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 $\geq 20 \text{ mL/min/1.73m}^2$; or
  - eGFR $\geq 45 \text{ mL/min/1.73m}^2$ 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 pharmacokinetics 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

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)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sacubitril/valsartan (n=207)</th>
<th>Irbesartan (n=207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62.0 (14.1)</td>
<td>63.6 (13.4)</td>
</tr>
<tr>
<td>Men</td>
<td>71%</td>
<td>72%</td>
</tr>
<tr>
<td>Systolic/diastolic blood pressure, mmHg</td>
<td>146 (16) / 81 (11)</td>
<td>146 (16) / 80 (11)</td>
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<tr>
<td>Cause of kidney disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular disease</td>
<td>29%</td>
<td>25%</td>
</tr>
<tr>
<td>Diabetic kidney disease</td>
<td>17%</td>
<td>23%</td>
</tr>
<tr>
<td>Other known cause</td>
<td>35%</td>
<td>36%</td>
</tr>
<tr>
<td>Unknown</td>
<td>19%</td>
<td>16%</td>
</tr>
<tr>
<td>uACR, mg/mmol (median [IQR])</td>
<td>52 (11-162)</td>
<td>56 (11-146)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>35.4 (11.0)</td>
<td>35.5 (11.0)</td>
</tr>
</tbody>
</table>

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/1.73m², 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/1.73m²) | Sacubitril/valsartan (n=207) | Irbesartan (n=207) |
---------------|--------------------------------|-------------------------------|--------------------|
Randomization  | 34.0 (0.6)                      | 34.7 (0.6)                    |                    |
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

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


Acknowledgements

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