Randomized multicentre pilot study of sacubitril/valsartan versus irbesartan in patients with chronic kidney disease: United Kingdom Heart and Renal Protection (UK HARP)-III

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Introduction

- Patients with CKD are at increased risk of cardiovascular disease and renal progression.
- Among patients with heart failure, sacubitril/valsartan has been shown to reduce the risk of cardiovascular disease and preserve estimated glomerular filtration rate, but increases albuminuria.[1,2]
- The effects of sacubitril/valsartan in patients with established chronic kidney disease are not known.

Aims

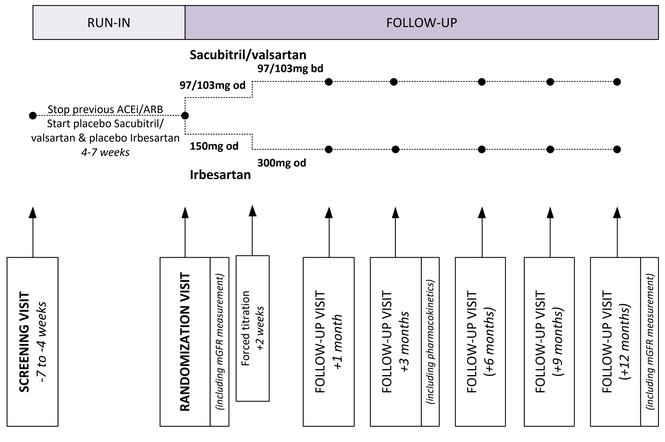
To compare the effects of sacubitril/valsartan and irbesartan on:

- Measured glomerular filtration rate (mGFR)
- Urine albumin:creatinine ratio (uACR)
- Estimated glomerular filtration rate (eGFR)
- Systolic and diastolic blood pressure
- Tolerability and safety

Methods

- Patients were eligible if they met the following criteria:
  - eGFR ≥20 <45 mL/min/1.73m^2; or
  - eGFR ≥45 <60 mL/min/1.73m^2 and uACR >20 mg/mmol
  - Potassium <5.5 mmol/L
  - No history of angioedema or other contraindication to sacubitril/valsartan or irbesartan
- Follow-up visits at 1, 3, 6, 9 and 12 months (Figure 1):
  - Serious adverse events and non-serious adverse reactions collected at each visit
  - Local laboratory measurement of creatinine, potassium, LFTs at each visit
  - Central samples (for creatinine and uACR) at 0, 3, 6 and 12 months
  - Sample for pharmacokinetic analyses at 3 months
  - GFR measured at randomization and 12 months
- Intention-to-treat ANCOVA analysis with multiple imputation for missing data.
- Standard log-rank methods for adverse event analyses

Figure 1: Design of UK HARP-III trial[3]



Results

- Between November 2014 and March 2016, 620 patients were screened at 24 sites across the UK.
- Of the 620 screened participants, 414 were randomized (see Table 1).

Table 1: Baseline characteristics (at Randomization visit)

Characteristic	Sacubitril/valsartan (n=207)	Irbesartan (n=207)
Age, years	62.0 (14.1)	63.6 (13.4)
Men	71%	72%
Systolic/diastolic blood pressure, mmHg	146 (16) / 81 (11)	146 (16) / 80 (11)
Cause of kidney disease		
Glomerular disease	29%	25%
Diabetic kidney disease	17%	23%
Other known cause	35%	36%
Unknown	19%	16%
uACR, mg/mmol (median [IQR])	52 (11-162)	56 (11-146)
eGFR, mL/min/1.73m^2	35.4 (11.0)	35.5 (11.0)

Data are mean (SD) or % unless otherwise indicated

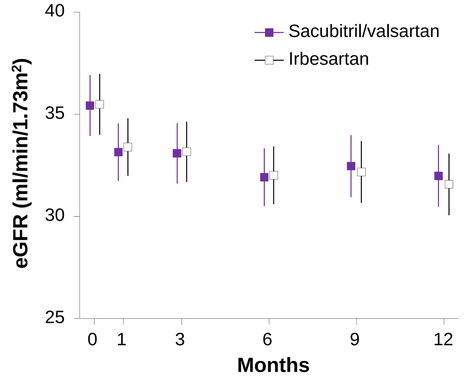
- By 12 months, 21% and 20% had stopped full-dose sacubitril/valsartan or irbesartan respectively.
- **Measured GFR at 12 months did not differ between the two groups: difference in means -0.1 (SE 0.7) mL/min/1.73m^2; p=0.86 (Table 2).**
- There was no evidence that the effect of treatment varied in any subgroup.

Table 2: Primary outcome

Visit	Mean mGFR (SE) (mL/min/1.73m^2) Sacubitril/valsartan (n=207)	Irbesartan (n=207)
Randomization	34.0 (0.8)	34.7 (0.8)
12 months	29.8 (0.5)	29.9 (0.5)

- There was no difference in eGFR at any time point (Figure 2).
- The slopes in eGFR were similar overall (0-12 months), and acutely (0-3 months) and after 3 months (3-12 months).

Figure 2: eGFR by time



- Allocation to sacubitril/valsartan compared to irbesartan was associated with:
  - a non-significant 9% (95% CI -1 to 18) reduction in study average uACR
  - a 5.4 (3.4-7.4) mmHg reduction in study average systolic blood pressure
  - a 2.1 (1.0-3.3) mmHg reduction in study average diastolic blood pressure
  - similar rates of serious adverse events (61 [29.5%] vs 59 [28.5%]; rate ratio 1.07 [0.75-1.53])
  - similar rates of non-serious adverse reactions (76 [36.7%] vs 58 [28.0%]; rate ratio 1.35 [0.96-1.90])
  - a similar proportion of participants experiencing hyperkalaemia (p=0.10) and ≥25% reduction in eGFR (p=0.75) (Table 3)

Table 3: Hyperkalaemia and renal safety

Outcome	Sacubitril/valsartan (n=207)	Irbesartan (n=207)
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%)
Any potassium ≥5.5	66 (32%)	50 (24%)
≥25% reduction in eGFR	71 (34%)	67 (32%)

Conclusions

- Compared to irbesartan, allocation to sacubitril/valsartan had no effect on kidney function over 1 year and did not increase albuminuria.
- Sacubitril/valsartan caused additional reductions in blood pressure compared to irbesartan.
- There was no difference in safety or tolerability between sacubitril/valsartan and irbesartan among patients with CKD.

References
1 JJV McMurray *et al*. New Engl J Med 2014; 371: 993-1004
2 Voors AA *et al*. Eur J Heart Fail 2015; 17: 510-7
3 UK HARP-III Collaborative Group. Nephrol Dial Transplant doi: 10.1093/ndt/gfw321

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UK HARP-III Steering Committee
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