Switching to sacubitril/valsartan or adding aldosterone antagonist: which first?

The PARADIGM-HF trial showed that among patients with symptomatic systolic heart failure (HF), compared with enalapril, adding sacubitril/valsartan to standard therapy was associated with significant reductions of cardiovascular death or HF hospitalization. Consequently, guidelines recommended switching from angiotensin-converting enzyme inhibitor (ACE-I) to sacubitril/valsartan to further reduce the risk of HF hospitalization and death in ambulatory patients with systolic HF who remain symptomatic despite optimal treatment with ACE-I, beta-blocker, and mineralocorticoid receptor antagonist (MRA).

More recently, the TRANSITION trial showed that treatment with sacubitril/valsartan could be initiated early and safely in patients who had been stabilized after hospitalization due to an acute HF episode, independently of prior HF therapy, suggesting that sacubitril/valsartan should be initiated earlier than guidelines recommend. In fact, the recent update on HF 2019 indicates that initiation of sacubitril/valsartan rather than an ACE-I may be considered for patients hospitalized with new-onset HF or decompensated HF.

On the other hand, in the PARADIGM-HF trial, 56% of patients were treated with MRA. Remarkably, the benefit of sacubitril/valsartan over enalapril was independent of the use of MRA. However, it has not been studied whether it is better among HF patients that remain symptomatic despite treatment with ACE-I and beta-blocker, switching to sacubitril/valsartan directly without the previous addition of MRA of, by contrast, delay switching after the addition of MRA. To answer this issue, using the data of PARADIGM-HF, we compared the primary endpoint of the study (cardiovascular death of HF hospitalization) in those patients treated with enalapril with those treated with sacubitril/valsartan according to the use of MRA (Table 1).

As PARADIGM-HF was not specifically performed to answer this question and the baseline clinical profile of patients was quite different according to the use of MRA, only indirect comparisons can be performed. In all cases, treatment with sacubitril/valsartan was better than enalapril. Of note, the primary endpoint occurred more frequently in the enalapril with MRA group than in the group of sacubitril/valsartan without MRA (Figure 1). In addition, as Kaplan–Meier curves showed, the beneficial effect of sacubitril/valsartan compared with enalapril plus MRA increased over time. However, due to the limitations previously commented, these data should be taken with caution.

In summary, despite a specific clinical trial should be performed, these data suggest that among patients with HF and reduced ejection fraction that remain symptomatic despite treatment with ACE-I and beta-blocker, switching to sacubitril/valsartan could be considered before than the addition of MRA.

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Table 1 Cardiovascular death of HF hospitalization according to treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Enalapril vs. sacubitril/valsartan (%)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril with MRA vs. sacubitril/valsartan without MRA</td>
<td>26.0 vs. 20.8</td>
<td>0.75 (0.65–0.87)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Enalapril without MRA vs. sacubitril/valsartan with MRA</td>
<td>27.2 vs. 22.7</td>
<td>0.83 (0.75–0.93)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Enalapril without MRA vs. sacubitril/valsartan without MRA</td>
<td>27.2 vs. 20.8</td>
<td>0.74 (0.65–0.84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Enalapril with MRA vs. sacubitril/valsartan with MRA</td>
<td>26.0 vs. 22.7</td>
<td>0.85 (0.76–0.96)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist.
Figure 1 Cumulative incidence of outcome events (cardiovascular death or HF hospitalization) according to treatments (enalapril plus mineralocorticoid receptor antagonist vs. sacubitril/valsartan without mineralocorticoid receptor antagonist).

References


