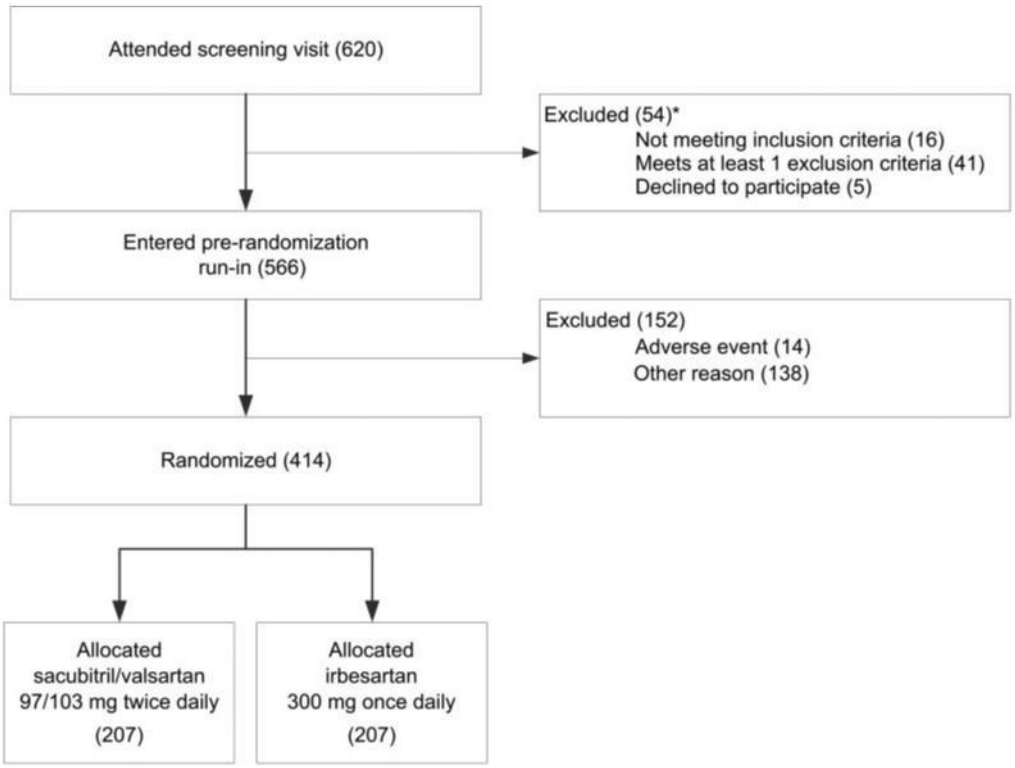
Participant Flow



*Indicates that participants may have more than one reason

Baseline Characteristics

	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%)
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 (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 (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)		
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)		

	Sacubitril/valsartan (n=207)	Irbesartan (n=207)
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.

Outcome measures

Primary outcome measures

Effect of allocation to sacubitril/valsartan on measured glomerular filtration rate at 12 months

Follow-up visit	No. with mGFR value	No. with mGFR value imputed*		Mean mGFR (SE) (mL/min/1.73m^2)			p value
		Dialysis	Other	Sacubitril/valsartan (n=207)	Irbesartan (n=207)	Difference in means (SE)†	
12 months	371	2	41	29.8 (0.5)	29.9 (0.5)	-0.1 (0.7)	0.86

mGFR=measured glomerular filtration rate.
*Missing mGFR values at randomisation had eGFR values at randomisation imputed and missing mGFR values at 12 months were imputed with the use of multiple imputation. For patients who commenced chronic dialysis during the study, a value of 0 was imputed for their 12 month mGFR. 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.
†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.

Secondary outcome measures

Effect of allocation to sacubitril/valsartan on urinary albumin:creatinine ratio

Follow-up visit	No. with value	No. with value imputed*	Mean (SE)§		p value
			Sacubitril/valsartan (n=207)	Irbesartan (n=207)	
Urinary albumin:creatinine ratio (mg/mmol)					
Randomisation	414	0	34.1 (4.6)	33.9 (4.5)	
3 months	396	18	17.0 (1.0)	17.8 (1.0)	0.58
6 months	394	20	15.6 (1.0)	18.4 (1.1)	0.06
12 months	378	36	16.4 (1.2)	17.6 (1.3)	0.52
Study average			16.3 (0.6)	17.9 (0.7)	0.08

CKD-EPI=Chronic kidney disease Epidemiology Collaboration.
*Any missing data were imputed with the use of multiple imputation.
§Geometric means (approx SE) are presented for urinary albumin:creatinine ratio and arithmetic means (SE) are presented for CKD-EPI estimated glomerular filtration rate.

Associations between baseline characteristics and sacubitril/valsartan metabolite values at the 3 month visit

	Sacubitril		Sacubitrilat		Valsartan	
	Percentage change		Absolute change in ng/mL		Percentage change	
Characteristic	(95% CI)	p value	(95% CI)	p value	(95% CI)	p value
Age, per decade higher	22% (1 to 48%)	0.04	889 (-30 to 1808)	0.06	14% (-2 to 33%)	0.09
Race*		0.78		0.71		0.22
Black	-60% (-95 to 252%)		-4856 (-15440 to 5729)		-63% (-94 to 112%)	
Other	-44% (-89 to 175%)		539 (-7208 to 8286)		5% (-71 to 276%)	
South Asian	7% (-71 to 297%)		1947 (-3684 to 7578)		-59% (-84 to 5%)	
Sex†	-25% (-67 to 71%)	0.48	-4413 (-8444 to -381)	0.03	-37% (-67 to 23%)	0.18
Body surface area, per 0.1 m^2 higher	-32% (-64 to 31%)	0.25	-3327 (-6500 to -154)	0.04	-23% (-54 to 31%)	0.34
Weight, per 5 kg higher	20% (-20 to 78%)	0.37	1915 (-25 to 3854)	0.05	13% (-18 to 56%)	0.44
mGFR (unadjusted for BSA), per 10 mL/min/1.73m^2 lower	-17% (-32 to 1%)	0.06	1485 (572 to 2397)	0.002	-3% (-17 to 13%)	0.65
Log albumin:creatinine ratio, per 5-fold increase	-7% (-24 to 13%)	0.44	-622 (-1590 to 346)	0.21	-14% (-27 to 1%)	0.07

mGFR=measured glomerular filtration rate. BSA=body surface area.

Models adjusted for all characteristics shown in table and additionally for time since last dose.

*White ethnicity used as reference category. Race was not prespecified for inclusion in the models.

†Males used as reference category. Values for sacubitril and valsartan were log transformed due to skewed distributions.

Adverse Events

	Sacubitril/valsartan (n=207)	Irbesartan (n=207)	Rate ratio (95% CI)	p value
Any fatal serious adverse event	1 (0.5%)	1 (0.5%)		
Non-fatal serious adverse events				
Angioedema	1 (0.5%)	0 (0.0%)		
Hypotension	1 (0.5%)	1 (0.5%)		
Dialysis	2 (1.0%)	3 (1.4%)		
Other non-fatal SAEs (by MedDRA System, Organ, Class [SOC] category)				
Respiratory, thoracic and mediastinal disorders	6 (2.9%)	6 (2.9%)		
Infection and infestations	16 (7.7%)	15 (7.2%)		
Blood and lymphatics system	2 (1.0%)	2 (1.0%)		
Cardiac disorders	6 (2.9%)	5 (2.4%)		
Gastrointestinal disorders	5 (2.4%)	6 (2.9%)		
Metabolism and nutrition disorders				
Diabetes/glucose	3 (1.4%)	1 (0.5%)		
Other metabolism/nutrition	7 (3.4%)	6 (2.9%)		
Cancer	4 (1.9%)	5 (2.4%)		
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2 (1.0%)	3 (1.4%)		
Nervous system disorders	3 (1.4%)	3 (1.4%)		
Renal and urinary disorders	10 (4.8%)	5 (2.4%)		
Other medical	30 (14.5%)	29 (14.0%)		
Investigations	8 (3.9%)	13 (6.3%)		
Surgical and medical procedures (excluding dialysis)	18 (8.7%)	14 (6.8%)		
Miscellaneous medical*	13 (6.3%)	8 (3.9%)		
Non-medical (including trauma)	7 (3.4%)	5 (2.4%)		
Total: Any non-fatal serious adverse event	61 (29.5%)	59 (28.5%)	1.07 (0.75-1.53)	0.7
Total: Any serious adverse event	61 (29.5%)	59 (28.5%)	1.07 (0.75-1.53)	0.7
Non-serious adverse reactions				
Hypotension	17 (8.2%)	7 (3.4%)	2.36 (1.06-5.26)	0.04
Hyperkalaemia	6 (2.9%)	1 (0.5%)	4.23 (0.96-18.61)	0.06
Acute kidney injury	3 (1.4%)	6 (2.9%)	0.51 (0.14-1.90)	0.32
Other NSAR (by MedDRA System, Organ, Class [SOC] category)				
Respiratory, thoracic and mediastinal disorders	4 (1.9%)	4 (1.9%)		
Gastrointestinal disorders	18 (8.7%)	10 (4.8%)		
Metabolism and nutrition disorders (excluding hyperkalaemia)	3 (1.4%)	1 (0.5%)		
Musculoskeletal and connective tissue disorders	6 (2.9%)	5 (2.4%)		
Nervous system disorders	20 (9.7%)	18 (8.7%)		

	Sacubitril/valsartan (n=207)	Irbesartan (n=207)	Rate ratio (95% CI)	p value
Renal and urinary disorders (excluding acute kidney injury)	2 (1.0%)	2 (1.0%)		
Reproductive system and breast disorders	2 (1.0%)	3 (1.4%)		
Skin and subcutaneous tissue disorders (excluding angioedema)	18 (8.7%)	6 (2.9%)		
Other medical	6 (2.9%)	7 (3.4%)		
Investigations	3 (1.4%)	1 (0.5%)		
Miscellaneous medical**	8 (3.9%)	12 (5.8%)		
Total: Any non-serious adverse reaction* **	76 (36.7%)	58 (28.0%)	1.35 (0.96-1.90)	0.08

SAE=serious adverse event.
NSAR=non-serious adverse reaction.
*Made up of SOC categories: Ear disorders, Endocrine disorders, Eye disorders, Hepatobiliary disorders, Immune system disorders, Musculoskeletal and connective tissue disorders, Psychiatric disorders, Reproductive system and breast disorders, Skin and subcutaneous tissue disorders (excluding angioedema), Vascular disorders (excluding hypotension), Congenital, familial and genetic disorders, General disorders and administration site conditions, and Pregnancy, puerperium and perinatal conditions.
**Made up of SOC categories: Infection and infestations, Blood and lymphatics system, Cardiac disorders, Ear disorders, Endocrine disorders, Eye disorders, Hepatobiliary disorders, Immune system disorders, Cancer, Neoplasms benign, malignant and unspecified (incl. cysts and polyps), Psychiatric disorders, Skin and subcutaneous tissue disorders (excluding angioedema), Vascular disorders (excluding hypotension), Surgical and medical procedures, Congenital, familial and genetic disorders, General disorders and administration site conditions, and Pregnancy, puerperium and perinatal conditions.
***Excluding angioedema.