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Effects of Sacubitril/Valsartan Versus Irbesartan in Patients With Chronic Kidney Disease

A Randomized Double-Blind Trial

Editorial, see p 1515

Richard Haynes, DM
Parminder K. Judge, MRCP
Natalie Staplin, PhD
William G. Herrington, MD
Benjamin C. Storey, MRCP
Angelyn Bethel, MD
Louise Bowman, MD
Nigel Brunskill, PhD
Paul Cockwell, PhD
Michael Hill, PhD
Philip A. Kalra, MD
John J.V. McMurray, MD
Maarten Taal, MD
David C. Wheeler, MD
Martin J. Landray, PhD
Colin Baigent, FRCP
On behalf of the UK HARP-III Collaborative Group

BACKGROUND: Sacubitril/valsartan reduces the risk of cardiovascular mortality among patients with heart failure with reduced ejection fraction, but its effects on kidney function and cardiac biomarkers in people with moderate to severe chronic kidney disease are unknown.

METHODS: The UK HARP-III trial (United Kingdom Heart and Renal Protection-III), a randomized double-blind trial, included 414 participants with an estimated glomerular filtration rate (GFR) 20 to 60 mL/min/1.73 m^2 who were randomly assigned to sacubitril/valsartan 97/103 mg twice daily versus irbesartan 300 mg once daily. The primary outcome was measured GFR at 12 months using ANCOVA with adjustment for each individual's baseline measured GFR. All analyses were by intention to treat.

RESULTS: In total, 207 participants were assigned to sacubitril/valsartan and 207 to irbesartan. Baseline measured GFR was 34.0 (SE, 0.8) and 34.7 (SE, 0.8) mL/min/1.73 m^2, respectively. At 12 months, there was no difference in measured GFR: 29.8 (SE 0.5) among those assigned sacubitril/valsartan versus 29.9 (SE, 0.5) mL/min/1.73 m^2 among those assigned irbesartan; difference, −0.1 (0.7) mL/min/1.73 m^2. Effects were similar in all prespecified subgroups. There was also no significant difference in estimated GFR at 3, 6, 9, or 12 months and no clear difference in urinary albumin:creatinine ratio between treatment arms (study average difference, −9%; 95% CI, −18 to 1). However, compared with irbesartan, allocation to sacubitril/valsartan reduced study average systolic and diastolic blood pressure by 5.4 (95% CI, 3.4–7.4) and 2.1 (95% CI, 1.0–3.3) mm Hg and levels of troponin I and N terminal of prohormone brain natriuretic peptide (tertiary end points) by 16% (95% CI, 8–23) and 18% (95% CI, 11–25), respectively. The incidence of serious adverse events (29.5% versus 28.5%; rate ratio, 1.07; 95% CI, 0.75–1.53), nonserious adverse reactions (36.7% versus 28.0%; rate ratio, 1.35; 95% CI, 0.96–1.90), and potassium ≥5.5 mmol/L (32% versus 24%, *P*=0.10) was not significantly different between randomized groups.

CONCLUSIONS: Over 12 months, sacubitril/valsartan has similar effects on kidney function and albuminuria to irbesartan, but it has the additional effect of lowering blood pressure and cardiac biomarkers in people with chronic kidney disease.

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Key Words: chronic kidney disease ■ neprilysin inhibition ■ renin-angiotensin system

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Clinical Perspective

What Is New?

- The UK HARP-III trial (United Kingdom Heart and Renal Protection-III) has demonstrated that, in a wide range of people with proteinuric chronic kidney disease, adding neprilysin inhibition to angiotensin II receptor blockade has no additional effect on kidney function or albuminuria compared with irbesartan.
- The tolerability and safety profiles of the 2 treatments were not different. However, compared with irbesartan, sacubitril/valsartan further reduces both blood pressure and biomarkers of cardiovascular risk (troponin I and N-terminal pro-B-type natriuretic peptide).

What Are the Clinical Implications?

- UK HARP-III raises the hypothesis that sacubitril/valsartan could be an acceptable treatment to reduce cardiovascular risk in people with chronic kidney disease, a high-risk population with an unmet need.

Patients with chronic kidney disease (CKD) are at increased risk of both progression to end-stage renal disease and cardiovascular events compared with patients with normal kidney function.[1–3] Randomized controlled trials have shown that renin-angiotensin system (RAS) inhibitors slow the progression of diabetic and nondiabetic proteinuric CKD,[4–7] and lowering low-density lipoprotein cholesterol reduces the risk of atherosclerotic vascular events.[8] However, despite such treatments, a significant risk of progression to end-stage renal disease and cardiovascular events remains. In particular, patients with CKD are at increased risk of events related to structural heart disease (such as heart failure and arrhythmias), with many dying of cardiovascular disease before they reach end-stage renal disease.[9]

Natriuretic peptides have a range of potentially beneficial effects, including natriuresis, diuresis, vasodilatation, and inhibition of RAS.[10,11] Neprilysin (NEP or neutral endopeptidase) is the key enzyme responsible for degrading natriuretic peptides and other vasoactive peptides, such as angiotensin II, bradykinin, endothelin, and substance P.[10,12] Although inhibition of NEP (NEPi) raises concentrations of circulating natriuretic peptides, it also leads to reflex RAS activation and inhibits angiotensin II breakdown, counteracting any potentially beneficial effects, so NEPi must be combined with RAS inhibition. Combinations of NEPi and angiotensin-converting enzyme inhibitors are associated with a high risk of angioedema (because of excessive inhibition of bradykinin degradation),[13] so the chosen method of RAS inhibition for use with NEPi is an angiotensin receptor blocker. Sacubitril/valsartan, which combines an angiotensin receptor blocker (valsartan) with a NEPi (sacubitril), was the first angiotensin receptor–neprilysin inhibitor to be developed.

The PARADIGM-HF trial (Prospective Comparison of an Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitors to Determine Impact on Global Mortality and Morbidity in Heart Failure) showed that sacubitril/valsartan reduced the risk of cardiovascular mortality among patients with heart failure with reduced ejection fraction when compared with the angiotensin-converting enzyme inhibitor enalapril (hazard ratio, 0.80; 95% CI, 0.71–0.89).[14] Several trials in populations with heart failure, including PARADIGM-HF, suggest that sacubitril/valsartan slows the decline in kidney function compared with RAS inhibition alone, but that it slightly increased albuminuria.[15–17] Animal studies have shown that combining NEP and RAS inhibition can reduce proteinuria and histological evidence of kidney damage.[18–21] The UK HARP-III trial (United Kingdom Heart and Renal Protection-III) aimed to compare the effects of sacubitril/valsartan versus irbesartan (a licensed angiotensin receptor blocker for diabetic nephropathy) on kidney function and other outcomes in people with CKD.

METHODS

Trial Design and Participants

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results from the Richard Doll Centenary Archive according to the Nuffield Department for Population Health's Data Sharing Policy.[22] Details of the UK HARP-III trial objectives, design, and methods have been reported previously.[23] Ethical (Nottingham Research Ethics Committee 2 [13/EM/0434]) and regulatory approvals were obtained before the enrollment of any study participants. Participants ≥18 years of age were eligible to participate if they had CKD with either (1) an estimated glomerular filtration rate (eGFR) of ≥45 and <60 mL/min/1.73 m^2 and a urine albumin:creatinine ratio (uACR) >20 mg/mmol (177 mg/g), or (2) an eGFR of ≥20 and <45 mL/min/1.73 m^2 (regardless of uACR).

Potentially eligible participants attended a screening visit at which medical history and eligibility criteria were checked, written informed consent was obtained, and blood and urine samples were taken for local laboratory analysis. Any current RAS inhibitor was stopped, and the participant entered the 4- to 7-week single-blind prerandomization run-in phase, during which they took 1 placebo sacubitril/valsartan tablet and 1 placebo irbesartan capsule daily. The aims of the run-in phase were to (1) enable a washout of any angiotensin-converting enzyme inhibitors before introduction of NEPi (to reduce the risk of angioedema), (2) allow a comparison of the acute effects of the study treatments on eGFR, and (3) identify and exclude those less likely to adhere to study treatment and

trial procedures before randomization to maintain statistical sensitivity.[24,25]

Randomization and Masking

At the end of the run-in period, glomerular filtration rate (GFR) was measured, and willing and eligible participants were randomized 1:1 to sacubitril/valsartan or irbesartan by an internet-based system with minimized randomization (which helped ensure balance for categories of age, sex, systolic blood pressure, previous diabetes mellitus, eGFR, and uACR).[23] Treatment allocation was concealed, so investigators, clinicians, and patients had no foreknowledge of the upcoming treatment allocation.[26] A double-dummy approach was used to ensure participants and study staff remained blind to treatment allocation: participants were issued 2 bottles of study treatments, 1 containing sacubitril/valsartan 97/103 mg or placebo tablets and the other containing irbesartan 150 mg or placebo capsules.[27]

Procedures

After randomization, participants were initially instructed to take 1 tablet and 1 capsule daily of study treatment (ie, either sacubitril/valsartan 97/103 mg or irbesartan 150 mg); this dosage was increased to sacubitril/valsartan 97/103 mg twice daily or irbesartan 300 mg once daily after 2 weeks unless potassium or change in kidney function precluded a dose increase. Study visits were scheduled at 1, 3, 6, 9, and 12 months after randomization (and additional visits arranged where necessary to monitor participant safety). At each follow-up, study staff sought information on all serious adverse events and any nonserious adverse events considered with reasonable probability to be related to study treatment. Compliance with study treatments was assessed by self-report, and blood pressure and weight were measured at every visit. Blood and urine samples were collected at every study visit for local analysis of creatinine, potassium, liver function tests (bilirubin, liver transaminase, and alkaline phosphatase), and uACR. Central laboratory assays of creatinine, uACR, and cardiac biomarkers (troponin I and NT-proBNP [N-terminal pro-B-type natriuretic peptide]) were conducted at randomization, 6 months, and 12 months. Additionally, participants were advised not to take their morning dose of study treatment on the day of their 3-month visit so that creatinine, uACR, and trough blood levels of sacubitril, sacubitrilat (the primary metabolite of sacubitril), and valsartan could be collected. GFR was measured at or just before the 12-month visit, and paper results of all GFR measurements were sent to the coordinating center for verification blind to treatment allocation. If participants were unwilling or no longer able to attend follow-up visits, information was obtained by telephone or from relatives or caregivers wherever possible. The original protocol specified that 360 participants would be followed for 6 months; before the completion of recruitment (and blind to any interim results), the steering committee decided to extend follow-up to 12 months (because of results from other trials suggesting that the effect on kidney function may take ≥9 months to fully emerge) and to increase the sample size to ≥400 participants (to increase the statistical power).

Laboratory Methods

GFR was measured in the study centers using ^{51}Cr-EDTA, ^{99m}Tc-DTPA (diethylenetriaminepentaacetic acid), or iohexol methods depending on local practice (with each center using the same method at baseline and 12 months). Creatinine was assayed in the central laboratory on a Beckman Coulter AU680 analyzer using a kinetic alkaline picrate method and calibrated using material traceable to isotope dilution mass spectrometry (using the National Institute of Standards and Technology Standard Reference Material 967); troponin I was measured by immunoassay on an Architect system and NT-proBNP by immunoassay on an Elecsys system.

Statistical Analysis

The primary outcome was measured GFR (mGFR), and ANCOVA was used to compare mean mGFR at 12 months between patients allocated sacubitril/valsartan and irbesartan patients, with adjustment for each individual's baseline mGFR.[28] Assuming a between-person SD in mGFR of 15 mL/min/1.73 m^2 and a correlation between an individual's baseline and follow-up mGFR of 0.8, randomization of 400 participants would provide ≥80% power (at P=0.05) to detect a difference in mGFR at the final follow-up (adjusted for baseline values) of 3 mL/min/1.73 m^2, even if 15% of participants discontinued allocated study treatment.

All analyses were performed according to the intention-to-treat principle among all randomized participants.[29,30] Comparisons of continuous outcomes were performed using ANCOVA adjusted for each participant's baseline value, after appropriate transformation if required. Multiple imputation methods were used to account for missing data.[31] Time-to-event analyses used log-rank methods to calculate event rate ratios, 95% CIs, and associated 2-sided P values.[29,30] Pharmacokinetic analyses involved multiple linear regression of each sacubitril/valsartan metabolite against a number of prespecified baseline variables, adjusted for time since the last dose of sacubitril/valsartan. The primary pharmacokinetic analysis restricted the dataset to those participants assigned sacubitril/valsartan who had last taken the drug 10 to 16 hours before the sample being collected. Further details (including secondary and tertiary outcomes) are available in the prespecified data analysis plan.[23] Analyses were done using SAS version 9.3 (SAS Institute) and R version 3.3.3 (www.R-Project.org).

RESULTS

Between November 1, 2014, and January 31, 2016, 620 participants attended screening visits, and 566 (91%) entered the prerandomization run-in (Figure 1). In total, 414 participants were randomized: 207 to sacubitril/valsartan and 207 to irbesartan. The mean age was 62.8 years (SD, 13.7), 298 (72%) were male, and the mean blood pressure was 146/81 mm Hg (Table 1). Mean eGFR at baseline was 35.5 (10.9) mL/min/1.73 m^2, and the median uACR was 54 (interquartile range, 11–153) mg/mmol (Table 1).

By 12 months, similar proportions of participants in each arm had stopped study treatment (33 [16%]

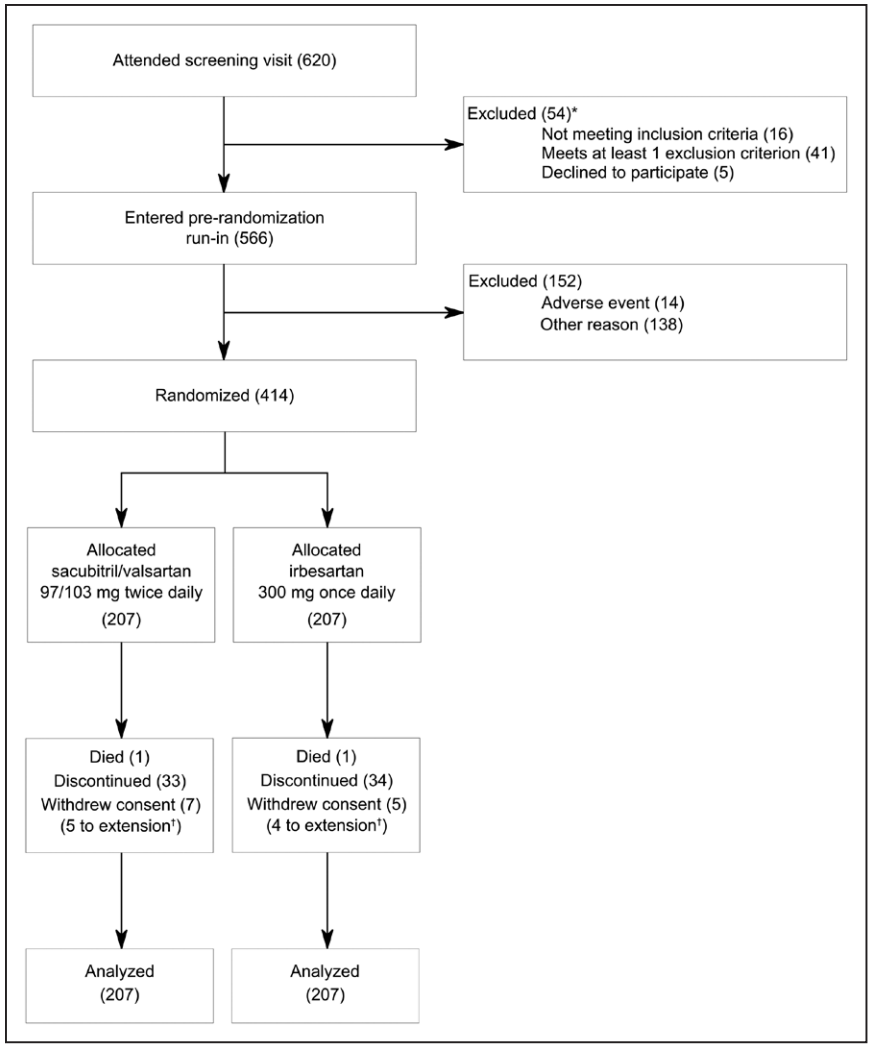

Figure 1. Flow of participants.
*Participants could report >1 reason. †Duration of the trial was increased from 6 to 12 months, and 9 participants did not consent to this extension and so completed follow-up at 6 months.

of those assigned sacubitril/valsartan and 34 [16%] of those assigned irbesartan), and the reasons for stopping full dose study treatment were similar. There was no excess of discontinuations because of serious adverse events, nonserious adverse reactions, or other reasons in those allocated sacubitril/valsartan (Table I in the online-only Data Supplement).

At 12 months, the mean (SE) mGFR was 29.8 (0.5) mL/min/1.73 m^2 among those assigned to the sacubitril/valsartan group compared with 29.9 (0.5) mL/min/1.7 $3m^2$ among those assigned irbesartan, a nonsignificant difference of 0.1 (0.7) mL/min/1.73 m^2 (P=0.86) (Table 2). Neither a prespecified complete case analysis (ie, without imputation: difference −0.4 [0.7] mL/min/1.73 m^2) nor an "on-treatment" analysis (difference −0.5 [0.7] mL/min/1.73 m^2) materially affected this finding. There was no evidence that the difference between sacubitril/valsartan and irbesartan in effect on mGFR differed by age (χ_1^2=0.45, P=0.50), sex (χ_1^2=0.70, P=0.4), baseline mGFR (χ_1^2=0.42, P=0.52), baseline uACR (χ_1^2=0.76, P=0.38), cause of kidney disease (χ_6^2=2.24, P=0.90), or any other prespecified baseline characteristic (Figure I in the online-only Data Supplement).

Compared with irbesartan, allocation to sacubitril/valsartan was not associated with any significant effect on eGFR at any time point (Figure 2). The rate of change in eGFR did not differ significantly between arms, whether measured from randomization to 12 months, from randomization to 3 months, or from 3 to 12 months (Table II in the online-only Data Supplement).

Allocation to sacubitril/valsartan produced a nonsignificant 9% (−18% to 1%, P=0.08) reduction in study-average uACR (Table 3) and was associated with a reduction in blood pressure compared with irbesartan. Overall, the mean systolic blood pressure was 5.4 (95% CI, −7.4 to −3.4) mm Hg lower, and the mean diastolic blood pressure was 2.1 (95% CI, −3.3 to −1.0) mm Hg lower among those allocated to sacubitril/valsartan (Table 3). Exploratory analyses did not show any differences in the intensity of nonstudy antihypertensive agents between the treatment arms during follow-up.

Table 1. Baseline Characteristics by Randomized Treatment Allocation

Variable	Sacubitril/ Valsartan (n=207)	Irbesartan (n=207)
Age at randomization, y		
Mean age (SD)	62.0 (14.1)	63.6 (13.4)
<50	37 (18%)	36 (17%)
≥50 to <70	97 (47%)	99 (48%)
≥70	73 (35%)	72 (35%)
Sex		
Male	148 (71%)	150 (72%)
Female	59 (29%)	57 (28%)
Ethnicity		
White	186 (90%)	191 (92%)
Black	3 (1%)	4 (2%)
South Asian	11 (5%)	7 (3%)
Other	7 (3%)	5 (2%)
Self-reported prior disease		
Coronary heart disease	21 (10%)	33 (16%)
Cerebrovascular disease	16 (8%)	15 (7%)
Peripheral vascular disease	22 (11%)	22 (11%)
Heart failure	8 (4%)	7 (3%)
Diabetes mellitus	81 (39%)	83 (40%)
Systolic blood pressure at randomization (mm Hg)		
Mean systolic blood pressure (SD)	146 (16)	146 (16)
<140	76 (37%)	85 (41%)
≥140 to <160	93 (45%)	84 (41%)
≥160	38 (18%)	38 (18%)
Diastolic blood pressure at randomization (mm Hg)		
Mean diastolic blood pressure (SD)	81 (11)	80 (11)
<80	96 (46%)	105 (51%)
≥80 to <90	68 (33%)	58 (28%)
≥90	43 (21%)	44 (21%)
Body mass index, kg/m^2		
Mean body mass index (SD)	30 (6)	31 (6)
<25	35 (17%)	33 (16%)
≥25 to <30	74 (36%)	73 (35%)
≥30	95 (46%)	100 (48%)
Not available	3	1
Medication		
Antiplatelet therapy	64 (31%)	75 (36%)
Oral anticoagulant	13 (6%)	15 (7%)
Diuretic	79 (38%)	85 (41%)
Calcium channel blocker	104 (50%)	103 (50%)
β-Blocker	50 (24%)	62 (30%)
α-Blocker	58 (28%)	55 (27%)
LDL-lowering agent	126 (61%)	137 (66%)
Use of RAS blockade at screening visit		
Yes	173 (84%)	166 (80%)
No	34 (16%)	41 (20%)
CKD-EPI estimated glomerular filtration rate at randomization, mL/min/1.73 m^2		
Mean (SD)	35.4 (11.0)	35.5 (11.0)
<30	79 (38%)	77 (37%)
≥30 to <45	86 (42%)	91 (44%)
≥45	41 (20%)	39 (19%)
Not available	1	0
Urine albumin:creatinine ratio at randomization, mg/mmol		
Geometric mean (≈SE)	34 (5)	34 (5)
Median (IQR)	52 (11–162)	56 (11–146)
<3	30 (14%)	28 (14%)
≥3 to <30	43 (21%)	45 (22%)
≥30	134 (65%)	134 (65%)
Cause of kidney disease		
Glomerular disease	60 (29%)	51 (25%)
Tubulointerstitial disease*	18 (9%)	32 (15%)
Diabetic kidney disease†	36 (17%)	47 (23%)
Hypertensive/renovascular disease†	18 (9%)	24 (12%)
Other systemic diseases affecting the kidneys†	1 (0%)	2 (1%)
Familial/hereditary nephropathies	30 (14%)	13 (6%)
Other known causes‡	5 (2%)	4 (2%)
Unknown‡	39 (19%)	34 (16%)
24-h urinary sodium excretion during run-in, mg/24 h		
Geometric mean (≈SE)	2245 (183)	2585 (187)
Median (IQR)	2484 (1794–3795)	2875 (1932–4232)
Not available	100	110

Values are n (%), mean (SD), geometric mean (≈SE), or median (IQR). CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; ERA-EDTA, European Renal Association-European Dialysis and Transplant Association; IQR, interquartile range; LDL, low-density lipoprotein; and RAS, renin–angiotensin system.

*Includes obstructive renal diseases.

†All considered systemic diseases affecting the kidney by the ERA-EDTA registry.

‡All considered miscellaneous renal disorders by the ERA-EDTA registry.

Allocation to sacubitril/valsartan was associated with significant reductions in levels of cardiac biomarkers compared with irbesartan. Study average NT-proBNP concentrations were 18% (−25 to −11%) lower and troponin I levels were 16% (−23% to −8%) lower among participants assigned sacubitril/valsartan (Table 3).

Using data from 87 participants who had taken their last dose of sacubitril/valsartan 10 to 16 hours previously, no significant determinants of sacubitril or valsartan concentration were identified (Table III in the online-only Data Supplement). However, kidney function was a major determinant of sacubitrilat

Table 2. Effect of Allocation to Sacubitril/Valsartan Versus Irbesartan on Measured Glomerular Filtration Rate at 12 Months

Follow-Up Visit	Mean mGFR (SE) (mL/min/1.73 m²)		Difference in Means (SE)*	*P* Value
	Sacubitril/ Valsartan (n=207)	Irbesartan (n=207)		
Randomization	34.0 (0.8)	34.7 (0.8)		
12 mo	29.8 (0.5)	29.9 (0.5)	–0.1 (0.7)	0.86

Where the difference between mGFR and central eGFR at the corresponding time point was more extreme than the first or 99th percentile of the distribution of differences, the value of mGFR was set to missing. Ten missing mGFR values at randomization had eGFR values at randomization imputed, and 41 missing mGFR values at 12 mo were imputed with the use of multiple imputation. For the 2 patients who commenced chronic dialysis during the study, a value of 0 was imputed for their 12-mo mGFR. eGFR indicates estimated glomerular filtration rate; and mGFR, measured glomerular filtration rate.

*Values are absolute differences in arithmetic means (SE). The 12-mo estimates and *P* values were derived from ANCOVA with adjustment for the randomization value.

concentration, with each 10 mL/min lower mGFR being associated with a 1485 (572–2397) ng/mL higher sacubitrilat concentration (Table III in the online-only Data Supplement).

Allocation to sacubitril/valsartan had no significant effect on fatal serious adverse events (1 [0.5%] versus 1 [0.5%]) or on any nonfatal serious adverse events (61 [29.5%] versus 59 [28.5%]; rate ratio, 1.07; 95% CI, 0.75–1.53; *P*=0.70) (Table IV in the online-only Data Supplement). One case of angioedema occurred in a participant allocated sacubitril/valsartan, but the participant did not attend hospital or require any specific treatment. There was no difference overall in the number of nonserious adverse reactions (76 [36.7%] versus 58 [28.0%]; rate ratio, 1.35; 95% CI, 0.96–1.90; *P*=0.08) (Table IV in the online-only Data Supplement). Allocation to sacubitril/valsartan was associated with higher rates of nonserious hypotension (17 [8.2%] versus 7 [3.4%]; rate ratio, 2.36; 95% CI, 1.06–5.26; *P*=0.04). There was no difference between treatments in the number of participants experiencing hyperkalemia (66 [32%] versus 50 [24%], *P*=0.10) or in the proportion experiencing a significant decline in eGFR (defined as ≥25% reduction; 71 [34%] versus 67 [32%], *P*=0.75) (Table 4). There were no cases of significant liver injury.

DISCUSSION

The UK HARP-III trial has shown that, compared with irbesartan, 12 months of treatment with sacubitril/valsartan did not significantly affect kidney function in people with CKD. Sacubitril/valsartan had no additional effect on albuminuria compared with irbesartan and was as well tolerated, with no major safety concerns identified. Sacubitril/valsartan was also found to reduce blood pressure and biomarkers of cardiovascular risk (troponin I and NT-proBNP) compared with irbesartan.

The kidney function results from the UK HARP-III trial do not confirm findings from the analyses of kidney disease progression outcomes from other NEPi trials among patients with heart failure. In a trial among patients with heart failure with preserved ejection fraction, kidney function declined more slowly with sacubitril/valsartan compared with valsartan.[15] In the large PARADIGM-HF trial, a marginally

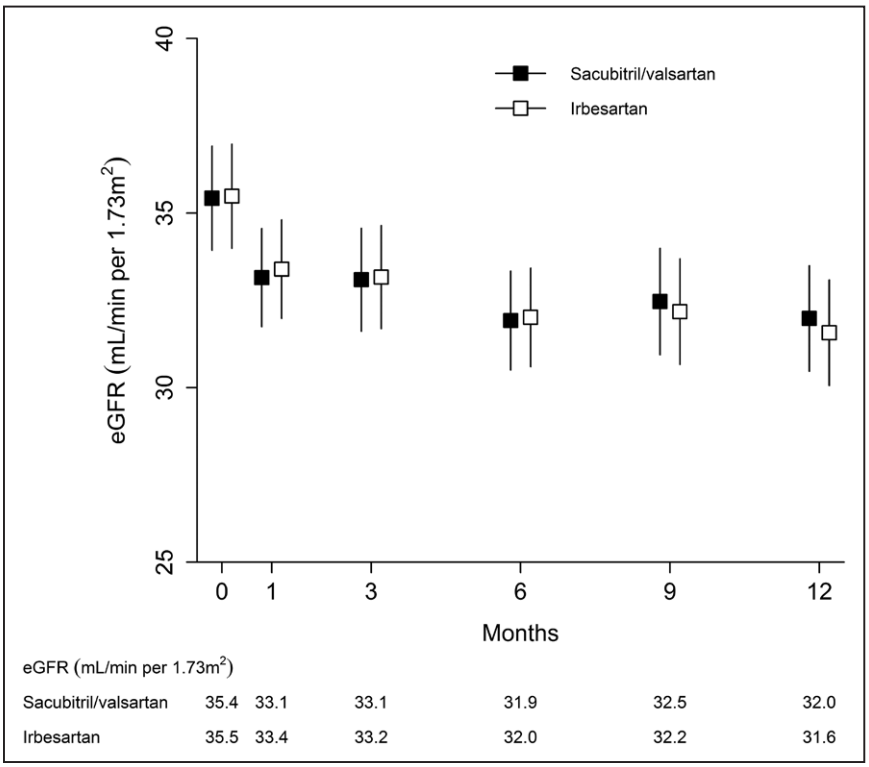

Figure 2. Effect of allocation to sacubitril/valsartan versus irbesartan on estimated glomerular filtration rate (eGFR). Creatinine measured in the central laboratory except for 1- and 9-month visits when creatinine was measured in the local laboratory. Error bars presented are 95% CIs.

Table 3. Effect of Allocation to Sacubitril/Valsartan Versus Irbesartan on Urinary Albumin:Creatinine Ratio, Systolic and Diastolic Blood Pressure, and Cardiac Biomarkers

Follow-Up Visit	Mean (SE)*		Difference in Means (95% CI)†	*P* Value
	Sacubitril/ Valsartan (n=207)	Irbesartan (n=207)		
Urinary albumin:creatinine ratio, mg/mmol				
Randomization	34.1 (4.6)	33.9 (4.5)		
3 mo	17.0 (1.0)	17.8 (1.0)	−4% (−19 to 12)	
6 mo	15.6 (1.0)	18.4 (1.1)	−15% (−28 to 0)	
12 mo	16.4 (1.2)	17.6 (1.3)	−6% (−23 to 14)	
Study average	16.3 (0.6)	17.9 (0.7)	−9% (−18 to 1)	0.08
Systolic blood pressure, mm Hg				
Randomization	146 (1.1)	146 (1.1)		
1 mo	129 (1.1)	132 (1.1)	−3.5 (−6.5 to −0.6)	
3 mo	129 (1.1)	137 (1.1)	−7.3 (−10.3 to −4.3)	
6 mo	128 (1.1)	135 (1.1)	−6.9 (−10.0 to −3.7)	
9 mo	130 (1.2)	134 (1.2)	−4.0 (−7.3 to −0.8)	
12 mo	128 (2.5)	133 (2.2)	−4.4 (−10.9 to 2.1)	
Study average	129 (0.8)	134 (0.7)	−5.4 (−7.4 to −3.4)	<0.001
Diastolic blood pressure, mm Hg				
Randomization	81 (0.8)	80 (0.8)		
1 mo	73 (0.6)	74 (0.6)	−0.8 (−2.5 to 0.9)	
3 mo	73 (0.6)	76 (0.6)	−2.6 (−4.3 to −0.9)	
6 mo	72 (0.6)	75 (0.6)	−2.5 (−4.2 to −0.8)	
9 mo	73 (0.6)	74 (0.6)	−1.8 (−3.6 to −0.1)	
12 mo	72 (1.6)	75 (1.3)	−2.2 (−6.2 to 1.9)	
Study average	73 (0.5)	75 (0.4)	−2.1 (−3.3 to −1.0)	<0.001
N-terminal pro-B-type natriuretic peptide, ng/L				
Randomization	254.5 (22)	250.9 (22)		
6 mo	175.6 (7.2)	219.7 (8.9)	−20% (−29 to −11)	
12 mo	210.2 (11)	247.5 (12)	−15% (−26 to −2)	
Study average	188.7 (6.0)	230.4 (7.3)	−18% (−25 to −11)	<0.001
Troponin I, ng/L				
Randomization	7.3 (0.5)	7.5 (0.5)		
6 mo	5.4 (0.2)	6.6 (0.2)	−19% (−27 to −10)	
12 mo	6.3 (0.4)	7.1 (0.4)	−11% (−24 to 4)	
Study average	5.7 (0.2)	6.8 (0.2)	−16% (−23 to −8)	<0.001

Any missing data were imputed with the use of multiple imputation.

*Geometric means (≈SE) are presented for urinary albumin:creatinine ratio and cardiac biomarkers, and arithmetic means (SE) are presented for blood pressure.

†Values are percentage changes in geometric means (95% CI) for urinary albumin:creatinine ratio and cardiac biomarkers, and absolute differences in arithmetic means (95% CI) for blood pressure. The estimates and *P* values at each follow-up visit were derived from ANCOVA with adjustment for the randomization value.

slower decline in eGFR was also observed with sacubitril/valsartan compared with enalapril (−1.3 [95% CI, −1.2 to −1.4] versus −1.8 [95% CI, −1.8 to −1.7] mL/min/1.73 m^2 per year; $P<0.0001$).[16] The lack of any additional effect of sacubitril/valsartan on kidney function in the UK HARP-III trial may reflect differing determinants of kidney disease progression in a proteinuric CKD population compared with heart failure populations. If cardiac function is a more important determinant of kidney function in a heart failure population than in proteinuric CKD, then a treatment that improves cardiac function, such as sacubitril/valsartan, might be more likely to affect kidney function in a heart failure population.

Studies using animal models of established kidney disease have found that combinations of NEP and

Table 4. Effect of Allocation to Sacubitril/Valsartan Versus Irbesartan on Biochemical Safety Data

Outcome	Sacubitril/ Valsartan (n=207)	Irbesartan (n=207)	*P* Value
Potassium, mmol/L			
≥5.5 to <6.0	44 (21%)	38 (18%)	
≥6.0 to <6.5	20 (10%)	7 (3%)	
≥6.5	2 (1%)	5 (2%)	
Total: Any potassium ≥5.5 mmol/L	66 (32%)	50 (24%)	0.10
Estimated glomerular filtration rate			
≥25% reduction in CKD-EPI eGFR*	71 (34%)	67 (32%)	0.75

Based on local laboratory measurements. CKD-EPI indicates Chronic kidney Disease Epidemiology Collaboration; and eGFR, estimated glomerular filtration rate.

*Compared to eGFR at randomization visit.

RAS inhibition are not associated with significant differences in GFR compared with isolated RAS inhibition.[18,19,21,32] However, histology results from these animals demonstrated that combined NEP/RAS inhibition was associated with greater reductions in histological markers of CKD progression (glomerulosclerosis and tubulointerstitial fibrosis), compared with isolated RAS inhibition.[12,18–20] It should be noted that the largest decline in eGFR was observed during the first month, likely attributable to the known glomerular hemodynamic effects of RAS inhibition. In the remaining 11 months of observation, eGFR decline was slow in both groups, implying that a longer observation period may have been necessary to observe the full effect on kidney function.

Allocation to sacubitril/valsartan did not increase albuminuria, in contrast with trials among patients with heart failure, among whom sacubitril/valsartan causes statistically significant (but clinically modest) increases in albuminuria (from a much lower baseline).[15] If similar increases in albuminuria had developed in people with proteinuric CKD, this would have been of concern because albuminuria is associated with an increased risk of progression to end-stage renal disease (although whether this association is directly causal remains uncertain).[33–35] Nonetheless, the lack of effect on albuminuria despite the observed blood pressure difference raises the possibility that the effect on systemic blood pressure does not lead to a reduction in intraglomerular pressure.

Sacubitril/valsartan lowered blood pressure compared with irbesartan. Similar additional reductions in blood pressure compared with RAS inhibition have been shown in populations with heart failure or hypertension.[14,36–39] These differences were observed in the context of a median of 1 other antihypertensive medication being used in addition to study treatment in both groups. It remains uncertain whether lowering blood pressure reduces the rate of progression of kidney disease,[40,41] but there is strong evidence that it reduces the risk of cardiovascular events.[41] Patients with CKD are at increased risk of cardiovascular events.[42] Indeed, most patients with CKD are at higher risk of cardiovascular mortality than progression to end-stage kidney disease (ie, dialysis or transplantation).[9] As kidney function declines, the nature of cardiovascular disease changes from a typical atherosclerotic phenotype to one of structural heart disease, which becomes increasingly prevalent such that 80% of patients starting dialysis have evidence of it.[43,44] The finding that NT-proBNP (an indicator of cardiac wall stress and not a substrate of neprilysin) and troponin levels (a marker of cardiomyocyte necrosis) were both lower among participants assigned sacubitril/valsartan compared with irbesartan has also been observed among patients with heart failure.[39,45,46] Recent animal data also demonstrated that sacubitril/valsartan attenuates cardiac hypertrophy and fibrosis in an animal model of CKD.[47] These findings raise the hypothesis that sacubitril/valsartan may have cardiovascular benefits among patients with advanced CKD and provides a rationale for a clinical outcome trial.

Sacubitril/valsartan was generally well tolerated, and no major hazards were observed; although there were numerically more nonserious adverse reactions in the sacubitril/valsartan group, this difference was not statistically significant. These randomized comparisons follow a placebo run-in during which 152/566 (26%) of participants withdrew, mostly for nonmedical reasons.[23] Compared with those allocated to irbesartan, participants allocated sacubitril/valsartan reported more symptoms of hypotension, which is expected given its larger blood pressure-lowering effect. Because kidney function is a major determinant of sacubitrilat concentration, it is possible that higher concentrations of sacubitrilat in this population contributed to this excess in hypotension. Both treatments had similar effects on the incidence of hyperkalemia, and no cases of significant liver injury were observed despite high blood concentrations of sacubitrilat resulting from reduced renal excretion. One participant allocated sacubitril/valsartan developed angioedema but did not require medical intervention, and it resolved spontaneously.

Study limitations include the short duration of follow-up and the sample size, which was not sufficiently large to test the effect of sacubitril/valsartan on clinical outcomes. The choice of comparator (irbesartan) also might have an effect on the interpretation of the results because it has a different pharmacological profile from valsartan and may provide more intense angiotensin receptor blockade.[48] This would suggest that the additional BP reduction and effects on cardiac biomarkers are an underestimate of the effect of neprilysin inhibition.

CONCLUSIONS

In conclusion, over 12 months in people with CKD, the combination of sacubitril and valsartan is well tolerated and has similar effects on kidney function and albuminuria to irbesartan, but it has additional blood pressure– and cardiac biomarker–lowering effects.

ARTICLE INFORMATION

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Correspondence

Richard Haynes, DM, Medical Research Council Population Health Research Unit, Nuffield Department of Population Health, Richard Doll Building, Old Road Campus, Roosevelt Dr, Oxford OX3 7LF, United Kingdom. Email harp3@ndph.ox.ac.uk

Affiliations

Medical Research Council Population Health Research Unit (R.H., P.K.J., W.G.H., B.C.S., M.H., M.J.L., C.B.), Clinical Trial Service Unit (R.H., P.K.J., N.S., W.G.H., B.C.S., L.B., M.H., M.J.L., C.B.), Nuffield Department of Population Health, and Diabetes Trials Unit, Radcliffe Department of Medicine (A.B.), University of Oxford, UK. Department of Infection, Immunity and Inflammation, University of Leicester, UK (N.B.). Department of Nephrology, University Hospitals Birmingham, UK (P.C.). Department of Nephrology, Salford Royal Hospital NHS Foundation Trust, UK (P.A.K.). Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK (J.J.V.M.). Faculty of Medicine and Health Sciences, University of Nottingham, UK (M.T.). Centre for Nephrology, University College London, UK (D.C.W.).

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