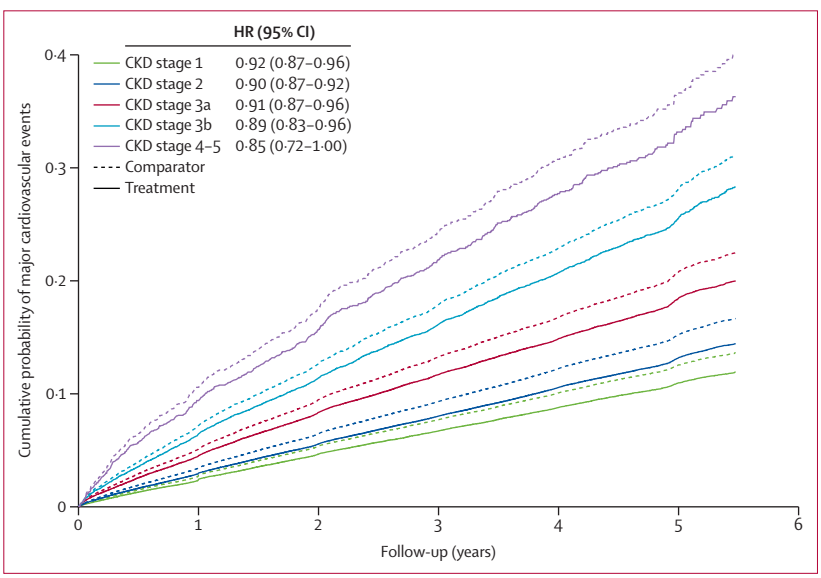


Figure 1: **Kaplan–Meier curves for major cardiovascular disease, by treatment allocation and CKD stage**
Cumulative incidence curves for major cardiovascular events stratified by CKD stage, with solid lines representing the treatment arm and dashed lines representing the comparator arm. Number-at-risk data are given in the appendix (p 25). HRs with 95% CIs were standardised to a 5 mm Hg reduction in systolic blood pressure, estimated from one-stage stratified Cox proportional hazards models. CKD stages were defined with the CKD Epidemiology Collaboration 2021 race-free equations:[18] stage 1 (eGFR ≥90 mL/min per 1·73 m²), stage 2 (60–89 mL/min per 1·73 m²), stage 3a (45–59 mL/min per 1·73 m²), stage 3b (30–44 mL/min per 1·73 m²), and stages 4–5 (<30 mL/min per 1·73 m²). Major cardiovascular events were defined as fatal or non-fatal stroke or other cerebrovascular disease, fatal or non-fatal ischaemic heart disease, or heart failure leading to death or hospitalisation. The increasing cumulative incidence with advancing CKD stage reflects the higher baseline cardiovascular risk among patients with more severe CKD. Relative treatment benefit was consistent across all CKD stages ($p_{interaction}$>0·99). CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. HR=hazard ratio.

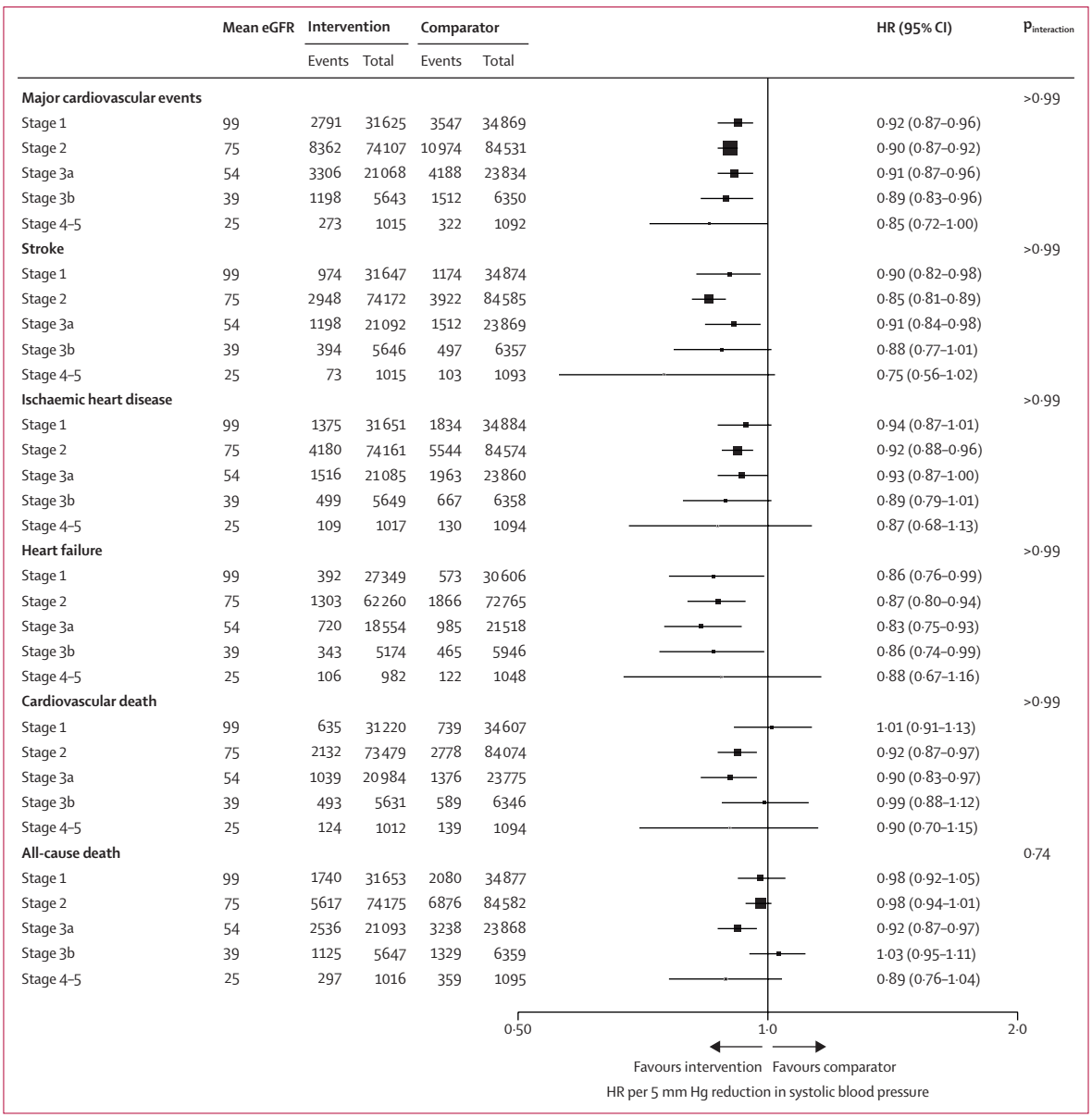


Figure 2: **Effects of blood-pressure-lowering treatment on primary and secondary outcomes by CKD stage**
The forest plot shows HRs and 95% CIs per 5 mm Hg reduction in systolic blood pressure, separately for each outcome. HRs and 95% CIs were standardised to a 5 mm Hg reduction in systolic blood pressure, estimated from one-stage stratified Cox proportional hazards models. CKD stages were defined with the CKD Epidemiology Collaboration 2021 race-free equations:[18] stage 1 (eGFR ≥90 mL/min per 1·73 m^2), stage 2 (60–89 mL/min per 1·73 m^2), stage 3a (45–59 mL/min per 1·73 m^2), stage 3b (30–44 mL/min per 1·73 m^2), and stages 4–5 (<30 mL/min per 1·73 m^2). Mean eGFR values within each stage represent the baseline eGFR of participants classified in that subgroup. p values for interaction were derived from likelihood ratio tests comparing models with and without treatment-by-CKD stage interaction terms, assessing heterogeneity of treatment effect across the five CKD stages, and were adjusted for multiple testing with Hommel's method. Events denotes the number of participants who had 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 an HR of 1·0 (ie, no effect). CKD=chronic kidney disease. HR=hazard ratio.

down to less than 120/70 mm Hg, and irrespective of proteinuria status. Notably, patients with CKD and coexisting diabetes derived substantially smaller relative benefits from blood-pressure lowering than those without diabetes, highlighting a high-risk CKD subgroup that might warrant optimised cardiovascular risk management.

Few meta-analyses have examined the effect of blood-pressure lowering on major cardiovascular disease and death in patients with CKD, and the available evidence has yielded conflicting results. A Cochrane meta-analysis incorporating six trials comparing more-intensive versus less-intensive blood-pressure targets (n=7348) found no treatment effect on total cardiovascular disease

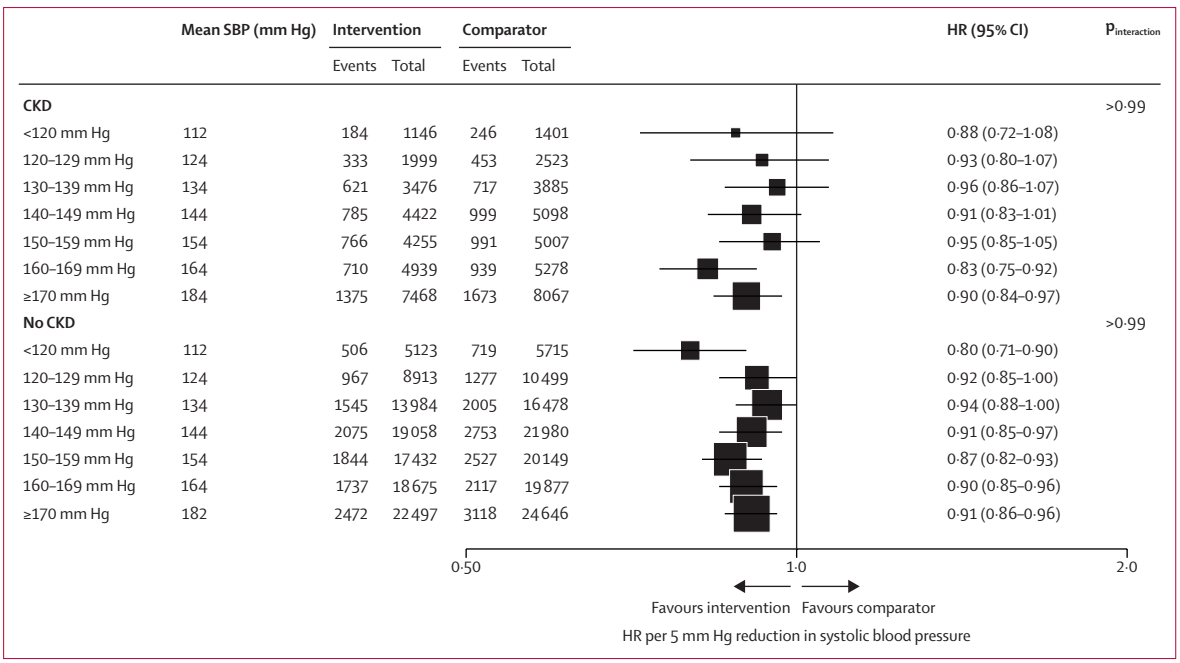


Figure 3: **Effects of blood-pressure-lowering treatment on major cardiovascular events by baseline CKD status and SBP**
The forest plot shows HRs and 95% CIs for major cardiovascular events by baseline SBP categories, separately for participants with and without CKD. HRs and 95% CIs were standardised to a 5 mm Hg reduction in systolic blood pressure, estimated from one-stage stratified Cox proportional hazards models. Mean SBP values within each category represent the baseline SBP of participants classified in that subgroup. p values for interaction were derived from likelihood ratio tests comparing models with and without treatment-by-baseline SBP category interaction terms, assessing heterogeneity of treatment effect across the seven SBP categories within each CKD stratum, and were adjusted for multiple testing with Hommel's method. Events denotes the number of participants who had 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 an HR of 1·0 (ie, no effect). CKD=chronic kidney disease. HR=hazard ratio. SBP=systolic blood pressure.

(relative risk 1·00 [95% CI 0·87–1·15]), cardiovascular cause death (0·90 [0·70–1·16]), and all-cause death (0·90 [0·76–1·06]).[41] These null findings persisted in analyses stratified by only two eGFR categories (<30 mL/min *vs* 30–60 mL/min). An earlier meta-analysis of 11 trials comparing intensive versus standard blood-pressure targets (n=9287) reported concordant results, showing no benefit for cardiovascular disease and no effect on all-cause death.[42] In contrast, a meta-analysis using broader eligibility criteria with respect to trial design and intervention (18 trials; n=60178) found that a 10 mm Hg reduction in systolic blood pressure was associated with a reduction in the risk of major cardiovascular disease among patients with CKD.[13] Moreover, this study also identified significant effect modification by baseline CKD status, with a more pronounced relative risk reduction in HR observed in the non-CKD group.[13] Our study—constituting the largest analysis of trial data to date—addressed the uncertainties inherent in individual RCTs and previous meta-analyses that did not have sufficient statistical power and generalisability across the CKD spectrum. In contrast to previous investigations, we stratified treatment effects by granular CKD stage while simultaneously comparing individuals with and without CKD, and we incorporated comprehensive subgroup analyses by blood-pressure threshold, proteinuria, and diabetes status. Our study fills a crucial evidence gap

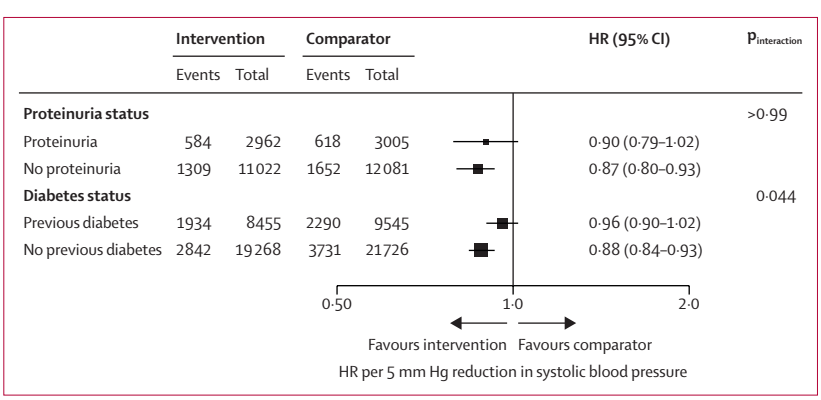
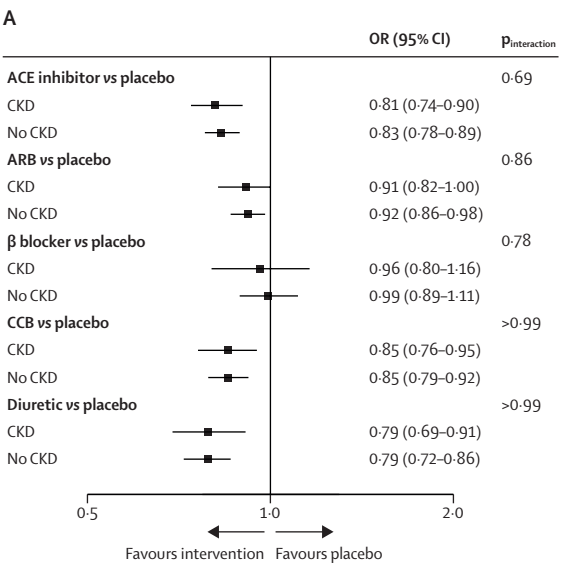
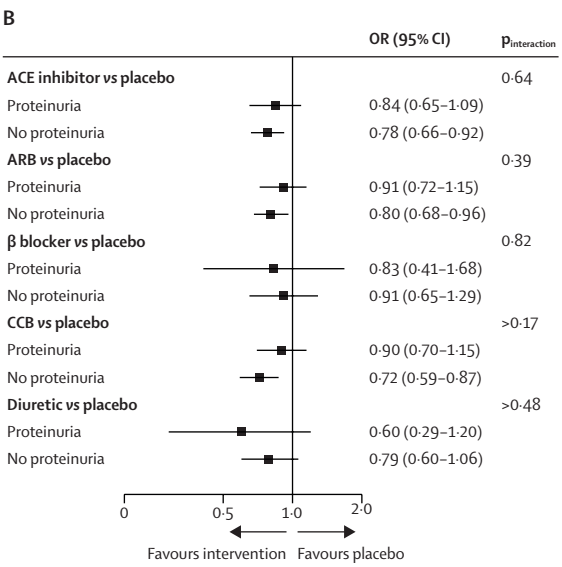


Figure 4: **Effects of blood-pressure-lowering treatment on major cardiovascular disease in people with CKD, stratified by baseline diabetes and proteinuria status**
The forest plot shows HRs and 95% CIs for major cardiovascular events within participants with CKD, stratified by proteinuria and diabetes status. HRs and 95% CIs were standardised to a 5 mm Hg reduction in systolic blood pressure, estimated from one-stage stratified Cox proportional hazards models. Proteinuria was defined as urine albumin-to-creatinine ratio of ≥30 mg/g or urine protein-to-creatinine ratio of ≥0·22 or dipstick ≥1. Previous diabetes was defined as a history of diabetes at baseline. p values for interaction were derived from likelihood ratio tests comparing models with and without treatment-by-subgroup interaction terms, assessing heterogeneity of treatment effect, and were adjusted for multiple testing with Hommel's method. Sample sizes for proteinuria analysis are smaller because proteinuria data were available only in a subset of trials. Events denotes the number of participants who had 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 an HR of 1·0 (ie, no effect). CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. HR=hazard ratio.

concerning the efficacy of blood-pressure-lowering therapy for cardiovascular risk reduction in patients with CKD.

Clinical guidelines' recommendations for blood-pressure management in CKD vary considerably.[7,43–45] The 2021 Kidney Disease: Improving Global Outcomes





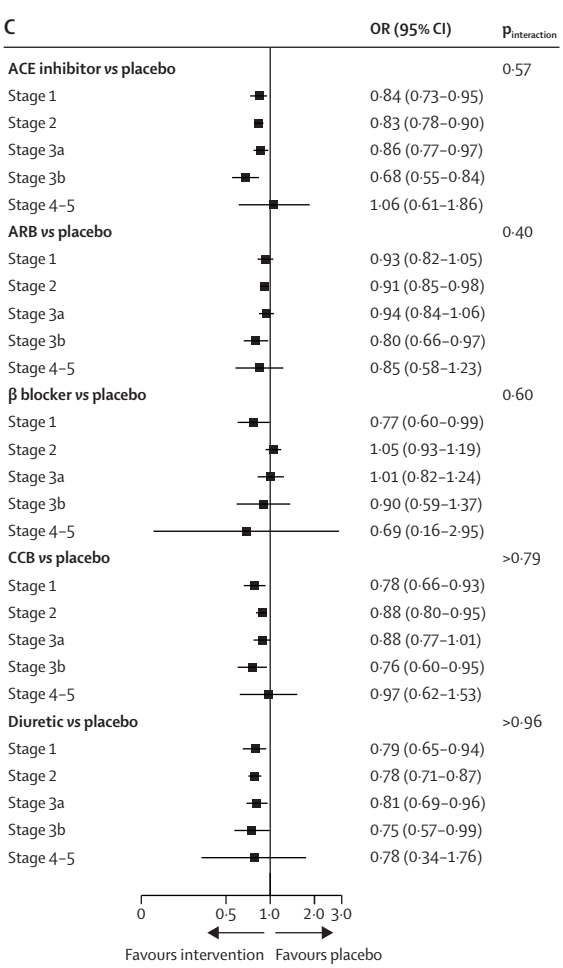


Figure 5: **Class-specific effects of antihypertensive drugs on the risk of major cardiovascular disease, stratified by CKD status, stage, and proteinuria**

The forest plots show ORs as the relative treatment effect and their corresponding 95% CIs for major cardiovascular events stratified by CKD status (A), proteinuria existence (B), and CKD stage (C), comparing each antihypertensive drug class with placebo, estimated from a Bayesian network meta-analysis with fixed-effects models. p values for interaction were derived from meta-regression comparing treatment effects across subgroups. The size of each square is proportional to the inverse variance of the log OR. The vertical line indicates an OR of 1·0 (ie, no effect). CKD stages were defined with the CKD Epidemiology Collaboration 2021 race-free equations:[18] stage 1 (eGFR ≥90 mL/min per 1·73 m²), stage 2 (60–89 mL/min per 1·73 m²), stage 3a (45–59 mL/min per 1·73 m²), stage 3b (30–44 mL/min per 1·73 m²), and stages 4–5 (<30 mL/min per 1·73 m²). ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. CCB=calcium channel blocker. CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. OR=odds ratio.

(KDIGO) guidelines[7] recommend a systolic blood-pressure target of <120 mm Hg for non-dialysis CKD. Although this target represents the most intensive recommendation among major guidelines, it is assigned a weak strength of recommendation (grade 2B), reflecting an evidence base largely derived from a single RCT (the SPRINT trial) with a predefined CKD subgroup.[7] In contrast, the European Society of Hypertension adopts a more conservative primary target of below 140/90 mm Hg, with consideration of below 130/80 mm Hg if well tolerated,[46] and the American College of Cardiology–American Heart Association recommends below 130/80 mm Hg, encouraging systolic values below 120 mm Hg.[45] Our stratified analyses provide evidence to inform this debate: relative treatment benefits for major cardiovascular disease are consistent across baseline blood-pressure categories, extending to values below 120/70 mm Hg. These findings support the more intensive KDIGO recommendations and strengthen the evidentiary foundation for lower blood-pressure targets in patients with CKD than for those without.

Current guidelines uniformly acknowledge the scarcity of randomised evidence for blood-pressure management in patients with more advanced stages of CKD.[7,43–46] Our study fills this gap and shows consistent relative treatment effects across CKD stages 1–5. Notably, our analysis included 14 148 participants with CKD stage 3b or higher, of whom 2107 had stage 4–5 disease with a mean baseline eGFR of 25 mL/min per 1·73 m². Likewise, our finding of attenuated relative benefit in patients with CKD and coexisting diabetes addresses another explicitly acknowledged evidence gap. KDIGO notes that cardiovascular benefits of intensive blood-pressure lowering cannot be excluded in diabetic CKD, but remain uncertain.[7] Our subgroup analysis suggests that in individuals with both CKD and diabetes, blood-pressure lowering offers little or no relative benefit. To mitigate risk in this subgroup, therapeutic regimens might require the integration of antihypertensives with agents such as SGLT2 inhibitors or GLP-1 receptor agonists, which provide robust cardiorenal protection and enhance glycaemic regulation.[47–49] For SGLT2 inhibitors specifically, these benefits are preserved in patients with low eGFR despite reduced glucose-lowering efficacy.[50,51] Given their distinct mechanisms from antihypertensive drugs, additive or adjunctive effects on cardiovascular risk seem plausible, especially in CKD with diabetes, thus dedicated trials are warranted.

Renin-angiotensin system (RAS) inhibitors are widely recommended as the cornerstone of antihypertensive therapy for patients with CKD,[7,43–45] driven primarily by the proven renoprotective effects of RAS inhibitors rather than by definitive evidence of cardiovascular protection in this population. Our network meta-analysis provides direct evidence of this gap and carries several key implications for clinical practice. First, the relative risk reduction in cardiovascular disease conferred by each antihypertensive class in CKD mirrors that observed in individuals with preserved renal function. Consequently, class-specific evidence of cardiovascular protection from broader populations can be extrapolated to patients with CKD, including those at more severe stages. Next, hypertension in CKD is typically driven by the convergence of multiple biological pathways, including sodium retention, neurohormonal activation, endothelial dysfunction, and reduced large-artery compliance. Consequently, monotherapy with a single antihypertensive class is often inadequate. Optimal risk management might require a combination therapy utilising agents from different classes. Our findings affirm that such multiclass regimens can be recommended flexibly, with consistent cardiovascular efficacy across CKD severity and proteinuria values.

Although these findings show that blood-pressure reduction confers cardiovascular protection across the spectrum of CKD and baseline blood pressure, they should not drive an indiscriminate approach to initiating therapy in every clinical setting. From a clinical perspective, these findings suggest that single baseline characteristics (eg, CKD stage, blood pressure, and proteinuria) are not determinants of proportional benefit. Instead, clinicians should anticipate consistent relative risk reductions across all CKD stages, proteinuria values, and blood-pressure strata, similar to those observed in the broader population. Initiating treatment necessitates a multifactorial evaluation that weighs absolute cardiovascular risk against the likelihood of adverse events, such as acute kidney injury, hyperkalaemia, and symptomatic hypotension. This decision-making process must balance preventive efficacy with safety while considering comorbidities, polypharmacy, and patient values. Furthermore, our stratified analyses examined each clinical factor in isolation to provide clear evidence across the full spectrum of each characteristic. Real-world decisions require a multidimensional risk–benefit assessment to establish whether the cardiovascular protection conferred by blood-pressure-lowering therapy outweighs the potential harms for a given patient.

Several limitations should be considered when interpreting and generalising the findings of this study. We evaluated only relative treatment effects on cardiovascular outcomes; treatment-related adverse events and kidney-specific outcomes were not examined because their scope and methodological requirements differ from those of the present analysis. In the context of the benefit–harm balance, concerns have been raised particularly in people with advanced CKD. However, trials published in 2025 conducted exclusively in this population did not show an excess risk of serious adverse events,[11,12] although evidence from a larger dataset is still needed. A new round of BPLTTC data acquisition, focused on adverse events, benefit–harm evaluation, and cost-effectiveness, is underway and will provide comprehensive evidence to address these endpoints and

refine the overall benefit–harm profile of blood-pressure-lowering treatment. Furthermore, we stratified analyses by individual clinical features, which is often insufficient for identifying distinct patient groups.[52] Further research is warranted to explore potential heterogeneity of treatment effects using other phenotypes, including novel approaches to multivariable and high-dimensional participant stratification.[53] For example, compared with the widely recommended treat-all policy for patients with diabetes, a novel AI-based approach to treatment selection successfully deselected 24·3% of individuals, with only a very small proportion of false negatives (0·2% of the cohort).[54] Data supporting their clinical utility in CKD warrant further study.

This meta-analysis, drawing on the largest body of randomised evidence to date, carries direct and actionable implications for the management of blood pressure in individuals with CKD, specifically for the prevention of major cardiovascular outcomes rather than kidney outcomes or renoprotection. Clinicians should recommend blood-pressure-lowering treatment for patients at any stage of CKD and at any baseline blood pressure because it consistently reduces cardiovascular risk, irrespective of CKD stage or baseline blood pressure. Nonetheless, treatment decisions should also consider the balance of benefits and potential risks, including adverse effects and patient-specific factors. Our results also indicate no evidence that the effects of antihypertensive drug classes differ across the investigated CKD subgroups, providing clinicians with the flexibility to select agents based on patient characteristics, preferences, and tolerability. Notably, the attenuated treatment effect observed in participants with coexisting diabetes underscores the need for an adopted risk-management strategy in this subgroup of patients with high-risk CKD. Although blood-pressure lowering remains imperative in patients with CKD and diabetes due to their higher absolute risk, these findings highlight the necessity of considering antihypertensive therapy with other evidence-based interventions to maximise cardiovascular risk reduction in this specific subgroup.

Contributors

GZ, MN, and KR conceptualised the study. GZ, MN, KR, ZB, and DC were responsible for data acquisition, harmonisation, and curation. All authors, as members of the working group, were responsible for writing the protocol and conducting the investigation. GZ, MN, ZB, and KR directly accessed data. MN and ZB verified data, analytical codes, and results. All authors interpreted the data. GZ and MN drafted the original manuscript, which was reviewed and edited by all authors. GZ and MN were responsible for data visualisation. KR, DC, and MN acquired the funding for the study. MN and KR supervised the project. All authors (including members of the Blood Pressure Lowering Treatment Trialists' Collaboration Core Analytic group [ZB, MN, and DC]) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

KR reports grants to his institution from the National Institute for Health Research (NIHR304997), the Medical Research Council (MR/Y030419/1), the British Heart Foundation (FS/PhD/22/29321, FS/PhD/21/29110, and FS/PhD/25/29632), the EU (101080430), Roche (R94776/CN002), and the Novo Nordisk Oxford Big Data Partnership; royalties or licences from Lucem Health (personal and institutional); personal fees from Radcliffe Cardiology for speaking; personal fees as Editor-in-Chief of *Heart*; and participation on a Medtronic Advisory Board for Renal Denervation (institutional). DC has received support from the UK Research and Innovation Medical Research Council (MR/Y010825/1), the Dunhill Medical Trust (ARVHF2402/7), and the National Institute for Health and Care Research (NIR203982) outside of the submitted work (the views expressed are not necessarily those of these funders); and received an honorarium as Specialty Chief Editor of *Frontiers in Cardiovascular Medicine* (Cardiovascular Epidemiology and Prevention). ZB has received a doctoral fellowship from the British Heart Foundation (FS/PhD/25/29632). MN is supported by an individual research fellowship from the British Heart Foundation (grant FS/IPBSRF/22/27060); has received reimbursement and honoraria from AstraZeneca, Nemysis, and Albus Health outside the submitted work; and is the statistical adviser of *Heart* (BMJ Publishing Group). MW has received personal fees from Amgen, Kyowa Kirin, and Freeline. SEK has received lecture honoraria from Emcure, Getz, Hikma, JB Pharma, Merck, Vector-Intas, and Zydus; and support from the Research Council of Norway (grant number 273563). JC has received grants from the National Health and Medical Research Council of Australia. GZ was funded by the China Scholarship Council. WCC has received consulting fees from Alnylam, Idorsia, and Azurity Pharmaceuticals, and a grant from George Medicines. All other authors declare no competing interests.

Data sharing

The governance of the BPLTTC has been reported previously.[15] The study is governed by the University of Oxford's (Oxford, UK) policies on research integrity and codes of practice, and follows the university's policy on the management of research data and records. The Steering Committee oversees scientific activities based on BPLTTC datasets. All trial data shared with the BPLTTC is considered confidential and will not be provided to any third party. Requests for data should be made directly to the data custodians for each trial, whose contact details are available through the original trial publications. Information about individual projects is posted on the BPLTTC website (https://www.wrh.ox.ac.uk/research/Blood_Pressure_Lowering_Treatment_Trialists_Collaboration_BPLTTC). To ensure transparency and facilitate reproducibility, all statistical source code and documentation are deposited in an open-access GitHub repository (https://github.com/deepmedicine/BPLTTC-CKD-at-baseline-and-spectrum) hosted by the DeepMedicine research group (https://www.wrh.ox.ac.uk/research/deep-medicine).

Acknowledgments

The third cycle of the BPLTTC was funded by the British Heart Foundation (PG/18/65/33872). This study also received support via an individual research fellowship from the British Heart Foundation (grant FS/IPBSRF/22/27060). This study was prepared with research materials from the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial, which were obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Centre. The views expressed do not necessarily reflect the opinions or views of the ALLHAT, PEACE, or the NHLBI. We acknowledge the original depositors of the Australian National Blood Pressure Study data and the Australian Data Archive and confirm that those who performed the original analysis and data collection bear no responsibility for the further analysis or interpretation of these data. This study utilised data from a trial supported by Boehringer Ingelheim. Boehringer Ingelheim had no role in the design, analysis, or interpretation of the results; however, they were given the opportunity to review the manuscript for medical and scientific accuracy regarding Boehringer Ingelheim substances and for intellectual property considerations. During the preparation of this work we used Grammarly, integrated into Microsoft Word (Pro, version 1.2.246.1869), to check grammar, punctuation, and clarity. Claude (Anthropic; Opus 4.5) and ChatGPT Edu (OpenAI; GPT-5) were used for debugging R code and structuring the GitHub repository. After using these tools, we reviewed and edited the content as needed

and take full responsibility for the content of the publication. The authors followed the University of Oxford guidance on the safe and responsible use of generative AI tools.

References

1 Rahimi K, Bidel Z, Nazarzadeh M, et al, and the Blood Pressure Lowering Treatment Trialists' Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet* 2021; **397:** 1625–36.

2 Rahimi K, Bidel Z, Nazarzadeh M, et al, and the Blood Pressure Lowering Treatment Trialists' Collaboration. Age-stratified and blood-pressure-stratified effects of blood-pressure-lowering pharmacotherapy for the prevention of cardiovascular disease and death: an individual participant-level data meta-analysis. *Lancet* 2021; **398:** 1053–64.

3 Nazarzadeh M, Bidel Z, Canoy D, et al, and the Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment for prevention of major cardiovascular diseases in people with and without type 2 diabetes: an individual participant-level data meta-analysis. *Lancet Diabetes Endocrinol* 2022; **10:** 645–54.

4 Li J, An J, Huang M, et al. Representation of real-world adults with chronic kidney disease in clinical trials supporting blood pressure treatment targets. *J Am Heart Assoc* 2024; **13:** e031742.

5 Ishida JH, Chauhan C, Gillespie B, et al. Understanding and overcoming the challenges related to cardiovascular trials involving patients with kidney disease. *Clin J Am Soc Nephrol* 2021; **16:** 1435–44.

6 Colombijn JMT, Idema DL, van Beem S, et al. Representation of patients with chronic kidney disease in clinical trials of cardiovascular disease medications: a systematic review. *JAMA Netw Open* 2024; **7:** e240427.

7 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2021; **99:** S1–87.

8 Norris K, Bourgoigne J, Gassman J, et al, and the AASK Study Group. Cardiovascular outcomes in the African American Study of Kidney Disease and Hypertension (AASK) trial. *Am J Kidney Dis* 2006; **48:** 739–51.

9 Beddhu S, Rocco MV, Toto R, et al, and the SPRINT Research Group. Effects of intensive systolic blood pressure control on kidney and cardiovascular outcomes in persons without kidney disease: a secondary analysis of a randomized trial. *Ann Intern Med* 2017; **167:** 375–83.

10 Cheung AK, Rahman M, Reboussin DM, et al, and the SPRINT Research Group. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017; **28:** 2812–23.

11 Rossignol P, Zannad F, Massy Z, et al, and the ALCHEMIST study group. Spironolactone in patients on chronic haemodialysis at high risk of adverse cardiovascular outcomes (ALCHEMIST): a multicentre, double-blind, randomised, placebo-controlled trial and updated meta-analysis. *Lancet* 2025; **406:** 705–18.

12 Walsh M, Collister D, Gallagher M, et al, and the ACHIEVE Investigators. Spironolactone versus placebo in patients undergoing maintenance dialysis (ACHIEVE): an international, parallel-group, randomised controlled trial. *Lancet* 2025; **406:** 695–704.

13 Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; **387:** 957–67.

14 Ninomiya T, Perkovic V, Turnbull F, et al, and the Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. *BMJ* 2013; **347:** f5680.

15 Rahimi K, Canoy D, Nazarzadeh M, et al, and the Blood Pressure Lowering Treatment Trialists' Collaboration. Investigating the stratified efficacy and safety of pharmacological blood pressure-lowering: an overall protocol for individual patient-level data meta-analyses of over 300 000 randomised participants in the new phase of the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC). *BMJ Open* 2019; **9:** e028698.

16 WHO–International Society of Hypertension Blood Pressure Lowering Treatment Trialists' Collaboration. Protocol for prospective collaborative overviews of major randomized trials of blood-pressure-lowering treatments. *J Hypertens* 1998; **16:** 127–37.

17 Canoy D, Copland E, Nazarzadeh M, et al, and the Blood Pressure Lowering Treatment Trialists' Collaboration. Antihypertensive drug effects on long-term blood pressure: an individual-level data meta-analysis of randomised clinical trials. *Heart* 2022; **108:** 1281–89.

18 Miller WG, Kaufman HW, Levey AS, et al. National Kidney Foundation Laboratory Engagement Working Group recommendations for implementing the CKD-EPI 2021 race-free equations for estimated glomerular filtration rate: practical guidance for clinical laboratories. *Clin Chem* 2022; **68:** 511–20.

19 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2024; **105:** S117–314.

20 Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003; **108:** 2154–69.

21 Appel LJ, Wright JT Jr, Greene T, et al, and the AASK Collaborative Research Group. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010; **363:** 918–29.

22 Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis* 2014; **63:** 713–35.

23 Nazarzadeh M, Bidel Z, Canoy D, et al, and the Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure lowering and risk of new-onset type 2 diabetes: an individual participant data meta-analysis. *Lancet* 2021; **398:** 1803–10.

24 Bidel Z, Nazarzadeh M, Canoy D, et al, and the Blood Pressure Lowering Treatment Trialists' Collaboration. Sex-specific effects of blood pressure lowering pharmacotherapy for the prevention of cardiovascular disease: an individual participant-level data meta-analysis. *Hypertension* 2023; **80:** 2293–302.

25 Tudur Smith C, Williamson PR. A comparison of methods for fixed effects meta-analysis of individual patient data with time to event outcomes. *Clin Trials* 2007; **4:** 621–30.

26 Nazarzadeh M, Canoy D, Bidel Z, et al, and the The Blood Pressure Lowering Treatment Trialists' Collaboration. Methodological clarifications of recent reports. *J Hypertens* 2022; **40:** 847–52.

27 Hommel G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika* 1988; **75:** 383–86.

28 European Medicines Agency. Guideline on the investigation of subgroups in confirmatory clinical trials. Jan 31, 2019. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-subgroups-confirmatory-clinical-trials_en.pdf (accessed Dec 15, 2025).

29 Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine—reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007; **357:** 2189–94.

30 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009; **338:** b1665.

31 Wang N, Salam A, Pant R, et al. Blood pressure-lowering efficacy of antihypertensive drugs and their combinations: a systematic review and meta-analysis of randomised, double-blind, placebo-controlled trials. *Lancet* 2025; **406:** 915–25.

32 van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. *Res Synth Methods* 2012; **3:** 285–99.

33 Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003; **326:** 219.

34 Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002; **21:** 1559–73.

35 Suzuki H, Kanno Y, and the Efficacy of Candesartan on Outcome in Saitama Trial (E-COST) Group. Effects of candesartan on cardiovascular outcomes in Japanese hypertensive patients. *Hypertens Res* 2005; **28:** 307–14.

36 The Australian therapeutic trial in mild hypertension. Report by the Management Committee. *Lancet* 1980; **1:** 1261–67.

37 Black HR, Elliott WJ, Grandits G, et al, and the CONVINCE Research Group. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA* 2003; **289:** 2073–82.

38 Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al, and the INVEST Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 2003; **290:** 2805–16.

39 Schrader J, Lüders S, Kulschewski A, et al, and the MOSES Study Group. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke* 2005; **36:** 1218–26.

40 Braunwald E, Domanski MJ, Fowler SE, et al, and the PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004; **351:** 2058–68.

41 Erviti J, Saiz LC, Leache L, et al. Blood pressure targets for hypertension in people with chronic renal disease. *Cochrane Database Syst Rev* 2024; **10:** CD008564.

42 Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *CMAJ* 2013; **185:** 949–57.

43 NICE. Hypertension in adults: diagnosis and management. UK National Institute for Health and Care Excellence, 2019.

44 McEvoy JW, McCarthy CP, Bruno RM, et al, and the ESC Scientific Document Group. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J* 2024; **45:** 3912–4018.

45 Jones DW, Ferdinand KC, Taler SJ, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM guideline for the prevention, detection, evaluation and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2025; **152:** e114–218.

46 Kreutz R, Brunström M, Burnier M, et al. 2024 European Society of Hypertension clinical practice guidelines for the management of arterial hypertension. *Eur J Intern Med* 2024; **126:** 1–15.

47 Baker WL, Buckley LF, Kelly MS, et al. Effects of sodium-glucose cotransporter 2 inhibitors on 24-hour ambulatory blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc* 2017; **6:** e005686.

48 Ferdinand KC, White WB, Calhoun DA, et al. Effects of the once-weekly glucagon-like peptide-1 receptor agonist dulaglutide on ambulatory blood pressure and heart rate in patients with type 2 diabetes mellitus. *Hypertension* 2014; **64:** 731–37.

49 Kennedy C, Hayes P, Cicero AFG, et al. Semaglutide and blood pressure: an individual patient data meta-analysis. *Eur Heart J* 2024; **45:** 4124–34.

50 Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al, and the DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; **383:** 1436–46.

51 Herrington WG, Staplin N, Wanner C, et al, and the The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *N Engl J Med* 2023; **388:** 117–27.

52 Kent DM, Steyerberg E, van Klaveren D. Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects. *BMJ* 2018; **363:** k4245.

53 Li Y, Rao S, Solares JRA, et al. BEHRT: transformer for electronic health records. *Sci Rep* 2020; **10:** 7155.

54 Rao S, Li Y, Mamouei M, et al. Refined selection of individuals for preventive cardiovascular disease treatment with a transformer-based risk model. *Lancet Digit Health* 2025; **7:** 100873.