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Effects of Sacubitril/Valsartan Versus Irbesartan in Patients with Chronic Kidney Disease: A Randomised Double-Blind Trial

Running Title: *Haynes et al.; Effects of Sacubitril/Valsartan in CKD*

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Abstract

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—UK HARP-III was a randomised double-blind trial which included 414 participants with an estimated glomerular filtration rate (GFR) 20-60 mL/min/1.73m^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 (mGFR) at 12 months using analysis of covariance with adjustment for each individual's baseline mGFR. All analyses were by intention to treat. This trial is registered at ISRCTN11958993.
Results—207 participants were assigned to sacubitril/valsartan and 207 to irbesartan. Baseline mGFR was 34.0 (0.8) and 34.7 (0.8) mL/min/1.73m² respectively. At 12 months there was no difference in measured GFR: 29.8 (SE 0.5) among those assigned sacubitril/valsartan versus 29.9 (0.5) mL/min/1.73m^2 among those assigned irbesartan; difference -0.1 (0.7) mL/min/1.73m^2. Effects were similar in all pre-specified 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 to 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) mmHg, and levels of troponin I and N-terminal of pro-hormone brain natriuretic peptide (tertiary endpoints) by 16% (95% CI 8-23) and 18% (95% CI 11-25), respectively. The incidence of serious adverse events (29.5% vs 28.5%; rate ratio [RR] 1.07, 95% CI 0.75-1.53), non-serious adverse reactions (36.7% vs 28.0%; RR 1.35, 95% CI 0.96-1.90) and potassium ≥ 5.5 mmol/L (32% vs 24%; p=0.10) were not significantly different between randomized groups.
Conclusions—Over 12 months, sacubitril/valsartan has similar effects on kidney function and albuminuria to irbesartan, but has the additional effect of lowering blood pressure and cardiac biomarkers in people with chronic kidney disease.
Clinical Trial Registration—URL: www.isrctn.com Unique Identifier: ISRCTN11958993

Key Words: Chronic kidney disease; neprilysin inhibition; renin-angiotensin system

Clinical Perspective

What is new?

- UK HARP-III has demonstrated that, in a wide range of people with proteinuric CKD, adding neprilysin inhibition to angiotensin II receptor blockade has no additional effect on kidney function or albuminuria compared to irbesartan.
- The tolerability and safety profiles of the two treatments were not different, but as compared to irbesartan, sacubitril/valsartan further reduces both blood pressure and biomarkers of cardiovascular risk (troponin I and NT-proBNP) compared to irbesartan.

What are the clinical implications?

- UK HARP-III raises a 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.

Introduction

Patients with chronic kidney disease (CKD) are at increased risk of both progression to end-stage renal disease (ESRD) and cardiovascular events, compared to patients with normal kidney function.[1-3] Randomised controlled trials have shown that renin-angiotensin system (RAS) inhibitors slow the progression of diabetic and non-diabetic proteinuric CKD,[4-7] and lowering low density lipoprotein cholesterol reduces the risk of atherosclerotic vascular events.[8] However, despite such treatments, there remains a significant risk of progression to ESRD and cardiovascular events. 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 ESRD.[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 neprilysin (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 (ACEi) are associated with a high risk of angioedema (due to excessive inhibition of bradykinin degradation),[13] so the chosen method of RAS inhibition for user with NEPi is an angiotensin receptor blockers (ARB). Sacubitril/valsartan, which combines an ARB (valsartan) with a NEPi (sacubitril), was the first angiotensin receptor-neprilysin inhibitor (ARNI) to be developed.

The Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) showed that sacubitril/valsartan reduced the risk of cardiovascular mortality among patients with heart failure with reduced ejection fraction when compared to ACEi (enalapril) (HR 0.80; 95% confidence interval 0.71-0.89).[14] Several trials in heart failure populations, 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 United Kingdom Heart and Renal Protection (UK HARP)-III trial aimed to compare the effects of sacubitril/valsartan versus irbesartan (a licenced ARB 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 prior to the enrolment of any study participants. Participants aged 18 years and older were eligible to participate if they had chronic kidney disease with either (i) an estimated glomerular filtration rate (eGFR) of ≥45 and <60 mL/min/1.73m^2 and a urine albumin:creatinine ratio (uACR) >20 mg/mmol (177 mg/g); or (ii) 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 pre-randomisation run-in phase, during which they took one placebo sacubitril/valsartan tablet and one placebo irbesartan capsule daily. The aims of the run-in phase were to (i) enable a 'wash out' of any ACEi prior to introduction of NEPi (to reduce the risk of angioedema), (ii) allow a comparison of the acute effects of the study treatments on eGFR and (iii) identify and exclude those less likely to adhere to study treatment and trial procedures prior to randomisation in order to maintain statistical sensitivity.[24, 25]

Randomisation and masking

At the end of the run-in period, GFR was measured and willing and eligible participants were randomized 1:1 to sacubitril/valsartan or irbesartan by an internet-based system with minimized randomisation (which helped ensure balance for categories of age, sex, systolic blood pressure, previous diabetes, 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 two bottles of study treatments, one containing sacubitril/valsartan 97/103mg or placebo tablets and the other containing irbesartan 150mg or placebo capsules.[27]

Procedures

Following randomisation, participants were initially instructed to take one tablet and one capsule daily of study treatment (i.e. either sacubitril/valsartan 97/103mg or irbesartan 150mg); this was increased to sacubitril/valsartan 97/103mg twice daily or irbesartan 300mg once daily after two

weeks unless potassium or change in kidney function precluded a dose increase. Study visits were scheduled at 1, 3, 6, 9 and 12 months post-randomisation (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 non-serious 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 N-terminal pro-hormone of B-type natriuretic peptide, NT-proBNP) were conducted at randomisation, 6 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 prior to the 12 month visit, and paper results of all GFR measurements were sent to the coordinating centre 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 carers wherever possible. The original protocol specified that 360 participants would be followed for 6 months; prior to 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 the effect on kidney function may take at least 9 months to fully emerge) and to increase the sample size to at least 400 participants (to increase the statistical power).

Laboratory methods

GFR was measured in the study centres using ^{51}Cr-EDTA, ^{99m}Tc-DTPA or iohexol methods depending on local practice (with each centre using the same method used at baseline and 12 months). Creatinine was assayed in the central laboratory on a Beckman Coulter AU680 analyser 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), Analysis of covariance (ANCOVA) was used to compare mean mGFR at 12 months between sacubitril/valsartan and irbesartan-allocated patients, with adjustment for each individual's baseline mGFR.[28] Assuming a between-person standard deviation (SD) in mGFR of 15 mL/min/1.73m^2 and a correlation between an individual's baseline and follow-up mGFR of 0.8, randomisation of 400 participants would provide at least 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/1.73m^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 (RRs), 95% confidence intervals (CIs) and associated two-sided p values. [29, 30] Pharmacokinetic analyses involved multiple linear

regression of each sacubitril/valsartan metabolite against a number of pre-specified 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 10-16 hours prior to the sample being collected. Further details (including secondary and tertiary outcomes) are available in the pre-specified data analysis plan.[23] Analyses were done using SAS version 9.3 (SAS Institute, Cary) and R version 3.3.3 (www.R-Project.org).

Sources of Funding

The UK HARP-III trial was designed, conducted, and analysed by the MRC Population Health Research Unit, which is part of the Clinical Trial Service Unit and Epidemiological Studies Unit. The University of Oxford was the independent regulatory sponsor for the study. The study was funded by a grant to the University of Oxford from Novartis (manufacturers of sacubitril/valsartan). The funder had no involvement in the study conduct, analysis or the decision to submit for publication. All authors accept full responsibility for the content of this paper. The first author had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Clinical Trial Registration

The trial is registered at ISRCTN11958993 (www.isrctn.com)

Results

Between 1st November 2014 and 31st January 2016, 620 participants attended screening visits and 566 (91%) entered the pre-randomisation run-in (Figure 1). 414 participants were randomized: 207 to sacubitril/valsartan and 207 to irbesartan. Mean age was 62.8 years (SD

13.7), 298 (72%) were male and mean blood pressure was 146/81 mmHg (Table 1). Mean eGFR at baseline was 35.5 (10.9) mL/min/1.73m² and 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%] 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 due to serious adverse events, non-serious adverse reactions or other reasons in thos allocated sacubitril/valsartan (Supplementary Table 1).

At 12 months, the mean (SE) mGFR was 29.8 (0.5) mL/min/1.73m² among those assigned sacubitril/valsartan group compared with 29.9 (0.5) mL/min/1.73m² among those assigned irbesartan, a non-significant difference of 0.1 (0.7) mL/min/1.73m² (P=0.86; Table 2). Neither a pre-specified complete case analysis (i.e. without imputation: difference -0.4 (0.7) mL/min/1.73m²) nor an "on treatment" analysis (difference -0.5 (0.7) mL/min/1.73m²) 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), by 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 pre-specified baseline characteristic (Supplementary Figure 1).

As compared to 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 randomisation to 12 months, from randomisation to 3 months or from 3 to 12 months (Supplementary Table 2).

Allocation to sacubitril/valsartan produced a non-significant 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, mean systolic blood pressure was 5.4 (95% CI -7.4 to -3.4) mmHg lower, and mean diastolic blood pressure was 2.1 (95% CI -3.3 to -1.0) mmHg lower among those allocated to sacubitril/valsartan (Table 3). Exploratory analyses did not show any differences in the intensity of non-study anti-hypertensive agents between the treatment arms during follow-up.

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 10-16 hours previously, no significant determinants of sacubitril or valsartan concentration were identified (Supplementary Table 3). However, kidney function was a major determinant of sacubitrilat concentration, with each 10 mL/min lower mGFR being associated with a 1485 (572-2397) ng/mL higher sacubitrilat concentration (Supplementary Table 3).

Allocation to sacubitril/valsartan had no significant effect on fatal serious adverse events (1 [0.5%] vs 1 [0.5%]) or on any non-fatal serious adverse events (61 [29.5%] vs 59 [28.5%]; RR 1.07 [0.75-1.53]; p=0.70) (Supplementary Table 4). One case of angioedema occurred in a participant allocated sacubitril/valsartan, but they did not attend hospital or require any specific treatment. There was no difference overall in the number of non-serious adverse reactions (76 [36.7%] vs 58 [28.0%]; RR 1.35 [0.96-1.90]; p=0.08) (Supplementary Table 4). Allocation to sacubitril/valsartan was associated with higher rates of non-serious hypotension (17 [8.2%] vs 7 [3.4%]; RR 2.36 [1.06-5.26]; p=0.04). There was no difference between treatments in the number of participants experiencing hyperkalaemia (66 [32%] vs 50 [24%]; p=0.10) or in the

proportion experiencing a significant decline in eGFR (defined as 25% or greater reduction; 71 [34%] vs 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 to 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 to irbesartan.

The kidney function results from UK HARP-III 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 (HFpEF), kidney function declined more slowly with sacubitril/valsartan compared with valsartan.[15] In the large PARADIGM-HF trial, a marginally slower decline in eGFR was also observed with sacubitril/valsartan compared with enalapril (-1.3 [-1.2 to -1.4] versus -1.8 [-1.8 to -1.7] mL/min/1.73m^2 per year; p<0.0001).[16] The lack of any additional effect of sacubitril/valsartan on kidney function in UK HARP-III may reflect differing determinants of kidney disease progression in a proteinuric CKD population compared to 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 which improves cardiac function, like 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 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 haemodynamic 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, by 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 since albuminuria is associated with increased risk of progression to ESRD (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 one other anti-hypertensive 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 good 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 (i.e. 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 NTpro-BNP (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 non-serious adverse reactions in the sacubitril/valsartan group this difference was not statistically significant. These randomised comparisons follow a placebo run-in during which 152/566 (26%) of participants withdrew, mostly for non-medical reasons.[23] Compared to those allocated to irbesartan, there were more reports of symptoms of hypotension among participants allocated sacubitril/valsartan, 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 hyperkalaemia 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) might also have an effect on the interpretation of the results as it has a different pharmacological profile to valsartan and may provide more intense angiotensin receptor blockade.[48] This would suggest the additional BP reduction and effects on cardiac biomarkers are an underestimate of the effect of neprilysin inhibition.

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

Declaration of interests

CTSU has a staff policy of not accepting honoraria or other payments from the pharmaceutical industry, expect for the reimbursement of costs to participate in scientific meetings (www.ctsu.ox.ac.uk). JJVM's employer, Glasgow University, has been paid by Novartis for his time spent as Principal Investigator/Executive/Steering committee member for a number of clinical trials using sacubitril/valsartan and meetings and lectures related to sacubitril/valsartan. The other authors have no conflicts of interest to declare. The trial was supported by Novartis Pharma AG, the Medical Research Council (which funds the Medical Research Council

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References

1. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K and Wen CP. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet*. 2013;382:339-352.
2. Go AS, Chertow GM, Fan D, McCulloch CE and Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *New Engl J Med*. 2004;351:1296-1305.
3. Foley RN, Parfrey PS and Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kid Dis*. 1998;32:S112-S119.
4. Lewis EJ, Hunsicker LG, Bain RP and Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *New Engl J Med*. 1993;329:1456-1462.
5. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, Scolari F, Schena FP and Remuzzi G. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet*. 1999;354:359-364.
6. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I and Collaborative Study G. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *New Engl J Med*. 2001;345:851-860.
7. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S and Investigators RS. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861-869.
8. Cholesterol Treatment Trialists Collaboration, Herrington WG, Emberson J, Mihaylova B, Blackwell L, Reith C, Solbu MD, Mark PB, Fellstrom B, Jardine AG, Wanner C, Holdaas H, Fulcher J, Haynes R, Landray MJ, Keech A, Simes J, Collins R and Baigent C. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. *Lancet Diabetes Endocrinol*. 2016;4:829-839.

9. O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS, Walter LC, Mehta KM, Steinman MA, Allon M, McClellan WM and Landefeld CS. Age Affects Outcomes in Chronic Kidney Disease. *J Am Soc Nephrol*. 2007;18:2758-2765.
10. Wilkins MR, Redondo J and Brown LA. The natriuretic-peptide family. *Lancet*. 1997;349:1307-1310.
11. de Bold AJ. Atrial natriuretic factor: a hormone produced by the heart. *Science*. 1985;230:767-770.
12. Benigni A, Zoja C, Zatelli C, Corna D, Longaretti L, Rottoli D, Maggioni P, Todeschini M, Noris M and Remuzzi G. Vasopeptidase inhibitor restores the balance of vasoactive hormones in progressive nephropathy. *Kidney Int*. 2004;66:1959-1965.
13. Kostis JB, Packer M, Black HR, Schmieder R, Henry D and Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens*. 2004;17:103-111.
14. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Investigators P-H and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *New Engl J Med*. 2014;371:993-1004.
15. Voors AA, Gori M, Liu LC, Claggett B, Zile MR, Pieske B, McMurray JJ, Packer M, Shi V, Lefkowitz MP, Solomon SD and Investigators P. Renal effects of the angiotensin receptor neprilysin inhibitor LCZ696 in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail*. 2015;17:510-517.
16. Packer M, Claggett B, Lefkowitz MP, McMurray JJV, Rouleau JL, Solomon SD and Zile MR. Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial. *Lancet Diabetes Endocrinol*. 2018;6:547-554. doi 10.1016/S2213-8587(18)30100-1
17. Solomon SD, Claggett B, McMurray JJ, Hernandez AF and Fonarow GC. Combined neprilysin and renin-angiotensin system inhibition in heart failure with reduced ejection fraction: a meta-analysis. *Eur J Heart Fail*. 2016;18:1238-1243.
18. Taal MW, Nenov VD, Wong WC, Satyal SR, Sakharova O, Choi JH, Troy JL and Brenner BM. Vasopeptidase inhibition affords greater renoprotection than angiotensin-converting enzyme inhibition alone. *J Am Soc Nephrol*. 2001;12:2051-2059.
19. Cao Z, Burrell LM, Tikkanen I, Bonnet F, Cooper ME and Gilbert RE. Vasopeptidase inhibition attenuates the progression of renal injury in subtotal nephrectomized rats. *Kidney Int*. 2001;60:715-721.
20. Davis BJ, Johnston CI, Burrell LM, Burns WC, Kubota E, Cao Z, Cooper ME and Allen TJ. Renoprotective effects of vasopeptidase inhibition in an experimental model of diabetic nephropathy. *Diabetologia*. 2003;46:961-971.
21. Roksnoer LC, van Veghel R, van Groningen MC, de Vries R, Garrelds IM, Bhaggoe UM, van Gool JM, Friesema EC, Leijten FP, Hoorn EJ, Danser AH and Batenburg WW. Blood pressure-independent renoprotection in diabetic rats treated with AT1 receptor-neprilysin inhibition compared with AT1 receptor blockade alone. *Clinical Science* 2016;130:1209-1220.
22. Nuffield Department of Population Health. Data Access and Sharing Policy. https://www.ndph.ox.ac.uk/about/data-access-policy. 2018.
23. Judge PK, Haynes R, Herrington WG, Storey BC, Staplin N, Bethel A, Bowman L, Brunskill N, Cockwell P, Dayanandan R, Hill M, Kalra PA, McMurray JJ, Taal M, Wheeler DC, Landray MJ and C B. Randomized multicentre pilot study of sacubitril/valsartan versus

irbesartan in patients with chronic kidney disease: United Kingdom Heart and Renal Protection (HARP)- III-rationale, trial design and baseline data. *Nephrol Dial Transplant.* 2017; 32: 2043-2051
24. Lang JM. The use of a run-in to enhance compliance. *Stat Med*. 1990;9:87-93.
25. Lang JM, Buring JE, Rosner B, Cook N and Hennekens CH. Estimating the effect of the run-in on the power of the Physicians' Health Study. *Stat Med*. 1991;10:1585-1593.
26. Pocock SJ and Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975;31:103-115.
27. Schulz KF, Chalmers I, Hayes RJ and Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *J Am Med Assoc*. 1995;273:408-412.
28. Borm GF, Fransen J and Lemmens WA. A simple sample size formula for analysis of covariance in randomized clinical trials. *J Clin Epidemiol*. 2007;60:1234-1238.
29. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J and Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer*. 1976;34:585-612.
30. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J and Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. *Br J Cancer*. 1977;35:1-39.
31. Rubin D. *Multiple imputation for non-response in surveys.*: New York: John Wiley; 1987.
32. Ushijima K, Ando H, Arakawa Y, Aizawa K, Suzuki C, Shimada K, Tsuruoka SI and Fujimura A. Prevention against renal damage in rats with subtotal nephrectomy by sacubitril/valsartan (LCZ696), a dual-acting angiotensin receptor-neprilysin inhibitor. *Pharmacology Research Perspect*. 2017;5: doi: 10.1002/prp2.336.
33. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M and Alberta Kidney Disease N. Relation between kidney function, proteinuria, and adverse outcomes. *J Am Med Assoc*. 2010;303:423-429.
34. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J and Chronic Kidney Disease Prognosis C. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*. 2011;80:93-104.
35. Mafham MM, Staplin N, Emberson J, Haynes R, Herrington W, Reith C, Wanner C, Walker R, Cass A, Levin A, Fellstrom B, Jiang L, Holdaas H, Kasiske B, Wheeler DC, Landray MJ, Baigent C and Group SC. Prognostic utility of estimated albumin excretion rate in chronic kidney disease: results from the Study of Heart and Renal Protection. *Nephrol Dial Transplant*. 2018; 33: 257-264.
36. Ruilope LM, Dukat A, Bohm M, Lacourciere Y, Gong J and Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet*. 2010;375:1255-1266.
37. Williams B, Cockcroft JR, Kario K, Zappe DH, Brunel PC, Wang Q and Guo W. Effects of Sacubitril/Valsartan Versus Olmesartan on Central Hemodynamics in the Elderly With Systolic Hypertension: The PARAMETER Study. *Hypertension*. 2017; 69: 411-420.
38. Kario K, Sun N, Chiang FT, Supasyndh O, Baek SH, Inubushi-Molessa A, Zhang Y, Gotou H, Lefkowitz M and Zhang J. Efficacy and Safety of LCZ696, a First-in-Class

Angiotensin Receptor Neprilysin Inhibitor, in Asian Patients With Hypertension: A Randomized, Double-Blind, Placebo-Controlled Study. *Hypertension*. 2014;63:698-705.
39. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ and Prospective comparison of AwARBoMOhfwpefI. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380:1387-1395.
40. Lv J, Ehteshami P, Sarnak MJ, Tighiouart H, Jun M, Ninomiya T, Foote C, Rodgers A, Zhang H, Wang H, Strippoli GF and Perkovic V. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *Can Med Assoc J*. 2013;185:949-957.
41. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A and Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957-967.
42. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J and Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073-2081.
43. Park M, Hsu CY, Li Y, Mishra RK, Keane M, Rosas SE, Dries D, Xie D, Chen J, He J, Anderson A, Go AS, Shlipak MG and Chronic Renal Insufficiency Cohort Study G. Associations between kidney function and subclinical cardiac abnormalities in CKD. *J Am Soc Nephrol*. 2012;23:1725-1734.
44. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC and Barre PE. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int*. 1995;47:186-192.
45. Jhund PS, Claggett BL, Voors AA, Zile MR, Packer M, Pieske BM, Kraigher-Krainer E, Shah AM, Prescott MF, Shi V, Lefkowitz M, McMurray JJ, Solomon SD and Investigators P. Elevation in high-sensitivity troponin T in heart failure and preserved ejection fraction and influence of treatment with the angiotensin receptor neprilysin inhibitor LCZ696. *Circulation Heart Fail*. 2014;7:953-959.
46. Packer M, McMurray JJ, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile M, Andersen K, Arango JL, Arnold JM, Belohlavek J, Bohm M, Boytsov S, Burgess LJ, Cabrera W, Calvo C, Chen CH, Dukat A, Duarte YC, Erglis A, Fu M, Gomez E, Gonzalez-Medina A, Hagege AA, Huang J, Katova T, Kiatchoosakun S, Kim KS, Kozan O, Llamas EB, Martinez F, Merkely B, Mendoza I, Mosterd A, Negrusz-Kawecka M, Peuhkurinen K, Ramires FJ, Refsgaard J, Rosenthal A, Senni M, Sibulo AS, Jr., Silva-Cardoso J, Squire IB, Starling RC, Teerlink JR, Vanhaecke J, Vinereanu D, Wong RC, Investigators P-H and Coordinators. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation*. 2015;131:54-61.
47. Suematsu Y, Jing W, Nunes A, Kashyap ML, Khazaeli M, Vaziri ND and Moradi H. LCZ696 (Sacubitril/valsartan), an Angiotensin-Receptor Neprilysin Inhibitor, Attenuates Cardiac Hypertrophy, Fibrosis and Vasculopathy in a Rat Model of Chronic Kidney Disease. *J Card Fail*. 2018; 24: 266-275.
48. Belz GG, Breithaupt-Grogler K, Butzer R, Fuchs W, Hausdorf C and Mang C. The pharmacological potency of various AT(1) antagonists assessed by Schild regression technique in man. *J Renin Angiotensin Aldosterone Syst*. 2000;1:336-341.

Table 1. Baseline characteristics by randomised treatment allocation

	Sacubitril/valsartan (n=207)	Irbesartan (n=207)
Age at randomisation (years)	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 randomisation (mmHg)	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 randomisation (mmHg)	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/m²)	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%)
Beta blocker	50 (24%)	62 (30%)
Alpha 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 randomisation (mL/min/1.73m²)		

	Sacubitril/valsartan (n=207)	Irbesartan (n=207)
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 randomisation (mg/mmol)		
Geometric mean (approx 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 hour urinary sodium excretion during run-in (mg/24 hours)		
Geometric mean (approx SE)	2245 (183)	2585 (187)
Median (IQR)	2484 (1794-3795)	2875 (1932-4232)
Not available	100	110

Values are n (%), mean (SD), geometric mean (approx SE) or median (IQR). RAS=Renin–angiotensin system. CKD-EPI=Chronic kidney disease Epidemiology Collaboration. *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.

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/1.73m²)		Difference in means (SE)*	p value
	Sacubitril/valsartan (n=207)	Irbesartan (n=207)		
Randomisation	34.0 (0.8)	34.7 (0.8)		
12 months	29.8 (0.5)	29.9 (0.5)	-0.1 (0.7)	0.86

mGFR=measured glomerular filtration rate. Where the difference between mGFR and central eGFR at the corresponding time point was more extreme than the 1st or 99th centile of the distribution of differences, the value of mGFR was set to missing. 10 missing mGFR values at randomisation had eGFR values at randomisation imputed and 41 missing mGFR values at 12 months 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 month mGFR. *Values are absolute differences in arithmetic means (SE). The 12 month estimates and p values were derived from analysis of covariance with adjustment for the randomisation value.

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)				
Randomisation	34.1 (4.6)	33.9 (4.5)		
3 months	17.0 (1.0)	17.8 (1.0)	-4% (-19 to 12%)	
6 months	15.6 (1.0)	18.4 (1.1)	-15% (-28 to 0%)	
12 months	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 (mmHg)				
Randomisation	146 (1.1)	146 (1.1)		
1 month	129 (1.1)	132 (1.1)	-3.5 (-6.5 to -0.6)	
3 months	129 (1.1)	137 (1.1)	-7.3 (-10.3 to -4.3)	
6 months	128 (1.1)	135 (1.1)	-6.9 (-10.0 to -3.7)	
9 months	130 (1.2)	134 (1.2)	-4.0 (-7.3 to -0.8)	
12 months	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 (mmHg)				
Randomisation	81 (0.8)	80 (0.8)		
1 month	73 (0.6)	74 (0.6)	-0.8 (-2.5 to 0.9)	
3 months	73 (0.6)	76 (0.6)	-2.6 (-4.3 to -0.9)	
6 months	72 (0.6)	75 (0.6)	-2.5 (-4.2 to -0.8)	
9 months	73 (0.6)	74 (0.6)	-1.8 (-3.6 to -0.1)	
12 months	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)				
Randomisation	254.5 (22)	250.9 (22)		

Follow-up visit	Mean (SE)*		Difference in means (95% CI)†	p value
	Sacubitril/valsartan (n=207)	Irbesartan (n=207)		
6 months	175.6 (7.2)	219.7 (8.9)	-20% (-29 to -11%)	
12 months	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)				
Randomisation	7.3 (0.5)	7.5 (0.5)		
6 months	5.4 (0.2)	6.6 (0.2)	-19% (-27 to -10%)	
12 months	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 (approx 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 analysis of covariance with adjustment for the randomisation value.

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

CKD-EPI=Chronic kidney disease Epidemiology Collaboration. eGFR=estimated glomerular filtration rate. Based on local laboratory measurements. *compared to eGFR at randomisation visit.

Figure Legends

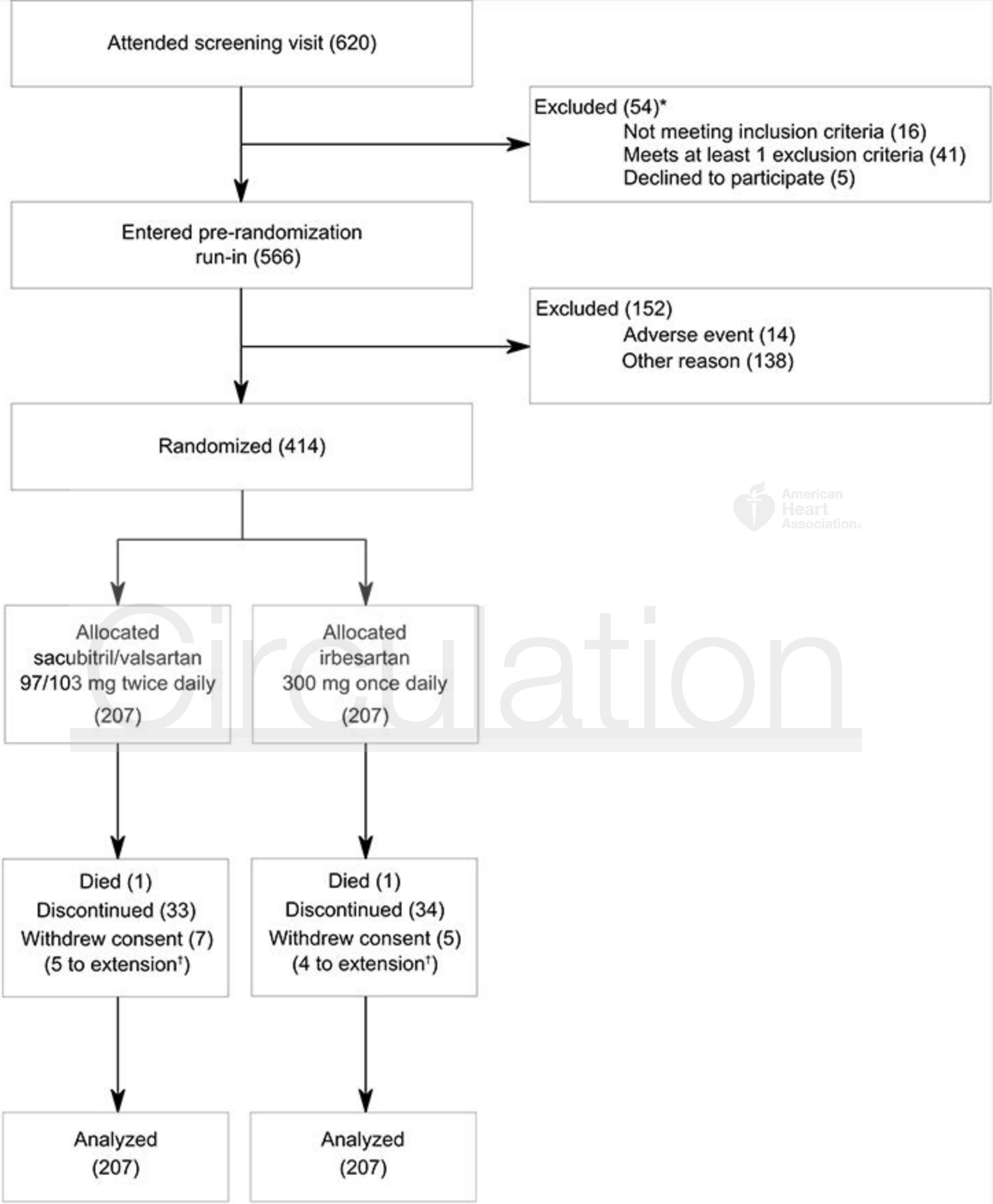
Figure 1. Flow of participants

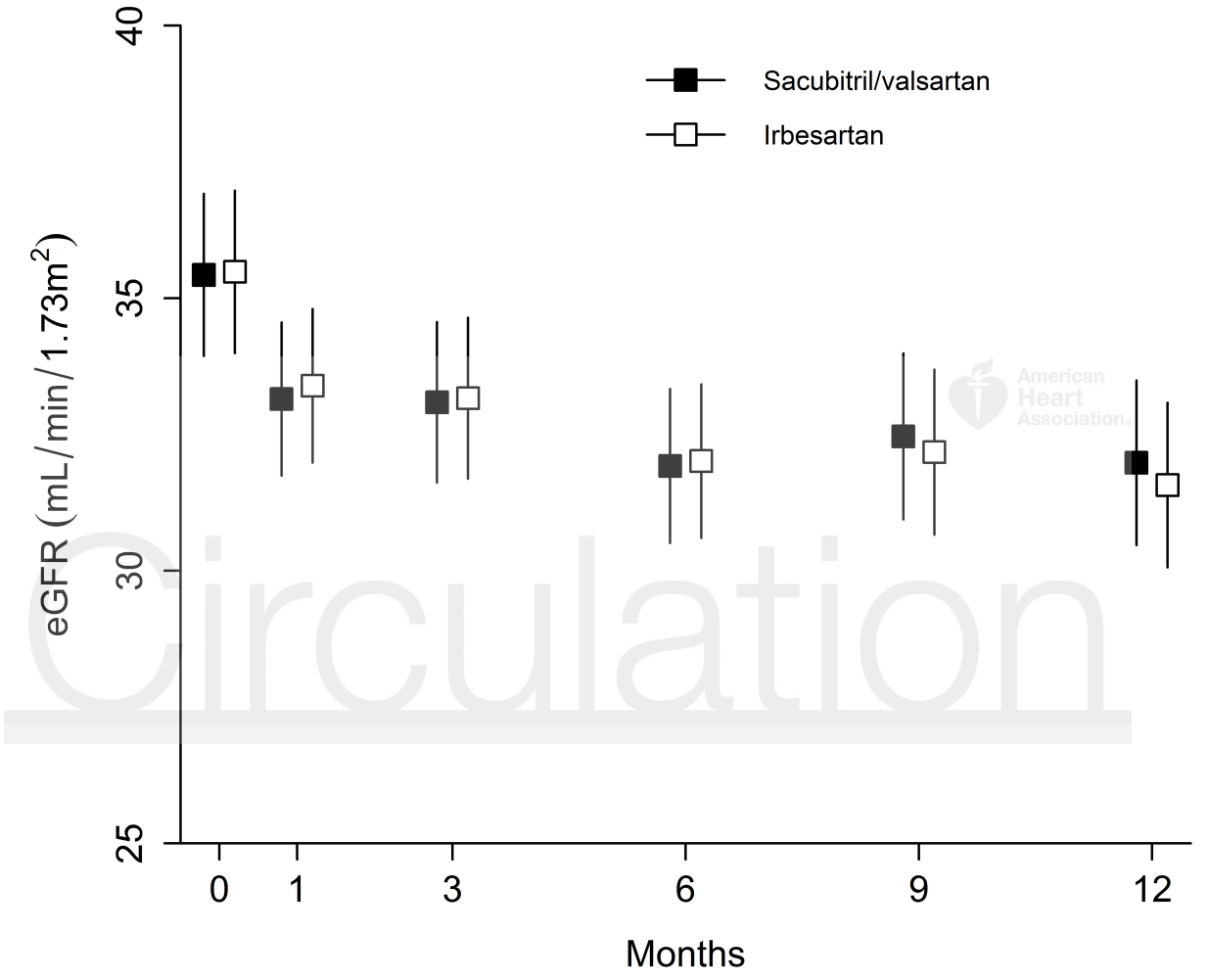
* Participants could report more than one reason

† The duration of the trial was increased from 6 to 12 months and 9 participants did not consent to this extension so completed follow-up at 6 months.

Figure 2. Effect of allocation to sacubitril/valsartan versus irbesartan on estimated glomerular filtration rate

Creatinine measured in central laboratory except for 1 and 9 month visits when creatinine was measured in local laboratory. Error bars presented are 95% confidence intervals.





eGFR (mL/min/1.73m^2)						
Sacubitril/valsartan	35.4	33.1	33.1	31.9	32.5	32.0
Irbesartan	35.5	33.4	33.2	32.0	32.2	31.6

Effects of Sacubitril/Valsartan Versus Irbesartan in Patients with Chronic Kidney Disease: A Randomised Double-Blind Trial

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Effects of Sacubitril/Valsartan Versus Irbesartan in Patients with Chronic Kidney Disease: A Randomised Double-Blind Trial

Running Title: *Haynes et al.; Effects of Sacubitril/Valsartan in CKD*

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Abstract

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—UK HARP-III was a randomised double-blind trial which included 414 participants with an estimated glomerular filtration rate (GFR) 20-60 mL/min/1.73m^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 (mGFR) at 12 months using analysis of covariance with adjustment for each individual's baseline mGFR. All analyses were by intention to treat. This trial is registered at ISRCTN11958993.
Results—207 participants were assigned to sacubitril/valsartan and 207 to irbesartan. Baseline mGFR was 34.0 (0.8) and 34.7 (0.8) mL/min/1.73m² respectively. At 12 months there was no difference in measured GFR: 29.8 (SE 0.5) among those assigned sacubitril/valsartan versus 29.9 (0.5) mL/min/1.73m^2 among those assigned irbesartan; difference -0.1 (0.7) mL/min/1.73m^2. Effects were similar in all pre-specified 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 to 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) mmHg, and levels of troponin I and N-terminal of pro-hormone brain natriuretic peptide (tertiary endpoints) by 16% (95% CI 8-23) and 18% (95% CI 11-25), respectively. The incidence of serious adverse events (29.5% vs 28.5%; rate ratio [RR] 1.07, 95% CI 0.75-1.53), non-serious adverse reactions (36.7% vs 28.0%; RR 1.35, 95% CI 0.96-1.90) and potassium ≥ 5.5 mmol/L (32% vs 24%; p=0.10) were not significantly different between randomized groups.
Conclusions—Over 12 months, sacubitril/valsartan has similar effects on kidney function and albuminuria to irbesartan, but has the additional effect of lowering blood pressure and cardiac biomarkers in people with chronic kidney disease.
Clinical Trial Registration—URL: www.isrctn.com Unique Identifier: ISRCTN11958993

Key Words: Chronic kidney disease; neprilysin inhibition; renin-angiotensin system

Clinical Perspective

What is new?

- UK HARP-III has demonstrated that, in a wide range of people with proteinuric CKD, adding neprilysin inhibition to angiotensin II receptor blockade has no additional effect on kidney function or albuminuria compared to irbesartan.
- The tolerability and safety profiles of the two treatments were not different, but as compared to irbesartan, sacubitril/valsartan further reduces both blood pressure and biomarkers of cardiovascular risk (troponin I and NT-proBNP) compared to irbesartan.

What are the clinical implications?

- UK HARP-III raises a 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.

Introduction

Patients with chronic kidney disease (CKD) are at increased risk of both progression to end-stage renal disease (ESRD) and cardiovascular events, compared to patients with normal kidney function.[1-3] Randomised controlled trials have shown that renin-angiotensin system (RAS) inhibitors slow the progression of diabetic and non-diabetic proteinuric CKD,[4-7] and lowering low density lipoprotein cholesterol reduces the risk of atherosclerotic vascular events.[8] However, despite such treatments, there remains a significant risk of progression to ESRD and cardiovascular events. 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 ESRD.[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 neprilysin (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 (ACEi) are associated with a high risk of angioedema (due to excessive inhibition of bradykinin degradation),[13] so the chosen method of RAS inhibition for user with NEPi is an angiotensin receptor blockers (ARB). Sacubitril/valsartan, which combines an ARB (valsartan) with a NEPi (sacubitril), was the first angiotensin receptor-neprilysin inhibitor (ARNI) to be developed.

The Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) showed that sacubitril/valsartan reduced the risk of cardiovascular mortality among patients with heart failure with reduced ejection fraction when compared to ACEi (enalapril) (HR 0.80; 95% confidence interval 0.71-0.89).[14] Several trials in heart failure populations, 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 United Kingdom Heart and Renal Protection (UK HARP)-III trial aimed to compare the effects of sacubitril/valsartan versus irbesartan (a licenced ARB 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 prior to the enrolment of any study participants. Participants aged 18 years and older were eligible to participate if they had chronic kidney disease with either (i) an estimated glomerular filtration rate (eGFR) of ≥45 and <60 mL/min/1.73m^2 and a urine albumin:creatinine ratio (uACR) >20 mg/mmol (177 mg/g); or (ii) 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 pre-randomisation run-in phase, during which they took one placebo sacubitril/valsartan tablet and one placebo irbesartan capsule daily. The aims of the run-in phase were to (i) enable a 'wash out' of any ACEi prior to introduction of NEPi (to reduce the risk of angioedema), (ii) allow a comparison of the acute effects of the study treatments on eGFR and (iii) identify and exclude those less likely to adhere to study treatment and trial procedures prior to randomisation in order to maintain statistical sensitivity.[24, 25]

Randomisation and masking

At the end of the run-in period, GFR was measured and willing and eligible participants were randomized 1:1 to sacubitril/valsartan or irbesartan by an internet-based system with minimized randomisation (which helped ensure balance for categories of age, sex, systolic blood pressure, previous diabetes, 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 two bottles of study treatments, one containing sacubitril/valsartan 97/103mg or placebo tablets and the other containing irbesartan 150mg or placebo capsules.[27]

Procedures

Following randomisation, participants were initially instructed to take one tablet and one capsule daily of study treatment (i.e. either sacubitril/valsartan 97/103mg or irbesartan 150mg); this was increased to sacubitril/valsartan 97/103mg twice daily or irbesartan 300mg once daily after two

weeks unless potassium or change in kidney function precluded a dose increase. Study visits were scheduled at 1, 3, 6, 9 and 12 months post-randomisation (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 non-serious 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 N-terminal pro-hormone of B-type natriuretic peptide, NT-proBNP) were conducted at randomisation, 6 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 prior to the 12 month visit, and paper results of all GFR measurements were sent to the coordinating centre 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 carers wherever possible. The original protocol specified that 360 participants would be followed for 6 months; prior to 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 the effect on kidney function may take at least 9 months to fully emerge) and to increase the sample size to at least 400 participants (to increase the statistical power).

Laboratory methods

GFR was measured in the study centres using ^{51}Cr-EDTA, ^{99m}Tc-DTPA or iohexol methods depending on local practice (with each centre using the same method used at baseline and 12 months). Creatinine was assayed in the central laboratory on a Beckman Coulter AU680 analyser 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), Analysis of covariance (ANCOVA) was used to compare mean mGFR at 12 months between sacubitril/valsartan and irbesartan-allocated patients, with adjustment for each individual's baseline mGFR.[28] Assuming a between-person standard deviation (SD) in mGFR of 15 mL/min/1.73m^2 and a correlation between an individual's baseline and follow-up mGFR of 0.8, randomisation of 400 participants would provide at least 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/1.73m^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 (RRs), 95% confidence intervals (CIs) and associated two-sided p values. [29, 30] Pharmacokinetic analyses involved multiple linear

regression of each sacubitril/valsartan metabolite against a number of pre-specified 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 10-16 hours prior to the sample being collected. Further details (including secondary and tertiary outcomes) are available in the pre-specified data analysis plan.[23] Analyses were done using SAS version 9.3 (SAS Institute, Cary) and R version 3.3.3 (www.R-Project.org).

Sources of Funding

The UK HARP-III trial was designed, conducted, and analysed by the MRC Population Health Research Unit, which is part of the Clinical Trial Service Unit and Epidemiological Studies Unit. The University of Oxford was the independent regulatory sponsor for the study. The study was funded by a grant to the University of Oxford from Novartis (manufacturers of sacubitril/valsartan). The funder had no involvement in the study conduct, analysis or the decision to submit for publication. All authors accept full responsibility for the content of this paper. The first author had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Clinical Trial Registration

The trial is registered at ISRCTN11958993 (www.isrctn.com)

Results

Between 1st November 2014 and 31st January 2016, 620 participants attended screening visits and 566 (91%) entered the pre-randomisation run-in (Figure 1). 414 participants were randomized: 207 to sacubitril/valsartan and 207 to irbesartan. Mean age was 62.8 years (SD

13.7), 298 (72%) were male and mean blood pressure was 146/81 mmHg (Table 1). Mean eGFR at baseline was 35.5 (10.9) mL/min/1.73m² and 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%] 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 due to serious adverse events, non-serious adverse reactions or other reasons in thos allocated sacubitril/valsartan (Supplementary Table 1).

At 12 months, the mean (SE) mGFR was 29.8 (0.5) mL/min/1.73m² among those assigned sacubitril/valsartan group compared with 29.9 (0.5) mL/min/1.73m² among those assigned irbesartan, a non-significant difference of 0.1 (0.7) mL/min/1.73m² (P=0.86; Table 2). Neither a pre-specified complete case analysis (i.e. without imputation: difference -0.4 (0.7) mL/min/1.73m²) nor an "on treatment" analysis (difference -0.5 (0.7) mL/min/1.73m²) 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), by 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 pre-specified baseline characteristic (Supplementary Figure 1).

As compared to 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 randomisation to 12 months, from randomisation to 3 months or from 3 to 12 months (Supplementary Table 2).

Allocation to sacubitril/valsartan produced a non-significant 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, mean systolic blood pressure was 5.4 (95% CI -7.4 to -3.4) mmHg lower, and mean diastolic blood pressure was 2.1 (95% CI -3.3 to -1.0) mmHg lower among those allocated to sacubitril/valsartan (Table 3). Exploratory analyses did not show any differences in the intensity of non-study anti-hypertensive agents between the treatment arms during follow-up.

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 10-16 hours previously, no significant determinants of sacubitril or valsartan concentration were identified (Supplementary Table 3). However, kidney function was a major determinant of sacubitrilat concentration, with each 10 mL/min lower mGFR being associated with a 1485 (572-2397) ng/mL higher sacubitrilat concentration (Supplementary Table 3).

Allocation to sacubitril/valsartan had no significant effect on fatal serious adverse events (1 [0.5%] vs 1 [0.5%]) or on any non-fatal serious adverse events (61 [29.5%] vs 59 [28.5%]; RR 1.07 [0.75-1.53]; p=0.70) (Supplementary Table 4). One case of angioedema occurred in a participant allocated sacubitril/valsartan, but they did not attend hospital or require any specific treatment. There was no difference overall in the number of non-serious adverse reactions (76 [36.7%] vs 58 [28.0%]; RR 1.35 [0.96-1.90]; p=0.08) (Supplementary Table 4). Allocation to sacubitril/valsartan was associated with higher rates of non-serious hypotension (17 [8.2%] vs 7 [3.4%]; RR 2.36 [1.06-5.26]; p=0.04). There was no difference between treatments in the number of participants experiencing hyperkalaemia (66 [32%] vs 50 [24%]; p=0.10) or in the

proportion experiencing a significant decline in eGFR (defined as 25% or greater reduction; 71 [34%] vs 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 to 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 to irbesartan.

The kidney function results from UK HARP-III 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 (HFpEF), kidney function declined more slowly with sacubitril/valsartan compared with valsartan.[15] In the large PARADIGM-HF trial, a marginally slower decline in eGFR was also observed with sacubitril/valsartan compared with enalapril (-1.3 [-1.2 to -1.4] versus -1.8 [-1.8 to -1.7] mL/min/1.73m^2 per year; p<0.0001).[16] The lack of any additional effect of sacubitril/valsartan on kidney function in UK HARP-III may reflect differing determinants of kidney disease progression in a proteinuric CKD population compared to 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 which improves cardiac function, like 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 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 haemodynamic 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, by 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 since albuminuria is associated with increased risk of progression to ESRD (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 one other anti-hypertensive 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 good 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 (i.e. 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 NTpro-BNP (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 non-serious adverse reactions in the sacubitril/valsartan group this difference was not statistically significant. These randomised comparisons follow a placebo run-in during which 152/566 (26%) of participants withdrew, mostly for non-medical reasons.[23] Compared to those allocated to irbesartan, there were more reports of symptoms of hypotension among participants allocated sacubitril/valsartan, 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 hyperkalaemia 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) might also have an effect on the interpretation of the results as it has a different pharmacological profile to valsartan and may provide more intense angiotensin receptor blockade.[48] This would suggest the additional BP reduction and effects on cardiac biomarkers are an underestimate of the effect of neprilysin inhibition.

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

Declaration of interests

CTSU has a staff policy of not accepting honoraria or other payments from the pharmaceutical industry, expect for the reimbursement of costs to participate in scientific meetings (www.ctsu.ox.ac.uk). JJVM's employer, Glasgow University, has been paid by Novartis for his time spent as Principal Investigator/Executive/Steering committee member for a number of clinical trials using sacubitril/valsartan and meetings and lectures related to sacubitril/valsartan. The other authors have no conflicts of interest to declare. The trial was supported by Novartis Pharma AG, the Medical Research Council (which funds the Medical Research Council

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References

1. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K and Wen CP. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet*. 2013;382:339-352.
2. Go AS, Chertow GM, Fan D, McCulloch CE and Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *New Engl J Med*. 2004;351:1296-1305.
3. Foley RN, Parfrey PS and Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kid Dis*. 1998;32:S112-S119.
4. Lewis EJ, Hunsicker LG, Bain RP and Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *New Engl J Med*. 1993;329:1456-1462.
5. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, Scolari F, Schena FP and Remuzzi G. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet*. 1999;354:359-364.
6. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I and Collaborative Study G. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *New Engl J Med*. 2001;345:851-860.
7. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S and Investigators RS. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861-869.
8. Cholesterol Treatment Trialists Collaboration, Herrington WG, Emberson J, Mihaylova B, Blackwell L, Reith C, Solbu MD, Mark PB, Fellstrom B, Jardine AG, Wanner C, Holdaas H, Fulcher J, Haynes R, Landray MJ, Keech A, Simes J, Collins R and Baigent C. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. *Lancet Diabetes Endocrinol*. 2016;4:829-839.

9. O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS, Walter LC, Mehta KM, Steinman MA, Allon M, McClellan WM and Landefeld CS. Age Affects Outcomes in Chronic Kidney Disease. *J Am Soc Nephrol*. 2007;18:2758-2765.
10. Wilkins MR, Redondo J and Brown LA. The natriuretic-peptide family. *Lancet*. 1997;349:1307-1310.
11. de Bold AJ. Atrial natriuretic factor: a hormone produced by the heart. *Science*. 1985;230:767-770.
12. Benigni A, Zoja C, Zatelli C, Corna D, Longaretti L, Rottoli D, Maggioni P, Todeschini M, Noris M and Remuzzi G. Vasopeptidase inhibitor restores the balance of vasoactive hormones in progressive nephropathy. *Kidney Int*. 2004;66:1959-1965.
13. Kostis JB, Packer M, Black HR, Schmieder R, Henry D and Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens*. 2004;17:103-111.
14. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Investigators P-H and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *New Engl J Med*. 2014;371:993-1004.
15. Voors AA, Gori M, Liu LC, Claggett B, Zile MR, Pieske B, McMurray JJ, Packer M, Shi V, Lefkowitz MP, Solomon SD and Investigators P. Renal effects of the angiotensin receptor neprilysin inhibitor LCZ696 in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail*. 2015;17:510-517.
16. Packer M, Claggett B, Lefkowitz MP, McMurray JJV, Rouleau JL, Solomon SD and Zile MR. Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial. *Lancet Diabetes Endocrinol*. 2018;6:547-554. doi 10.1016/S2213-8587(18)30100-1
17. Solomon SD, Claggett B, McMurray JJ, Hernandez AF and Fonarow GC. Combined neprilysin and renin-angiotensin system inhibition in heart failure with reduced ejection fraction: a meta-analysis. *Eur J Heart Fail*. 2016;18:1238-1243.
18. Taal MW, Nenov VD, Wong WC, Satyal SR, Sakharova O, Choi JH, Troy JL and Brenner BM. Vasopeptidase inhibition affords greater renoprotection than angiotensin-converting enzyme inhibition alone. *J Am Soc Nephrol*. 2001;12:2051-2059.
19. Cao Z, Burrell LM, Tikkanen I, Bonnet F, Cooper ME and Gilbert RE. Vasopeptidase inhibition attenuates the progression of renal injury in subtotal nephrectomized rats. *Kidney Int*. 2001;60:715-721.
20. Davis BJ, Johnston CI, Burrell LM, Burns WC, Kubota E, Cao Z, Cooper ME and Allen TJ. Renoprotective effects of vasopeptidase inhibition in an experimental model of diabetic nephropathy. *Diabetologia*. 2003;46:961-971.
21. Roksnoer LC, van Veghel R, van Groningen MC, de Vries R, Garrelds IM, Bhaggoe UM, van Gool JM, Friesema EC, Leijten FP, Hoorn EJ, Danser AH and Batenburg WW. Blood pressure-independent renoprotection in diabetic rats treated with AT1 receptor-neprilysin inhibition compared with AT1 receptor blockade alone. *Clinical Science* 2016;130:1209-1220.
22. Nuffield Department of Population Health. Data Access and Sharing Policy. https://www.ndph.ox.ac.uk/about/data-access-policy. 2018.
23. Judge PK, Haynes R, Herrington WG, Storey BC, Staplin N, Bethel A, Bowman L, Brunskill N, Cockwell P, Dayanandan R, Hill M, Kalra PA, McMurray JJ, Taal M, Wheeler DC, Landray MJ and C B. Randomized multicentre pilot study of sacubitril/valsartan versus

irbesartan in patients with chronic kidney disease: United Kingdom Heart and Renal Protection (HARP)- III-rationale, trial design and baseline data. *Nephrol Dial Transplant.* 2017; 32: 2043-2051
24. Lang JM. The use of a run-in to enhance compliance. *Stat Med*. 1990;9:87-93.
25. Lang JM, Buring JE, Rosner B, Cook N and Hennekens CH. Estimating the effect of the run-in on the power of the Physicians' Health Study. *Stat Med*. 1991;10:1585-1593.
26. Pocock SJ and Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975;31:103-115.
27. Schulz KF, Chalmers I, Hayes RJ and Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *J Am Med Assoc*. 1995;273:408-412.
28. Borm GF, Fransen J and Lemmens WA. A simple sample size formula for analysis of covariance in randomized clinical trials. *J Clin Epidemiol*. 2007;60:1234-1238.
29. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J and Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer*. 1976;34:585-612.
30. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J and Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. *Br J Cancer*. 1977;35:1-39.
31. Rubin D. *Multiple imputation for non-response in surveys.*: New York: John Wiley; 1987.
32. Ushijima K, Ando H, Arakawa Y, Aizawa K, Suzuki C, Shimada K, Tsuruoka SI and Fujimura A. Prevention against renal damage in rats with subtotal nephrectomy by sacubitril/valsartan (LCZ696), a dual-acting angiotensin receptor-neprilysin inhibitor. *Pharmacology Research Perspect*. 2017;5: doi: 10.1002/prp2.336.
33. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M and Alberta Kidney Disease N. Relation between kidney function, proteinuria, and adverse outcomes. *J Am Med Assoc*. 2010;303:423-429.
34. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J and Chronic Kidney Disease Prognosis C. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*. 2011;80:93-104.
35. Mafham MM, Staplin N, Emberson J, Haynes R, Herrington W, Reith C, Wanner C, Walker R, Cass A, Levin A, Fellstrom B, Jiang L, Holdaas H, Kasiske B, Wheeler DC, Landray MJ, Baigent C and Group SC. Prognostic utility of estimated albumin excretion rate in chronic kidney disease: results from the Study of Heart and Renal Protection. *Nephrol Dial Transplant*. 2018; 33: 257-264.
36. Ruilope LM, Dukat A, Bohm M, Lacourciere Y, Gong J and Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet*. 2010;375:1255-1266.
37. Williams B, Cockcroft JR, Kario K, Zappe DH, Brunel PC, Wang Q and Guo W. Effects of Sacubitril/Valsartan Versus Olmesartan on Central Hemodynamics in the Elderly With Systolic Hypertension: The PARAMETER Study. *Hypertension*. 2017; 69: 411-420.
38. Kario K, Sun N, Chiang FT, Supasyndh O, Baek SH, Inubushi-Molessa A, Zhang Y, Gotou H, Lefkowitz M and Zhang J. Efficacy and Safety of LCZ696, a First-in-Class

Angiotensin Receptor Neprilysin Inhibitor, in Asian Patients With Hypertension: A Randomized, Double-Blind, Placebo-Controlled Study. *Hypertension*. 2014;63:698-705.
39. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ and Prospective comparison of AwARBoMOhfwpefI. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380:1387-1395.
40. Lv J, Ehteshami P, Sarnak MJ, Tighiouart H, Jun M, Ninomiya T, Foote C, Rodgers A, Zhang H, Wang H, Strippoli GF and Perkovic V. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *Can Med Assoc J*. 2013;185:949-957.
41. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A and Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957-967.
42. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J and Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073-2081.
43. Park M, Hsu CY, Li Y, Mishra RK, Keane M, Rosas SE, Dries D, Xie D, Chen J, He J, Anderson A, Go AS, Shlipak MG and Chronic Renal Insufficiency Cohort Study G. Associations between kidney function and subclinical cardiac abnormalities in CKD. *J Am Soc Nephrol*. 2012;23:1725-1734.
44. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC and Barre PE. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int*. 1995;47:186-192.
45. Jhund PS, Claggett BL, Voors AA, Zile MR, Packer M, Pieske BM, Kraigher-Krainer E, Shah AM, Prescott MF, Shi V, Lefkowitz M, McMurray JJ, Solomon SD and Investigators P. Elevation in high-sensitivity troponin T in heart failure and preserved ejection fraction and influence of treatment with the angiotensin receptor neprilysin inhibitor LCZ696. *Circulation Heart Fail*. 2014;7:953-959.
46. Packer M, McMurray JJ, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile M, Andersen K, Arango JL, Arnold JM, Belohlavek J, Bohm M, Boytsov S, Burgess LJ, Cabrera W, Calvo C, Chen CH, Dukat A, Duarte YC, Erglis A, Fu M, Gomez E, Gonzalez-Medina A, Hagege AA, Huang J, Katova T, Kiatchoosakun S, Kim KS, Kozan O, Llamas EB, Martinez F, Merkely B, Mendoza I, Mosterd A, Negrusz-Kawecka M, Peuhkurinen K, Ramires FJ, Refsgaard J, Rosenthal A, Senni M, Sibulo AS, Jr., Silva-Cardoso J, Squire IB, Starling RC, Teerlink JR, Vanhaecke J, Vinereanu D, Wong RC, Investigators P-H and Coordinators. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation*. 2015;131:54-61.
47. Suematsu Y, Jing W, Nunes A, Kashyap ML, Khazaeli M, Vaziri ND and Moradi H. LCZ696 (Sacubitril/valsartan), an Angiotensin-Receptor Neprilysin Inhibitor, Attenuates Cardiac Hypertrophy, Fibrosis and Vasculopathy in a Rat Model of Chronic Kidney Disease. *J Card Fail*. 2018; 24: 266-275.
48. Belz GG, Breithaupt-Grogler K, Butzer R, Fuchs W, Hausdorf C and Mang C. The pharmacological potency of various AT(1) antagonists assessed by Schild regression technique in man. *J Renin Angiotensin Aldosterone Syst*. 2000;1:336-341.

Table 1. Baseline characteristics by randomised treatment allocation

	Sacubitril/valsartan (n=207)	Irbesartan (n=207)
Age at randomisation (years)	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 randomisation (mmHg)	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 randomisation (mmHg)	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)	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%)
Beta blocker	50 (24%)	62 (30%)
Alpha 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 randomisation (mL/min/1.73m^2)		

	Sacubitril/valsartan (n=207)	Irbesartan (n=207)
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 randomisation (mg/mmol)		
Geometric mean (approx 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 hour urinary sodium excretion during run-in (mg/24 hours)		
Geometric mean (approx SE)	2245 (183)	2585 (187)
Median (IQR)	2484 (1794-3795)	2875 (1932-4232)
Not available	100	110

Values are n (%), mean (SD), geometric mean (approx SE) or median (IQR). RAS=Renin–angiotensin system. CKD-EPI=Chronic kidney disease Epidemiology Collaboration. *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.

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/1.73m²)		Difference in means (SE)*	p value
	Sacubitril/valsartan (n=207)	Irbesartan (n=207)		
Randomisation	34.0 (0.8)	34.7 (0.8)		
12 months	29.8 (0.5)	29.9 (0.5)	-0.1 (0.7)	0.86

mGFR=measured glomerular filtration rate. Where the difference between mGFR and central eGFR at the corresponding time point was more extreme than the 1st or 99th centile of the distribution of differences, the value of mGFR was set to missing. 10 missing mGFR values at randomisation had eGFR values at randomisation imputed and 41 missing mGFR values at 12 months 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 month mGFR. *Values are absolute differences in arithmetic means (SE). The 12 month estimates and p values were derived from analysis of covariance with adjustment for the randomisation value.

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)				
Randomisation	34.1 (4.6)	33.9 (4.5)		
3 months	17.0 (1.0)	17.8 (1.0)	-4% (-19 to 12%)	
6 months	15.6 (1.0)	18.4 (1.1)	-15% (-28 to 0%)	
12 months	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 (mmHg)				
Randomisation	146 (1.1)	146 (1.1)		
1 month	129 (1.1)	132 (1.1)	-3.5 (-6.5 to -0.6)	
3 months	129 (1.1)	137 (1.1)	-7.3 (-10.3 to -4.3)	
6 months	128 (1.1)	135 (1.1)	-6.9 (-10.0 to -3.7)	
9 months	130 (1.2)	134 (1.2)	-4.0 (-7.3 to -0.8)	
12 months	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 (mmHg)				
Randomisation	81 (0.8)	80 (0.8)		
1 month	73 (0.6)	74 (0.6)	-0.8 (-2.5 to 0.9)	
3 months	73 (0.6)	76 (0.6)	-2.6 (-4.3 to -0.9)	
6 months	72 (0.6)	75 (0.6)	-2.5 (-4.2 to -0.8)	
9 months	73 (0.6)	74 (0.6)	-1.8 (-3.6 to -0.1)	
12 months	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)				
Randomisation	254.5 (22)	250.9 (22)		

Follow-up visit	Mean (SE)*		Difference in means (95% CI)†	p value
	Sacubitril/valsartan (n=207)	Irbesartan (n=207)		
6 months	175.6 (7.2)	219.7 (8.9)	-20% (-29 to -11%)	
12 months	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)				
Randomisation	7.3 (0.5)	7.5 (0.5)		
6 months	5.4 (0.2)	6.6 (0.2)	-19% (-27 to -10%)	
12 months	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 (approx 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 analysis of covariance with adjustment for the randomisation value.

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

CKD-EPI=Chronic kidney disease Epidemiology Collaboration. eGFR=estimated glomerular filtration rate. Based on local laboratory measurements. *compared to eGFR at randomisation visit.

Figure Legends

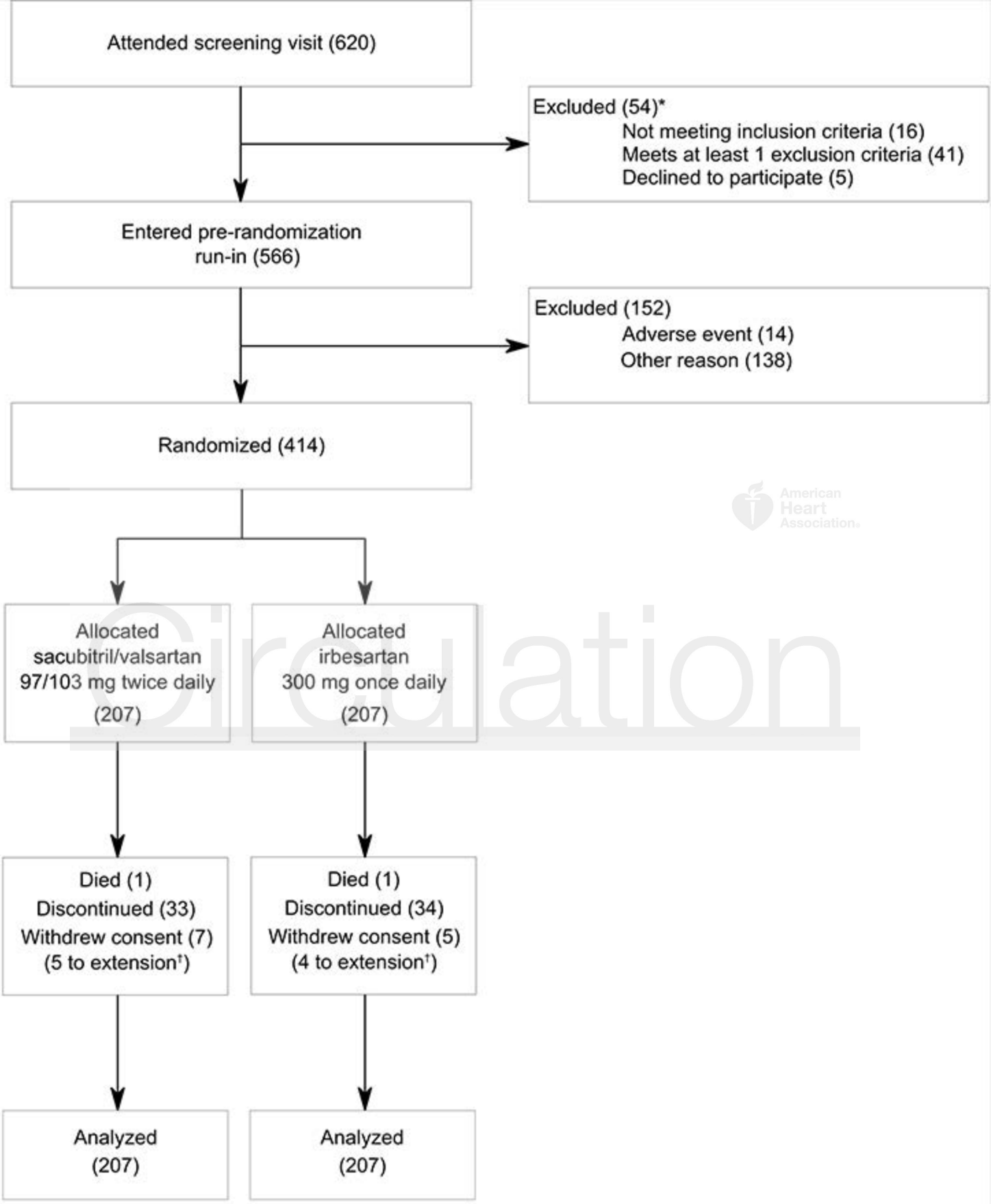
Figure 1. Flow of participants

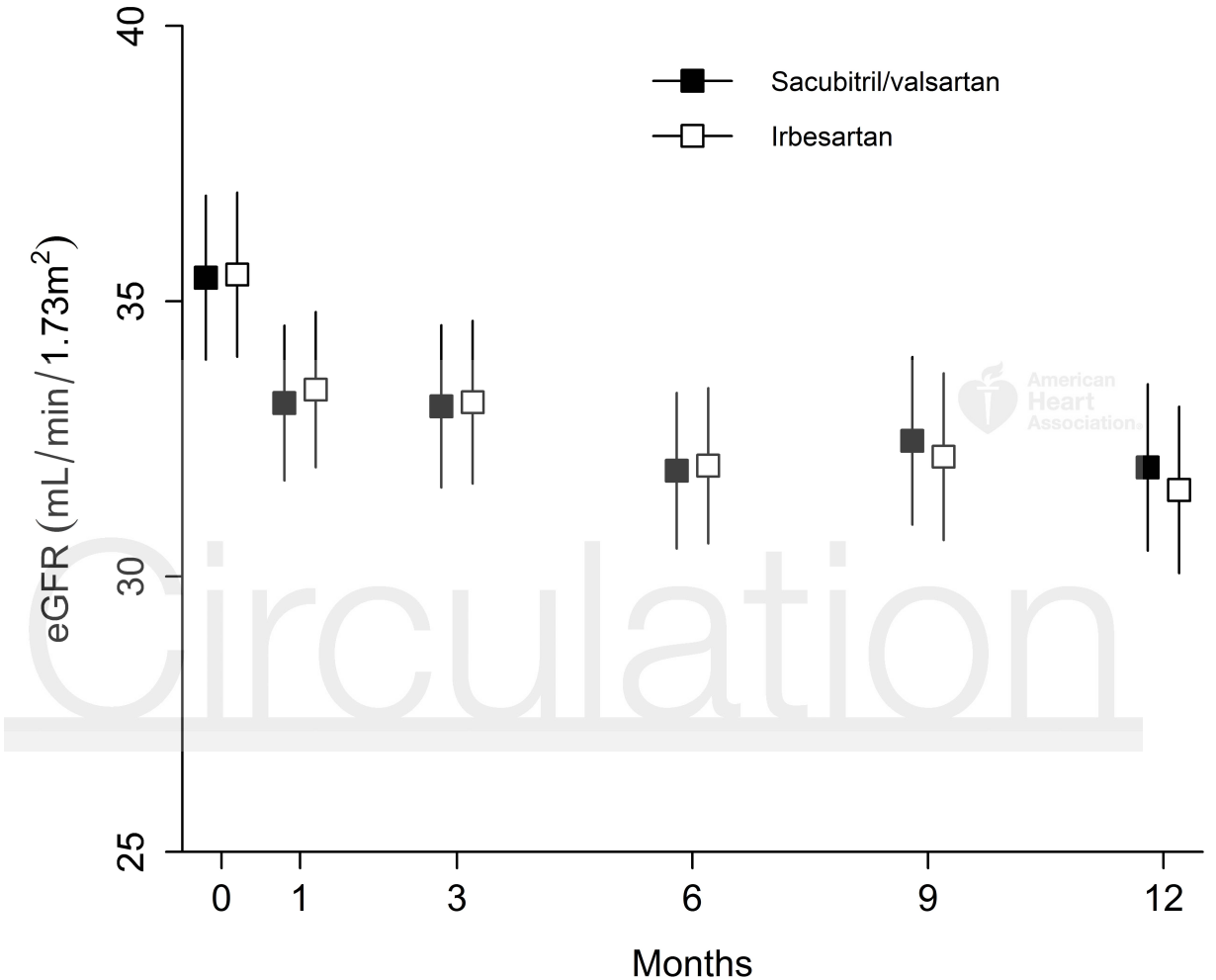
* Participants could report more than one reason

† The duration of the trial was increased from 6 to 12 months and 9 participants did not consent to this extension so completed follow-up at 6 months.

Figure 2. Effect of allocation to sacubitril/valsartan versus irbesartan on estimated glomerular filtration rate

Creatinine measured in central laboratory except for 1 and 9 month visits when creatinine was measured in local laboratory. Error bars presented are 95% confidence intervals.


Attended screening visit (620)
Excluded (54)*
Not meeting inclusion criteria (16)
Meets at least 1 exclusion criteria (41)
Declined to participate (5)
Entered pre-randomization run-in (566)
Excluded (152)
Adverse event (14)
Other reason (138)
Randomized (414)
Allocated sacubitril/valsartan 97/103 mg twice daily (207)
Allocated irbesartan 300 mg once daily (207)
Died (1)
Discontinued (33)
Withdrew consent (7)
(5 to extension†)
Died (1)
Discontinued (34)
Withdrew consent (5)
(4 to extension†)
Analyzed (207)
Analyzed (207)



eGFR (mL/min/1.73m^2)						
Sacubitril/valsartan	35.4	33.1	33.1	31.9	32.5	32.0
Irbesartan	35.5	33.4	33.2	32.0	32.2	31.6