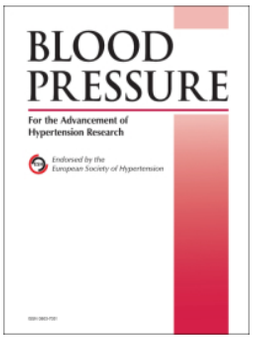

Blood Pressure

ISSN: 0803-7051 (Print) 1651-1999 (Online) Journal homepage: www.tandfonline.com/journals/iblo20

On-treatment systolic blood pressure and preserved kidney function in hypertensive patients with proteinuria. The VALUE Trial

Eirik Olsen, Julian E. Mariampillai, Roland E. Schmieder, Kenneth Jamerson, Camilla L. Søraas, Giuseppe Mancia, Maria H. Mehlum, Knut Liestøl, Anne C. K. Larstorp, Lene V. Halvorsen, Bård Waldum-Grevbo, Rune Mo, Sverre E. Kjeldsen, Michael A. Weber & for the Valsartan Antihypertensive Long-term Use Evaluation Trial (VALUE) Investigators

To cite this article: Eirik Olsen, Julian E. Mariampillai, Roland E. Schmieder, Kenneth Jamerson, Camilla L. Søraas, Giuseppe Mancia, Maria H. Mehlum, Knut Liestøl, Anne C. K. Larstorp, Lene V. Halvorsen, Bård Waldum-Grevbo, Rune Mo, Sverre E. Kjeldsen, Michael A. Weber & for the Valsartan Antihypertensive Long-term Use Evaluation Trial (VALUE) Investigators (2025) On-treatment systolic blood pressure and preserved kidney function in hypertensive patients with proteinuria. The VALUE Trial, Blood Pressure, 34:1, 2544715, DOI: 10.1080/08037051.2025.2544715

To link to this article: https://doi.org/10.1080/08037051.2025.2544715

Published online: 19 Aug 2025.

BLOOD PRESSURE
2025, VOL. 34, NO. 1, 2544715
https://doi.org/10.1080/08037051.2025.2544715

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

OPEN ACCESS Check for updates

On-treatment systolic blood pressure and preserved kidney function in hypertensive patients with proteinuria. The VALUE Trial

Eirik Olsen[a,b], Julian E. Mariampillai[c], Roland E. Schmieder[d], Kenneth Jamerson[e], Camilla L. Søraas[f], Giuseppe Mancia[g], Maria H. Mehlum[f], Knut Liestøl[h], Anne C. K. Larstorp[f,h], Lene V. Halvorsen[f,h], Bård Waldum-Grevbo[f,h], Rune Mo[a,b], Sverre E. Kjeldsen[e,f,h], and Michael A. Weber[i] for the Valsartan Antihypertensive Long-term Use Evaluation Trial (VALUE) Investigators

[a]Norwegian University of Science and Technology, Trondheim, Norway; [b]St. Olav's University Hospital, Trondheim, Norway; [c]Akershus University Hospital, Lørenskog, Norway; [d]University of Erlangen, Erlangen, Germany; [e]University of Michigan, Ann Arbor, MI, USA; [f]Oslo University Hospital, Oslo, Norway; [g]University of Milan Bicocca, Milan, Italy; [h]University of Oslo, Oslo, Norway; [i]SUNY Downstate College of Medicine, New York, NY, USA

ABSTRACT

Aims: We investigated on-treatment systolic BP (SBP) <130, 130–139 and ≥140 mmHg related to nephroprotection in 3065 patients with proteinuria and 10,738 patients without proteinuria in the VALUE Trial.

Method and results: Worsened kidney function (WKF) was ≥50% increase in serum creatinine, and end-stage kidney disease (ESKD) was dialysis/transplantation. Cox proportional hazards models were adjusted for covariates in the on-treatment SBP groups. Lower SBP was significantly related to less WKF ($p < .001$) in patients *with proteinuria*, both at <130 mmHg ($n = 14/529$, 2.6%) and 130–139 mmHg ($n = 46/1176$, 3.9%) compared to ≥140 mmHg ($n = 145/1358$, 10.7%). None of the 532 patients with proteinuria had ESKD at <130 mmHg, and only 11/1194 (0.9%) at 130–139 mmHg ($p = .098$) compared to 39/1339 (2.9%) at SBP ≥ 140 mmHg. In patients *without proteinuria* the relation between lower SBP and WKF was not significant ($p = .23$) at <130 mmHg ($n = 24/1927$, 1.2%) but significant ($p = .04$) at 130–139 mmHg ($n = 74/4611$, 1.6%) compared to SBP ≥ 140 mmHg ($n = 117/4199$, 2.8%). ESKD was 0.2%, 0.2% and 0.4% in the SBP groups, respectively. WKF fell from 12.1% in Q1 (highest SBP quartile) to 6.1% in Q2 ($p = .023$), 4.2% in Q3 ($p = .006$) and 2.8% in Q4 ($p < .001$) in patients *with proteinuria* and ESKD from 3.5% (Q1) to 1.6% (Q2) ($p = .13$), 0.7% (Q3) ($p = .027$) and 0.1% in Q4 ($p = .009$). In the patients *without proteinuria*, neither WKF nor ESKD showed statistically significant changes between SBP quartiles.

Conclusions: Our data suggest that, compared to SBP ≥ 140 mmHg, on-treatment SBP <130 and 130–139 mmHg were strongly related to nephroprotection in hypertensive patients with proteinuria.

PLAIN LANGUAGE SUMMARY

- We investigated whether on-treatment SBP < 130 and 130–139 mmHg was associated with nephroprotection compared to SBP ≥ 140 mmHg in 3065 hypertensive patients with proteinuria and in 10,738 hypertensive patients without proteinuria participating in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) Trial.
- Worsened kidney function (WKF) was defined as ≥50% increase in serum creatinine and end-stage kidney disease (ESKD) as dialysis or transplantation.
- Lower SBP was highly significantly related to less WKF ($p < .001$) in patients *with proteinuria* both at <130 and 130–139 compared to ≥140 mmHg.
- In the 531 patients *with proteinuria,* none had ESKD at <130 mmHg and only 11 of 1183 (0.9%) at 130–139 mmHg ($p = .098$), compared to 39 of 1351 (2.9%) at SBP ≥ 140 mmHg.
- Low SBP was not significantly related to WKF ($p = .23$) or ESKD in patients *without proteinuria.*
- Analysed in quartiles of achieved BP, WKF fell from 12.1% in Q1 (highest BP quartile) to 6.1% in Q2 ($p = .023$), 4.2% in Q3 ($p = .006$) and 2.8% in Q4 ($p < .001$), respectively, in patients *with proteinuria* and ESKD from 3.5% (Q1) to 1.6% (Q2) ($p = .13$), 0.7% (Q3) ($p = .027$) and 0.1% (Q4) ($p = .009$).

ARTICLE HISTORY

Received 7 July 2025
Revised 26 July 2025
Accepted 1 August 2025

KEYWORDS

Blood pressure; hypertension; kidney disease; nephropathy; proteinuria; renal disease

CONTACT Sverre E. Kjeldsen s.e.kjeldsen@medisin.uio.no Institute for Clinical Medicine, University of Oslo, Oslo University Hospital, Ullevaal, N-0407 Oslo, Norway

- In patients *without proteinuria* neither WKF nor ESKD showed statistically significant changes between quartiles.
- Our data suggest that lower on-treatment SBP is strongly related to nephroprotection in hypertensive patients with proteinuria.

Introduction

Hypertension and proteinuria are linked. Hypertension is one of the leading causes of nephropathy with proteinuria, whereas nephropathy with proteinuria of other aetiologies often proceeds secondary hypertension [1]. Antihypertensive treatment is therefore important in all forms of chronic kidney disease (CKD). Appropriate antihypertensive treatment will reduce proteinuria, which *per se* is nephrotoxic, and reduce hypertension-mediated kidney damage [2,3]. However, the optimal blood pressure (BP) target for patients with proteinuria has no clear consensus. Although based on the same available evidence, hypertension guidelines recommend different BP targets, weighing different aspects of the evidence differently [4]. The Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines recommend a systolic (S)BP target <120 mmHg, mainly based on the results of the Systolic Blood Pressure Intervention Trial (SPRINT), without differentiation between present proteinuria or not [5]. However, patients with diabetes were excluded from SPRINT, and the study did not show kidney protective effects of an intense BP-lowering strategy in patients with CKD [6]. Both American and European guidelines recommend BP target <130/80 mmHg, if well tolerated [7,8]. The American Diabetes Association (ADA) provides a Grade A recommendation for an on-treatment BP goal of <130/80 mmHg if it can be safely attained [9].

The mechanism for the interplay between diabetes mellitus (DM), hypertension and CKD is a complexity of factors beyond direct glomerular damage such as sodium retention, dyslipidemia, impaired microvascular function with pre-capillary re-modelling, endothelial dysfunction, large artery stiffness, sympathetic nervous system stimulation and activation of the renin-angiotensin-aldosterone system [10].

Observational data suggest a relationship between BP and CKD progression including progression to end-stage kidney disease (ESKD) [11,12]. There are few, if any, randomised, controlled trials (RCTs) investigating the effects of BP reduction on CKD in patients with proteinuria. However, a meta-analysis of RCTs, showed no effect of intensive BP lowering in patients with CKD for overall endpoints [13]. A meta-analysis from 2013 found a kidney-protective effect of intensive BP lowering in patients with CKD, especially in the presence of proteinuria [14]. The African-American Study of Kidney Disease and Hypertension (AASK) reported a marked reduction in CKD progression in the presence of baseline proteinuria with intensive BP lowering, although being neutral in its primary outcome [15].

The aim of the present study was to investigate the relationship between proteinuria, on-treatment SBP and kidney protection. Based on observational data from the prospective, randomised and controlled Valsartan Antihypertensive Long-term Use Evaluation Trial (the VALUE Trial), we investigated the relationships of various achieved average SBPs on progression of CKD in patients with or without proteinuria at baseline.

Patients and methods

The VALUE Trial, a multicentre, prospective, double-blinded, randomised, controlled clinical trial, was performed by 969 investigators between 1997 and 2004, and the protocol and main results have been reported previously [16]. The study was initiated and led by the investigators and was sponsored by Novartis. The aim was to compare two antihypertensive drug regimens for preventing cardiac morbidity and mortality in high-risk hypertensive patients aged 50 years or older. The study showed no difference between the amlodipine group and the valsartan group on the primary cardiac endpoint [16] and the two groups have later been combined for further observational analyses. In 2011, one of the authors (SEK) gained full access to and responsibility for the database, in agreement with the funder. Novartis has no role in the present study.

Participants

Hypertensive patients 50 years or older with high cardiovascular risk were included in the VALUE Trial [17,18]. The trial was approved by relevant ethics committees, and it included written informed consent from all the participants in 31 countries.

Investigators utilised a specific predefined age- and risk factor-dependent algorithm to recruit the high-risk hypertensives. The qualifying risk factors included DM, cigarette smoking, hypercholesterolaemia, electrocardiographic (ECG) left ventricular hypertrophy (LVH) without strain (ECG-LVH determined by Cornell voltage-duration product or Sokolow-Lyon voltage criteria), proteinuria (i.e. 1+ or more on dipstick in a morning urine specimen) at two independent occasions a minimum of 4 weeks apart, and serum creatinine >150 µmol/L. The qualifying disease factors included documented history of myocardial infarction or significant coronary heart disease (e.g. documented on arteriogram), peripheral vascular disease, cerebral stroke or transient ischaemic attack, or the presence of LVH with strain on ECG. For male patients aged between 50 and 59 years, at least three risk factors or one disease factor was required to be entered into the trial. For female patients between 50 and 59 years, at least two risk factors and one disease factor or two disease factors were required. For men and women between 60 and 69 years, at least two risk factors or one disease factor were required, and for patients above the age of 70 years, only one risk factor or one disease factor was required for randomisation.

Exclusion criteria included pregnancy, renal artery stenosis, either myocardial infarction, percutaneous coronary intervention or coronary artery bypass surgery during the last 3 months, medically relevant valvular disease, cerebrovascular events during the last 3 months, severe hepatic disease, severe CKD (defined as serum-creatinine >265 µmol/L), congestive heart failure requiring angiotensin converting enzyme inhibitor and patients using beta-blockers for both coronary artery disease and hypertension.

Patients with previously treated hypertension were eligible if SBP was <210 mmHg and diastolic (D)BP was <115 mmHg. Untreated hypertensive patients were eligible if SBP was between 160 and 210 mmHg, and DBP was <115 mmHg. Before randomisation, patients already on antihypertensive treatment discontinued their current medication and started randomised study drugs (valsartan or amlodipine) without a wash-out phase ('roll-over'). Drug regimens consisted of an initial dose of 80 mg valsartan or 5 mg amlodipine, with a treatment target of BP <140/90 mmHg. If target was not reached, the doses were doubled, and hydrochlorothiazide (12.5 mg and 25 mg) and other antihypertensive drugs were added to achieve BP target, according to a prespecified protocol.

Outcomes of interest

Patients were followed monthly during the first 6 months, thereafter every 6 months. BP was measured at each follow-up visit using a calibrated sphygmomanometer or a digital device after five minutes of seated rest, in accordance with the previous and current hypertension guidelines. In the VALUE Trial, patients were followed for 4–6 years, with a maximum of 72 months until first cardiac event, which was the primary endpoint of the study. This endpoint comprised fatal and non-fatal myocardial infarction, sudden cardiac death, death for revascularisation procedures, death from or hospitalisation for heart failure and emergency procedures to prevent myocardial infarction. Secondary endpoints included all cardiovascular events, non-cardiovascular and all-cause mortality. Among other pre-specified endpoints were worsened kidney function (WKF) and ESKD consisting of renal replacement therapy either as dialysis or kidney transplantation.

Statistical analysis

The present study is an observational sub-study based on the prospective and randomised data from the VALUE Trial. In the study, we have only included patients without cardiovascular events during the first 6 months after randomisation. This 6-month period represented an up-titration phase and BPs and possible endpoints from this period would not be representative due to roll-over

from previous antihypertensive medication (92% of included patients had prior antihypertensive treatment), as previously elaborated upon [19]. After the initial 6 months, patients with at least three study visits were included, and BP was registered as achieved average BP during the follow-up period.

In a preliminary analysis [19] we excluded patients with ECG-LVH because ECG-LVH may affect the relationships between achieved SBPs and outcomes [20]. However, in the main analysis of kidney endpoints in VALUE we maintained the large group of $n = 2458$ patients with ECG-LVH when investigating kidney protection related to achieved average BP [21]. Thus, with such precedence for investigating kidney outcomes related to achieved average SBPs with ECG-LVH patients included we have followed this approach also in the present study.

The endpoints in the present study were occurrence of WKF or ESKD. WKF was defined as at least 50% increase in serum creatinine from baseline at a minimum of two occasions with at least 4 weeks apart. ESKD was defined as initiation of renal replacement therapy either as dialysis or kidney transplantation. Both WKF and ESKD were pre-specified secondary endpoints in the VALUE Trial which were adjudicated by the endpoint committee during the trial.

Average achieved SBP was calculated until the occurrence of a prespecified event or end of study. Survival analyses were performed using Cox proportional hazards models with participants stratified into ranges of achieved average SBP throughout the follow-up period with ≥140 mmHg as reference. Subgroups of patients were divided according to achieved average SBP <130, 130–139 and ≥140 mmHg (Figure 1) like we recently analysed patients with or without diabetes at baseline [22]. Additional analyses were performed with participants divided into quartiles of achieved average SBP. Analyses were performed for the total population ($n = 13,803$), with subgroup analysis based on proteinuria present ($n = 3065$) or absent ($n = 10,738$) at inclusion. All regression analyses were adjusted for baseline variables: age, gender, SBP, DBP, body mass index, high serum cholesterol (>6.2 mmol/L or >240 mg/dL), smoking status, previous stroke, previous myocardial infarction, peripheral artery disease, treatment allocation, presence of LVH and estimated glomerular filtration rate (eGFR).

A limited number of patients had on-treatment DBP ≥ 90 mmHg ($n = 662$ in the main study and $n = 422$ in the present sub-study), and we have therefore not included results related to DBP.

Data are presented as mean with standard deviation (SD) or point estimates with 95% confidence interval. Between-group differences are presented as hazard ratios (HR), and level of significance was set to a two-sided p value of <.05. Statistics were performed using SPSS (IBM SPSS Statistics, version 28.0.1.0, Armonk, NY). We did not impute for some few missing data points exemplified by $n = 3063$ patients with proteinuria investigated for WKF.

Results

A total of 15,245 patients were enrolled in the VALUE Trial, and there was no difference in the primary cardiac outcome between the amlodipine and the valsartan treatment arms. Of these, 13,803 patients did not encounter cardiovascular events during the first 6 months of the study, and they had a minimum of three follow-up study visits thereafter. Thus, they were eligible for the present study (Figure 1). Mean follow-up time for the included patients ($n = 13,803$) was 52.2 months (SD 10.2).

Characteristics of participants

Baseline characteristics for the included patients, both the total population ($n = 13,803$) and patients with and without proteinuria at baseline, are presented in Table 1. Proteinuria was present at baseline in 3065 patients (22.2%), of which 43.6% were female and average age was 66.0 years (SD 8.0). In the non-proteinuria population ($n = 10,738$), 42.2% were female and average age was 67.4 years (SD 8.1). In the proteinuria and non-proteinuria populations, mean se-creatinine at baseline was 104.8 µmol/L (SD 29.8 µmol/L) and 99.2 µmol/L (SD 20.6 µmol/L), respectively. Thus, the presence of proteinuria shown with dipstick 1+ twice comes with a trend for slightly higher se-creatinine which has not been investigated further.

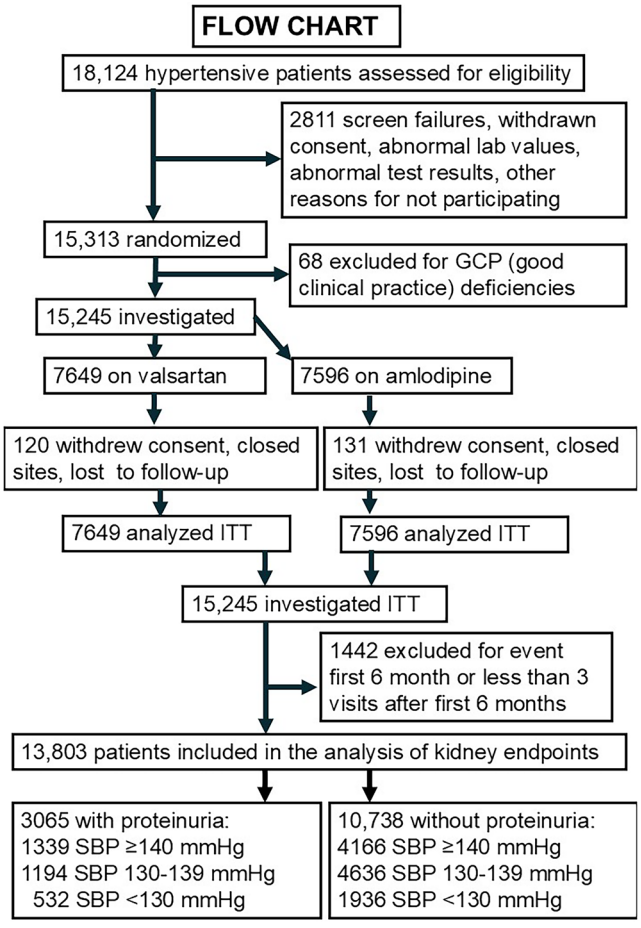

Figure 1. Flow chart.

Achieved average SBP in the groups of patients (<130, 130–139, ≥140 mmHg)

Achieved average SBP in the stratified study groups are shown in Figure 2. SBP averaged 149–150 mmHg in patients with SBP ≥140 mmHg, 135 mmHg in all three groups with SBP 130–139 mmHg and 125 mmHg for all three groups of patients with SBP <130 mmHg. The scatter was minimal for the range 130–139 mmHg whereas SBP ≥140 mmHg had scatter upwards and SBP <130 mmHg downwards (visualised in Figure 2, details not shown).

Kidney endpoints in patients with proteinuria at baseline according to achieved SBP

Lower SBP was significantly associated with less WKF ($p < .001$) in patients with proteinuria, both at <130 mmHg (HR = 0.41, 95% CI 0.23–0.73) and 130–139 mmHg (HR = 0.53, CI 0.37–0.75) compared to ≥140 mmHg (Table 2, Figure 3).

In the 532 patients with proteinuria, no patient experienced ESKD at <130 mmHg and only 11 of 1194 patients (0.9%) at 130–139 mmHg ($p = .098$) compared to 39 of 1339 patients (2.9%) at SBP ≥140 mmHg (Table 2, Figure 3).

Kidney endpoints in patients without proteinuria at baseline according to achieved SBP

The effects of low SBP on WKF was not significant ($p = .23$) in patients without proteinuria at <130 mmHg (HR = 0.75, CI 0.47–1.20) but significant ($p = .04$) at 130–139 mmHg (HR = 0.72, CI 0.53–0.99) compared to SBP ≥140 mmHg (Table 2, Figure 3).

Few patients without proteinuria at baseline had ESKD with no significant differences between groups (Table 2, Figure 3). The percentages were 0.2%, 0.2% and 0.4% in the SBP groups, respectively.

Table 1. Baseline characteristics.

	Total ($n = 13,803$)			≥140 mmHg ($n = 5505$)		130–139 mmHg ($n = 5830$)		<130 mmHg ($n = 2468$)	
Variable	All patients ($n = 13,803$)	Proteinuria ($n = 3065$)	Non-proteinuria ($n = 10,738$)	Proteinuria ($n = 1339$)	Non-proteinuria ($n = 4166$)	Proteinuria ($n = 1194$)	Non-proteinuria ($n = 4636$)	Proteinuria ($n = 532$)	Non-proteinuria ($n = 1936$)
Female sex (%)	5864 (42.5)	1337 (43.6)	4527 (42.2)	558 (41.7)	2013 (48.3)	549 (46.0)	1885 (40.7)	230 (43.2)	629 (32.5)
Age, years (SD)	67.1 (8.1)	66.0 (8.0)	67.4 (8.1)	66.9 (7.9)	68.8 (7.9)	65.8 (7.9)	67.1 (7.9)	66.0 (8.0)	65.0 (8.2)
BMI, kg/m^2 (SD)	28.6 (5.0)	29.2 (5.4)	28.4 (4.8)	29.6 (5.4)	28.5 (4.7)	29.0 (5.3)	28.4 (4.8)	28.8 (5.2)	28.3 (5.1)
Amlodipine (%)	6931 (50.2)	1557 (50.8)	5374 (50.0)	651 (48.6)	1912 (45.9)	630 (52.8)	2473 (53.3)	276 (51.9)	989 (51.1)
Valsartan (%)	6872 (49.8)	1508 (49.2)	5364 (50.0)	688 (51.4)	2254 (54.1)	564 (47.2)	2163 (46.7)	256 (48.1)	947 (48.9)
No. of visits[a] (SD)	8.7 (1.7)	8.6 (1.8)	8.7 (1.7)	8.4 (2.0)	8.6 (1.8)	8.8 (1.7)	8.9 (1.6)	8.6 (1.7)	8.7 (1.7)
Caucasian (%)	12364 (89.6)	2652 (86.5)	9712 (90.4)	1186 (88.6)	3890 (93.4)	1034 (86.6)	4171 (90.0)	432 (81.2)	1651 (85.3)
Black (%)	542 (3.9)	152 (5.0)	390 (3.6)	75 (5.6)	141 (3.4)	50 (4.2)	147 (3.2)	27 (5.1)	102 (5.3)
Asian (%)	495 (3.6)	126 (4.1)	369 (3.4)	27 (2.0)	62 (1.5)	62 (5.2)	206 (4.4)	37 (7.0)	101 (5.2)
Other ethnicity (%)	402 (2.9)	135 (4.4)	267 (2.5)	51 (3.8)	73 (1.8)	48 (4.0)	112 (2.4)	36 (6.8)	82 (4.2)
SBP mmHg (SD)	154.6 (19.0)	158.0 (19.2)	153.6 (18.8)	165.0 (18.6)	161.8 (18.3)	154.6 (17.0)	151.2 (16.2)	147.6 (18.5)	141.6 (17.3)
DBP mmHg (SD)	87.6 (10.8)	89.5 (10.7)	87.0 (10.7)	89.9 (10.9)	87.7 (11.1)	89.3 (10.2)	87.1 (10.2)	88.9 (11.2)	85.3 (10.9)
Heart rate/min (SD)	72.3 (10.7)	73.1 (10.6)	72.0 (10.7)	73.5 (10.9)	72.3 (10.9)	73.0 (10.5)	72.0 (10.7)	72.5 (10.2)	71.5 (10.2)
Creatinine µmol/L (SD)	100.5 (23.1)	104.8 (29.8)	99.2 (20.6)	108.9 (32.3)	99.3 (21.2)	101.7 (28.1)	99.0 (20.6)	101.3 (25.2)	99.6 (19.3)
Atrial fibrillation (%)	332 (2.4)	95 (3.1)	237 (2.2)	45 (3.4)	94 (2.3)	32 (2.7)	110 (2.4)	18 (3.4)	33 (1.7)
Smokers (%)	3328 (24.1)	911 (29.7)	2417 (22.5)	328 (24.5)	839 (20.1)	384 (32.2)	1102 (23.8)	199 (37.4)	476 (24.6)
History of MI (%)	6301 (45.6)	966 (31.5)	5335 (49.7)	370 (27.6)	1803 (43.3)	357 (29.9)	2299 (49.6)	239 (44.9)	1233 (63.7)
History of PAD (%)	1898 (13.8)	328 (10.7)	1570 (14.6)	166 (12.4)	658 (15.8)	116 (9.7)	681 (14.7)	46 (8.6)	231 (11.9)
History of stroke/TIA (%)	2699 (19.6)	454 (14.8)	2245 (20.9)	218 (16.3)	857 (20.6)	163 (13.7)	967 (20.9)	73 (13.7)	421 (21.7)
High cholesterol (%)	4645 (33.7)	976 (31.8)	3669 (34.2)	479 (35.8)	1580 (37.9)	355 (29.7)	1588 (34.3)	142 (26.7)	501 (25.9)
Diabetes mellitus (%)	4655 (33.7)	1299 (42.4)	3356 (31.3)	661 (49.4)	1471 (35.3)	465 (38.9)	1384 (29.9)	173 (32.5)	501 (25.9)

Categorical (%) and continuous (SD) variables according to BP strata and presence of proteinuria. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischaemic attack; high cholesterol, total serum cholesterol higher than 6.2 mmol/L (240 mg/dL).

[a]Number of study visits after 6 months.

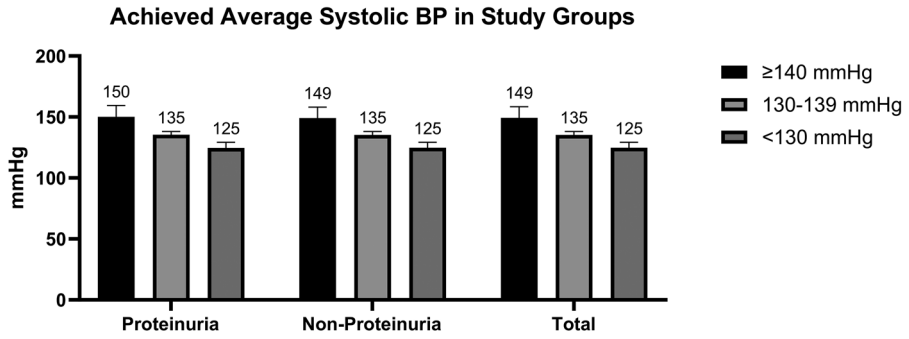

Figure 2. Achieved average SBP (SD) in the SBP ranges in the total group ($n = 13,803$), in patients with baseline proteinuria ($n = 3065$) and in patients without baseline proteinuria ($n = 10,738$).

Table 2. Kidney endpoints related to ranges of achieved average SBP in the total group ($n = 13,803$) and in groups with (+) ($n = 3065$) and without (–) ($n = 10,738$) proteinuria at baseline.

Kidney endpoints Groups	SBP ≥140 mmHg (reference)	SBP 130–139 mmHg	SBP <130 mmHg
Worsened kidney function (WKF) Total group ($n = 13,803$)	$n = 262/5557$ (4.7%)	$n = 120/5787$ (2.1%) HR = 0.590 (CI 0.469–0.742) $p < .001$	$n = 38/2456$ (1.5%) HR = 0.568 (CI 0.39–0.817) $p < 0.001$
Worsened kidney function (WKF) Proteinuria (+) baseline ($n = 3063$)	$n = 145/1358$ (10.7%)	$n = 46/1176$ (3.9%) HR = 0.531 (CI 0.374 – 0.754) $p < .001$	$n = 14/529$ (2.6%) HR = 0.412 (CI 0.232–0.732) $p < 0.001$
Worsened kidney function (WKF) Proteinuria (–) baseline ($n = 10,738$)	$n = 117/4199$ (2.8%)	$n = 74/4611$ (1.6%) HR = 0.723 (CI 0.530 – 0.985) $p = .040$	$n = 24/1927$ (1.2%) HR = 0.748 (CI 0.465–1.203) $p = 0.231$
End-stage kidney disease (ESKD) Total group ($n = 13,803$)	$n = 57/5546$ (1.0%)	$n = 21/5791$ (0.4%) HR = 0.532 (CI 0.313 – 0.903) $p = .019$	$n = 4/2465$ (0.2%) HR = 0.309 (CI 0.108–0.890) $p = 0.030$
End-stage kidney disease (ESKD) Proteinuria (+) baseline ($n = 3065$)	$n = 39/1351$ (2.9%)	$n = 11/1183$ (0.9%) HR = 0.550 (CI 0.271 – 1.117) $p = .098$	$n = 0/531$ (0%) *N/A due to no registered events*
End-stage kidney disease (ESKD) Proteinuria (–) baseline ($n = 10,738$)	$n = 18/4195$ (0.4%)	$n = 10/4608$ (0.2%) HR = 0.749 (CI 0.324–1.729) $p = .498$	$n = 4/1934$ (0.2%) HR = 1.123 (CI 0.335–3.770) $p = .851$

HR, hazard ratio; CI, confidence interval; *N* = events/patients (%).

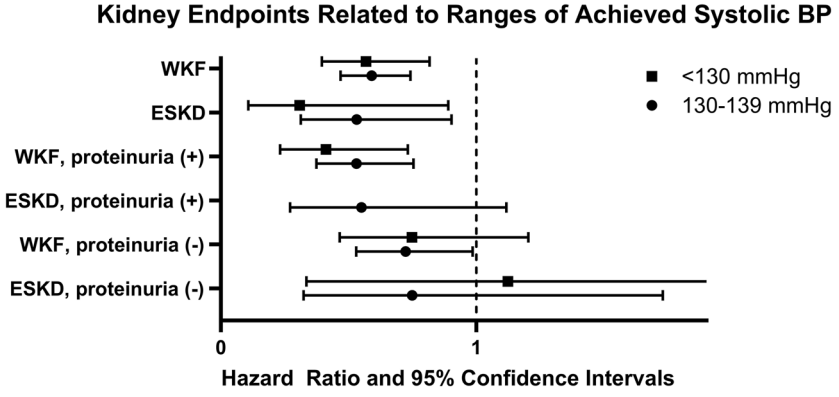

Figure 3. Forest plot of kidney endpoints (WKF, ESKD) in ranges of achieved average SBP in the total group ($n = 13,803$) and in groups with ($n = 3065$) and without ($n = 10,738$) proteinuria at baseline. Hazard ratios and 95% CIs compared with achieved average BP ≥140 mmHg. No patients with proteinuria at baseline had ESKD at achieved SBP <130 mmHg.

Kidney endpoints in patients with proteinuria at baseline according to SBP quartiles

Stratified analyses for BP quartiles showed that WKF fell from 12.1% in Q1 (highest achieved BP) to 6.1% in Q2 ($p = .023$), 4.2% in Q3 ($p = .006$) and 2.8% in Q4 ($p < .001$), respectively, in patients

with proteinuria and ESKD from 3.5% (Q1) to 1.6% (Q2) ($p = .13$), 0.7% (Q3) ($p = .027$) and 0.1% in Q4 ($p = .009$) (Table 3, Figure 4).

Kidney endpoints in patients without proteinuria at baseline according to SBP quartiles

In patients without proteinuria neither WKF nor ESKD showed statistically significant differences between quartiles (Table 3, Figure 4).

When the cohort of patients with and without proteinuria at baseline was combined (Tables 2 and 3, Figures 3 and 4), kidney endpoints and statistical effects were influenced by patients with and without proteinuria and the graphs visualised findings in-between the two groups.

On-treatment diastolic BP

Lower on-treatment ranges of DBP and quartile analyses did show less kidney endpoints with lower achieved average DBP (data not shown because of the uncertainty with only $n = 422$ patients with on-treatment DBP ≥90 mmHg).

Kidney endpoints in patients with proteinuria and treatment with amlodipine and valsartan

For WKF the difference between the two treatment arms in patients with proteinuria was not significant (HR 1.26, 95% CIs 0.97–1.65, $p = .085$). In patients without proteinuria the difference for WKF was highly significant in favour of amlodipine (HR 1.72, 95% CIs 1.32–2.25, $p = .001$) [21]. For ESKD there was no difference between the two treatment arms neither in patients with proteinuria (HR 0.91, 95% CIs 0.54–1.52, $p = .72$) nor in patients without proteinuria (HR 1.20, 95% CIs 0.63–2.29, $p = .59$).

Table 3. Kidney endpoints related to ranges of achieved average SBP in the total group ($n = 13{,}803$) and in groups with (+) ($n = 3065$) and without (–) ($n = 10{,}738$) proteinuria at baseline.

Groups	Quartile 1 (Reference)	Quartile 2	Quartile 3	Quartile 4
Worsened kidney function (WKF) Total group ($n = 13{,}803$)	SBP 153.8 (SD 9.1) $n = 186/3450$ (5.4%)	SBP 140.8 (SD 1.9) $n = 108/3447$ (3.1%) HR = 0.749 (CI 0.586–0.957) $p = .021$	SBP 135.1 (SD 1.6) $n = 71/3447$ (2.1%) HR = 0.577 (CI 0.431–0.772) $p < .001$	SBP 126.6 (SD 4.8) $n = 55/3456$ (1.6%) HR = 0.525 (CI 0.377–0.732) $p < .001$
Worsened kidney function (WKF) Proteinuria (+) baseline ($n = 3063$)	SBP 154.2 (SD 9.2) $n = 111/916$ (12.1%)	SBP 140.8 (SD 1.9) $n = 44/727$ (6.1%) HR = 0.655 (CI 0.455–0.942) $p = .023$	SBP 135.1 (SD 1.7) $n = 30/710$ (4.2%) HR = 0.547 (CI 0.357–0.840) $p = .006$	SBP 126.3 (SD 4.9) $n = 20/710$ (2.8%) HR = 0.400 (CI 0.239–0.670) $p < .001$
Worsened kidney function (WKF) Proteinuria (–) baseline ($n = 10{,}738$)	SBP 153.6 (SD 9.0) $n = 75/2534$ (2.9%)	SBP 140.8 (SD 1.9) $n = 64/2720$ (2.4%) HR = 0.974 (CI 0.690–1.375) $p = .881$	SBP 135.1 (SD 1.6) $n = 41/2737$ (1.5%) HR = 0.705 (CI 0.469–1.058) $p = .091$	SBP 126.7 (SD 4.7) $n = 35/2746$ (1.3%) HR = 0.729 (CI 0.467–1.140) $p = .166$
End–stage kidney disease (ESKD) Total group ($n = 13{,}803$)	SBP 153.7 (SD 9.0) $n = 45/3445$ (1.3%)	SBP 140.8 (SD 1.9) $n = 22/3451$ (0.6%) HR = 0.651 (CI 0.384–1.104) $p = .111$	SBP 135.1 (SD 1.6) $n = 10/3451$ (0.3%) HR = 0.377 (CI 0.183–0.777) $p = .008$	SBP 126.6 (SD 4.8) $n = 5/3451$ (0.1%) HR = 0.205 (CI 0.077–0.545) $p = .001$
End–stage kidney disease (ESKD) Proteinuria (+) baseline ($n = 3065$)	SBP 154.0 (SD 9.0) $n = 32/913$ (3.5%)	SBP 140.7 (SD 1.9) $n = 12/731$ (1.6%) HR = 0.585 (CI 0.291–1.178) $p = .133$	SBP 135.1 (SD 1.7) $n = 5/711$ (0.7%) HR = 0.327 (CI 0.121–0.879) $p = .027$	SBP 126.2 (SD 4.9) $n = 1/710$ (0.1%) HR = 0.067 (CI 0.009–0.509) $p = .009$
End–stage kidney disease (ESKD) Proteinuria (–) baseline ($n = 10{,}738$)	SBP 153.6 (SD 9.0) $n = 13/2532$ (0.5%)	SBP 140.8 (SD 1.9) $n = 10/2720$ (0.3%) HR = 0.989 (CI 0.413–2.369) $p = .981$	SBP 135.1(SD 1.6) $n = 5/2742$ (0.2%) HR = 0.607 (CI 0.199–1.849) $p = .379$	SBP 126.7 (SD 4.7) $n = 4/2732$ (0.1%) HR = 0.611 (CI 0.173–2.164) $p = .446$

HR, hazard ratio; CI, confidence interval; *N*, events/patients (%).

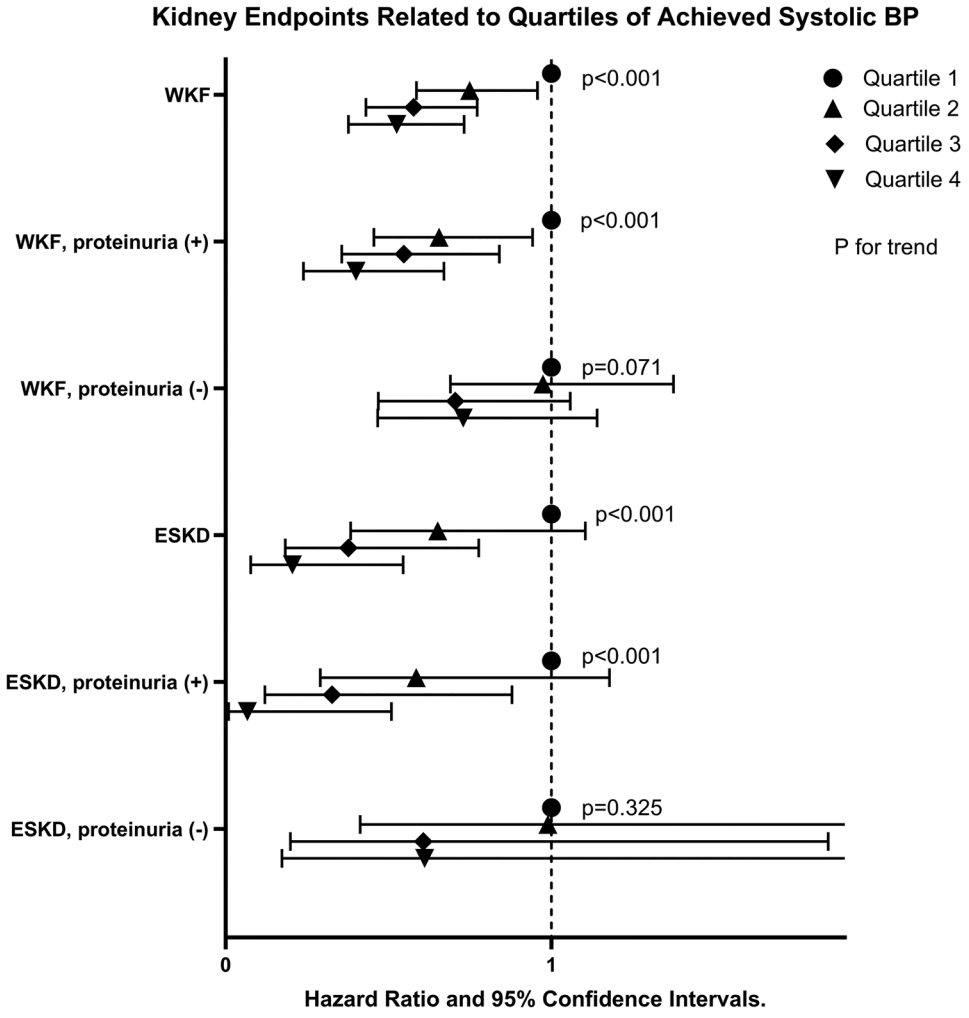

Figure 4. Forest plot of kidney endpoints (WKF, ESKD) in quartiles of achieved average SBP in the total group ($n = 13,803$) and in groups with ($n = 3065$) and without ($n = 10,738$) proteinuria at baseline. Hazard ratios and 95% CIs compared with achieved average SBP ≥140 mmHg.

Discussion

In the present study, we investigated whether on-treatment SBP < 130 and 130–139 mmHg inferred nephroprotection compared to SBP ≥ 140 mmHg in 3065 patients with proteinuria and 10,738 patients without proteinuria at baseline participating in the VALUE Trial. Lower achieved average SBP was highly significantly ($p < .001$) associated with less WKF in patients with proteinuria both at <130 and 130–139 compared to ≥140 mmHg. In the 531 patients with proteinuria none had ESKD at an achieved SBP <130 mmHg and only 11 of 1183 (0.9%) at SBP 130–139 mmHg ($p = .098$) compared to 39 of 1351 (2.9%) at SBP ≥ 140 mmHg. In contrast, lower achieved SBP was not significantly ($p = .23$) associated with less WKF in patients without proteinuria at <130 mmHg but significantly associated ($p = .04$) at 130–139 mmHg, compared to SBP ≥140 mmHg. ESKD was present in 0.2%, 0.2% and 0.4% in the SBP groups, respectively. In stratified analyses in quartiles of achieved SBP, WKF was found in 12.1% in Q1 (highest BP), 6.1% in Q2 ($p = 0.023$), 4.2% in Q3 ($p = 0.006$) and 2.8% in Q4 ($p < 0.001$), respectively, in patients with proteinuria. Furthermore, proteinuric patients demonstrated ESKD in 3.5% (Q1), 1.6% (Q2) ($p = .13$), 0.7% (Q3) ($p = .027$) and 0.1% (Q4), respectively ($p = .009$). In patients without proteinuria neither WKF nor ESKD were significantly different between quartiles.

The optimal BP target for patients with CKD has not been settled, and the major guidelines are conflicting. Earlier meta-analyses do not support lower treatment targets in patients with CKD, for the prevention of kidney endpoints [23,24], whereas other studies find effects, possibly more pronounced in the presence of proteinuria [14]. In the AASK, non-diabetic patients with hypertensive CKD

(glomerular filtration rate 20–60 ml/min), moderate proteinuria (protein-to-creatinine ratio < 2.5) and DBP >95 mmHg were randomly assigned to intensive or standard BP goals (mean arterial BP target <93 mmHg or 102–107 mmHg, respectively) and ramipril, amlodipine or metoprolol in a 3 × 2 factorial design [15]. The primary endpoint was progression of CKD defined as a decline in GFR using iothalamate clearance, ESKD or death. Of the 2808 screened patients, 1094 were included. Mean BPs in the intensive and standard BP target group were 130/78 mmHg and 141/86 mmHg, respectively. The study was neutral for the overall study population. In the subgroup with elevated baseline proteinuria, however, there was a significantly lower HR for the composite primary endpoint in the intensive treatment group compared to the standard treatment group (HR 0.73, 95% CI 0.58–0.93, $p = .01$). The same trend was seen for the secondary endpoint of doubled serum creatinine, ESKD or death, separately. In the intensive treatment group, proteinuria decreased by 17% compared to an increase of 7% in the standard treatment group [25]. Results of the present study are in line with but provide major extension of the AASK findings.

The KDIGO guidelines, which mainly are based on SPRINT results, recommend an intensive treatment strategy. However, it is hard to establish kidney protecting benefits from intensive BP reduction, that is, SBP <120 mmHg, as SPRINT data showed a rise, though temporarily, in serum creatinine. In SPRINT, patients with diabetes, the numerically largest population with hypertension and proteinuric CKD, were excluded and only patients with mild baseline proteinuria (24-hour urinary protein excretion <1 g/day) were included. SPRINT was powered for cardiovascular endpoints and only 1.2% of CKD patients experienced a composite kidney endpoint [6]. European and American guidelines for management of arterial hypertension do not distinguish between diabetic and non-diabetic patients, nor between proteinuric and non-proteinuric patients, and recommend a treatment target of <130/80 mmHg in all patients, if well tolerated [7,8]. The nephroprotection by lower achieved average SBP is the same in the patients with diabetes compared to the rest of the high-risk hypertensive population who participated in the VALUE Trial [22]. However, the results in our study, to our knowledge, provide the first true study findings supporting this BP treatment target to prevent kidney endpoints in proteinuric patients.

There may be further benefit from even more intensive reduction in SBP, but our data cannot fully explore this hypothesis, due to a low number of events in the groups with the lowest achieved SBP. In the ACCOMPLISH study, optimal treatment target for patients with CKD was <130 mmHg but not <120 mmHg [26]. In SPRINT, many patients with CKD had worsening of kidney function if treated <120 mmHg. A pooled analysis of all observational studies regarding optimal BP target in CKD patients would be interesting, since there has not been an RCT in patients with CKD and proteinuria investigating a treatment target of SBP <140, <130 or <120 mmHg.

We hypothesise a direct pathophysiological link between proteinuria and protective effects of SBP reduction. High SBPs reaching the glomerulus will lead to glomerular damage and subsequent proteinuria. Intense antihypertensive treatment will reduce this effect and slow the progression of CKD. Proteinuria is often more pronounced in diabetic kidney disease, due to several pathophysiological mechanisms and as opposed to early hypertensive nephrosclerosis, which may explain the effects of low average achieved BP in diabetic patients. However, the beneficial effect of intensive antihypertensive treatment is largest among those with baseline proteinuria, i.e. the participants with the most pronounced glomerular damage.

We mention specifically our recent two publications [21,22], which documented based on the results from the VALUE Trial, that lower SBP is associated with lower progression of CKD. It seems, however, that based on the present data these results are true first for subpopulation with proteinuria. This is important information for clinicians and in support for on-target SBP below 130 mmHg in high-risk hypertensive patients 50-80 years of age or even older in as much as about 5% of study participants were above 80 years at baseline and the trial lasted for up to 6 years.

The ADA recommends target BP <140/90 mmHg for patients with diabetes, with the results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study as the foundation for their recommendation [9]. ACCORD is the only RCT investigating optimal BP targets in a diabetic population [27]. Several aspects have been pointed out as possible explanation for the outcome of the study [28–30]. Further, the study compared SBP <140 mmHg to <120 mmHg, with the latter possibly being a too low treatment target, or difference that could not be shown as statistical power was lost

with few endpoints – a paradox partly seen in also our VALUE sub-study for the lowest achieved SBPs. As diabetes is the most common cause of CKD together with hypertension, it is important to establish the optimal targets for antihypertensive treatment in diabetic patients. An expected outcome for diabetic and hypertensive patients is progression to advanced CKD and proteinuria in the long-term perspective. Results from the present analysis suggest uniform and intensive BP lowering strategy with a target of <130/80 mmHg in the presence of proteinuria. There is limited literature regarding this topic but some support of such approach in patients with proteinuria can be found in a meta-analysis of 1860 patients published while the VALUE Trial was still in progress [31].

In this study, only participants without cardiovascular endpoints the first 6 months of the follow-up were included, and average achieved SBP is calculated from follow-up visits after the initial six-month run-in period. As previously elaborated upon [19], this was done to exclude non-representative BP measurements from a period of up-titration. Analysis of randomised treatment arms, amlodipine versus valsartan [21], included the initial 6 months but did not show any difference between the arms related to proteinuria or not for ESKD though WKF showed an apparent benefit for amlodipine in patients without proteinuria.

The achieved average BP in the VALUE Trial was not determined by patient specific factors but by the investigators' ability to up-titrate study medication according to the protocol. What we characterise as 'investigator inertia' was the main driver of achieved BP in the individual patients as discussed in detail [22]. The reasons for why study investigators had such reluctant attitude towards up-titrations of medication to achieve BP control in the VALUE Trial and in other RCTs are unknown. As always in outcome mega-trials the cause-consequence relationship cannot always be determined with 100% certainty though the outcomes that we report in the VALUE Trial were mainly due to the decreases in BP in the study in as much as achieved BP in individual patients was determined by the investigator's adherence with the up-titration scheme in the study protocol [22].

Our study had some *possible limitations*. Most importantly we report an observational aspect of an RCT. Thus, the data come from an RCT, the endpoints were prespecified, and they were adjudicated by an expert endpoint committee. There was a long follow-up time, and few patients were lost to follow-up. To consolidate our findings, we performed analyses both of on-target SBP *ranges* and of *quartiles*. And we compared with the study patients without proteinuria at baseline. Our conclusion is solely based on events of prespecified endpoints and not on the presence of adverse events of low achieved average SBP. RCTs are needed to investigate the optimal SBP levels to reduce endpoints as well as adverse events.

Our analyses do not account for patients who may have developed proteinuria throughout the follow-up time in as much as the presence of proteinuria was investigated at baseline only (for the purpose of identifying a qualifying risk variable for participation in the study). This may potentially impact results, although we believe that this will rather exacerbate the beneficial findings of low achieved SBP. The statistical power was estimated for the original VALUE Trial, rendering some of the analyses in the present study paradoxically underpowered.

A possible limitation is also the dipstick approach which was standardised to a morning urine specimen to minimise the influence by the concentration of the urine. Albumin/creatinine ratio (ACR) would have been recommended today for diagnosing proteinuria. The VALUE Trial was conducted several years ago explaining how we defined proteinuria at baseline simply by two dipstick readings of 1+ for urine protein performed at least 4 weeks apart. We did not quantify proteinuria but simply determined a yes/no decision for proteinuria in each patient. Using dipstick like this was chosen to facilitate the work for investigators to identify a high-risk characteristic and thus patient inclusion. Overall, however, it is our opinion that including patients with proteinuria by two dipstick readings of 1+ performed at least 4 weeks apart fulfilled its purpose and identified the patient group ($n = 3065$) investigated in the present study with quite remarkable beneficial kidney effects of low on-treatment SBP <130 mmHg.

The VALUE Trial was conducted more than 20 years ago, and the methods used for assessing kidney function and proteinuria reflect this. Kidney function was assessed as se-creatinine at baseline (Table 1) and at yearly follow-ups, and these analyses were performed at central laboratories. For the present analyses, we calculated eGFR (data not shown) and the statistical analyses were adjusted for eGFR at baseline (see Statistical analysis section). Proteinuria at baseline was based on morning urine dipstick measurement performed locally. Urine ACR was not measured.

Further, all participants were survivors of the first 6 months, and the patients who were investigated had to survive three later study visits which may have introduced a limited but unavoidable immortal time bias.

It needs to be highlighted that most patients in the lowest SBP quartile still had on-treatment SBP >120 mmHg (average approximately 126 mmHg, Table 3). The same for the achieved average SBP of 125 mmHg in the SBP range <130 mmHg (Figure 2). Thus, we can make no conclusion for on-treatment SBP <120 mmHg. In fact, the 2023 European Society of Hypertension guidelines [8] recommended that, due to cardiovascular concerns as demonstrated in patients with ECG-LVH [19,20], we should not lower SBP in middle-aged and older hypertensive patients to less than 120 mmHg and below 130 mmHg only if well tolerated.

To conclude, in hypertensive patients aged 50 to 80 years or older, with high cardiovascular risk, average on-treatment SBP 130-139 mmHg was related to fewer kidney endpoints, indicating preservation of kidney function, with the lowest risk achieved with on-treatment SBP <130 mmHg. Furthermore, intensive antihypertensive treatment was particularly beneficial in patients with proteinuria, e.g. in patients with mild CKD with already glomerular damage.

Acknowledgements

We are indebted to Dr. Tsushung A. Hua, PhD (deceased 2018), Unit of Biostatistics and Pharmacometrics, Novartis Pharmaceuticals Corporation, East Hanover, NJ, for invaluable help through many years, and Professor Stevo Julius, MD, ScD (deceased April 11, 2025) who chaired the VALUE Trial.

Disclosure statement

RES reports honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, MSD, Menarini Group, Novartis, Recor and Servier outside the present work. GM reports honoraria from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Menarini Group, Merck, Novartis, Recordati, Sandoz, Sanofi and Servier outside the present work. LVH reports lecture honoraria from AstraZeneca. BWG reports honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Novartis and Novo Nordisk. RM reports lecture honoraria from Novartis and AstraZeneca. SEK reports lecture honoraria from Emcure, Getz, Glenmark, J.B. Pharma, Merck Healthcare KGaA and Vector-Intas. MAW reports honoraria from Ablative Solutions, Johnson & Johnson, Medtronic, ReCor and Urovant outside the present work. The other authors report no conflicts.

Funding

An unrestricted grant from Novartis Pharma AG originally funded the VALUE Trial 1997-2004. Further work with the data base was supported by the Dam Foundation, through the Norwegian Health Association. The present work was supported by a grant from the Research Council of Norway (grant no. 273563). Neither current nor previous funder had any role in the present study.

ORCID

Eirik Olsen http://orcid.org/0009-0008-6187-658X
Julian E. Mariampillai http://orcid.org/0000-0002-3857-9797
Roland E. Schmieder http://orcid.org/0000-0003-2356-5883
Kenneth Jamerson http://orcid.org/ 0000-0003-2936-0619
Camilla L. Søraas http://orcid.org/0000-0002-3964-4351
Giuseppe Mancia http://orcid.org/0000-0003-0942-3176
Maria H. Mehlum http://orcid.org/0000-0002-8885-2798
Knut Liestøl http://orcid.org/0000-0002-7929-582X
Anne C. K. Larstorp http://orcid.org/0000-0002-0223-9248
Lene V. Halvorsen http://orcid.org/0000-0003-0411-2459
Bård Waldum-Grevbo http://orcid.org/0009-0009-5251-4832
Rune Mo http://orcid.org/0000-0003-3647-4796
Sverre E. Kjeldsen http://orcid.org/0000-0003-2389-0272
Michael A. Weber http://orcid.org/0000-0002-8504-0831

Data availability statement

The data file resides in the hands of the authors at Oslo University Hospital, Ullevaal, Oslo, Norway. The data that support the findings of this study are available for analysis from the corresponding author upon reasonable request. Study registration was provided at https://www.clinicaltrials.gov with the unique identifier NCT06395194.

References

[1] Rosario RF, Wesson DE. Primary hypertension and nephropathy. Curr Opin Nephrol Hypertens. 2006;15(2):130–134. doi:10.1097/01.mnh.0000214771.88737.ee.

[2] Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993;329(20):1456–1462. doi:10.1056/NEJM199311113292004.

[3] Parving HH, Lehnert H, Bröchner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001;345(12):870–878. doi:10.1056/NEJMoa011489.

[4] Carriazo S, Sarafidis P, Ferro CJ, et al. Blood pressure targets in CKD 2021: the never-ending guidelines debacle. Clin Kidney J. 2022;15(5):845–851. doi:10.1093/ckj/sfac014.

[5] Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2021;99(3s):S1–s87.

[6] Cheung AK, Rahman M, Reboussin DM, et al. Effects of intensive BP control in CKD. J Am Soc Nephrol. 2017;28(9):2812–2823. doi:10.1681/ASN.2017020148.

[7] Whelton PK, Carey RM, Aronow WS, et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269–1324. doi:10.1161/HYP.0000000000000066.

[8] Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41(12):1874–2071. doi:10.1097/HJH.0000000000003480.

[9] American Diabetes Association Professional Practice Committee. Cardiovascular disease and risk management: standards of care in diabetes-2025. Diabetes Care. 2025;48(Suppl. 1):S207–S238. doi:10.2337/dc25-S010.

[10] Ameer OZ. Hypertension in chronic kidney disease: what lies behind the scene. Front Pharmacol. 2022;13:949260. doi:10.3389/fphar.2022.949260.

[11] Klag MJ, Whelton PK, Randall BL, et al. End-stage renal disease in African-American and white men. 16-year MRFIT findings. Jama. 1997;277(16):1293–1298. doi:10.1001/jama.1997.03540400043029.

[12] Tozawa M, Iseki K, Iseki C, et al. Blood pressure predicts risk of developing end-stage renal disease in men and women. Hypertension. 2003;41(6):1341–1345. doi:10.1161/01.HYP.0000069699.92349.8C.

[13] Upadhyay A, Earley A, Haynes SM, et al. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Ann Intern Med. 2011;154(8):541–548. doi:10.7326/0003-4819-154-8-201104190-00335.

[14] 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(11):949–957. doi:10.1503/cmaj.121468.

[15] Appel LJ, Wright JT, Jr., Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med. 2010;363(10):918–929. doi:10.1056/NEJMoa0910975.

[16] Julius S, Kjeldsen SE, Weber MA, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004;363(9426):2022–2031. doi:10.1016/S0140-6736(04)16451-9.

[17] Mann J, Julius S. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial of cardiovascular events in hypertension. Rationale and design. Blood Press. 1998;7(3):176–183. doi:10.1080/080370598437394.

[18] Kjeldsen SE, Julius S, Brunner H, et al. Characteristics of 15,314 hypertensive patients at high coronary risk. The VALUE trial. The Valsartan Antihypertensive Long-term Use Evaluation. Blood Press. 2001;10(2):83–91. doi:10.1080/08037050152112069.

[19] Olsen E, Soraas CL, Schmieder RE, et al. Achieved systolic blood pressure below 130 mmHg preserves kidney function in diabetic and non-diabetic hypertensive patients without cardiac hypertrophy. J Hypertens. 2024;42(Suppl. 1):e114.

[20] Heimark S, Mehlum MH, Mancia G, et al. Middle-aged and older patients with left ventricular hypertrophy: higher mortality with drug treated systolic blood pressure below 130 mm Hg. Hypertension. 2023;80(8):1739–1748. doi:10.1161/HYPERTENSIONAHA.123.21454.

[21] Olsen E, Jamerson K, Schmieder RE, et al. Effects of valsartan vs amlodipine and achieved lower blood pressure on the incidence of end-stage kidney disease: the VALUE Trial. Eur J Intern Med. 2025;133:55–63. doi:10.1016/j.ejim.2024.12.021.
[22] Olsen E, Søraas CL, Schmieder RE, et al. Low achieved systolic blood pressure related to kidney protection in diabetic and non-diabetic high-risk hypertensive patients. Am J Hypertens. 2025 (E-pub ahead of print). doi:10.1093/ajh/hpaf093.
[23] Ku E, Gassman J, Appel LJ, et al. BP control and long-term risk of ESRD and mortality. J Am Soc Nephrol. 2017;28(2):671–677. doi:10.1681/ASN.2016030326.
[24] Tsai WC, Wu HY, Peng YS, et al. Association of intensive blood pressure control and kidney disease progression in nondiabetic patients with chronic kidney disease: a systematic review and meta-analysis. JAMA Intern Med. 2017;177(6):792–799. doi:10.1001/jamainternmed.2017.0197.
[25] Wright JT, Jr., Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA. 2002;288(19):2421–2431. doi:10.1001/jama.288.19.2421.
[26] Bakris GL, Sarafidis PA, Weir MR, et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. Lancet. 2010;375(9721):1173–1181. doi:10.1016/S0140-6736(09)62100-0.
[27] Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1575–1585. doi:10.1056/NEJMoa1001286.
[28] Margolis KL, O'Connor PJ, Morgan TM, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. Diabetes Care. 2014;37(6):1721–1728. doi:10.2337/dc13-2334.
[29] Kjeldsen SE, Os I, Nilsson PM. Does intensive glucose control cancel out benefits of systolic blood pressure target <120 mm hg in patients with diabetes mellitus participating in ACCORD? Hypertension. 2018;72(2):291–293. doi:10.1161/HYPERTENSIONAHA.118.11455.
[30] Mancia G, Grassi G. Blood pressure targets in type 2 diabetes. Evidence against or in favour of an aggressive approach. Diabetologia. 2018;61(3):517–525. doi:10.1007/s00125-017-4537-3.
[31] Jafar TH, Schmid CH, Landa M, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med. 2001;135(2):73–87. doi:10.7326/0003-4819-135-2-200107170-00007.