Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute Heart Failure Episode - PIONEER-HF

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References

Contribution To Literature:

The PIONEER-HF trial showed that sacubitril/valsartan reduced NT-proBNP to a greater degree than enalapril among eligible patients admitted with acute decompensated HF.

Description:

The goal of the trial was to assess the safety and efficacy of using sacubitril/valsartan among patients hospitalized with acute decompensated HF (ADHF).

Study Design

Eligible patients were randomized in a 1:1 fashion to sacubitril/valsartan (n = 440) or enalapril (n = 441). Initial dose of sacubitril/valsartan was 24/26 or 49/51 mg, and for enalapril was 2.5 or 5 mg, both given orally twice daily. A 36-hour washout period for sacubitril/valsartan was incorporated into the protocol. During the 8-week trial period, the goal was to increase sacubitril/valsartan to 97/103 mg twice daily and enalapril to 10 mg twice daily.

- Total number of enrollees: 881
- Duration of follow-up: 8 weeks
- Mean patient age: 61 years
- Percentage female: 28%

Inclusion criteria:

- Currently hospitalized for ADHF
- Randomized no earlier than 24 hours and up to 10 days after presentation while still hospitalized as long as it meets the following definition of stable status:
  - Systolic blood pressure ≥100 mm Hg for the preceding 6 hours prior to randomization; no symptomatic hypotension
  - No increase (intensification) in intravenous diuretic dose within the last 6 hours prior to randomization
  - No intravenous inotropic drugs for 24 hours prior to randomization
  - No intravenous vasodilators including nitrates within last 6 hours prior to randomization
- Left ventricular ejection fraction (LVEF) ≤40% within the past 6 months
- Elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥1600 pg/ml OR BNP ≥400 pg/ml during current hospitalization

Exclusion criteria:

- Currently taking sacubitril/valsartan tablets or any use within the past 30 days
- History of hypersensitivity, known or suspected contraindications, or intolerance to any of the study drugs, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), or sacubitril
- Patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy
- Requirement of treatment with both ACE inhibitor and ARB
- Estimated glomerular filtration rate <30 ml/min/1.73 m^2
- Serum potassium >5.2 mEq/L at screening
- Known hepatic impairment or history of cirrhosis with evidence of portal

hypertension
- Acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid, or other major CV surgery; percutaneous coronary intervention or carotid angioplasty, within the prior month

Other salient features/characteristics:

- Black race: 36%
- First episode of HF: 34%
- Time to enrollment from initial presentation: 68 hours
- LVEF: 25%
- Median NT-proBNP at screening: 4800 pg/ml

Principal Findings:

The primary outcome, time-averaged reduction in NT-proBNP, for sacubitril/valsartan vs. enalapril, was -46.7% vs. -25.3%, hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.63-0.81, $p < 0.001$.

Secondary outcomes:

- Change in troponin T: -36.6% vs. 25.2%, $p < 0.05$
- Worsening renal function: 13.6% vs. 14.7%, $p > 0.05$
- Hyperkalemia: 11.6% vs. 9.3%, $p > 0.05$
- Symptomatic hypotension: 15.0% vs. 12.7%, $p > 0.05$
- Death: 2.3% vs. 3.4%, $p > 0.05$
- Rehospitalization for HF: 8.0% vs. 13.8%, HR 0.56, 95% CI 0.37-0.84

Open-label extension: 8 weeks after randomization, patients in both arms (sacubitril/valsartan n = 417, lisinopril n = 415) received sacubitril/valsartan for 4 weeks in an open-label study.

- Change in NT-proBNP from 8 to 12 weeks for sacubitril/valsartan vs. enalapril: -18.5% vs. -35.8%
- Serious composite events (death, HF hospitalization, LV assist device [LVAD] implantation or listing for transplant): HR 0.66, 95% CI 0.47-0.93, $p = 0.016$
- Hyperkalemia: 2.4% vs. 4.1%, $p > 0.05$

Interpretation:

The results of this trial indicate that sacubitril/valsartan reduced NT-proBNP to a greater degree than enalapril among eligible patients admitted with ADHF. This reduction was noted as early as 1 week after drug initiation. There also was a reduction in troponin T, and although not powered for clinical endpoints, a

reduction in rehospitalization for HF was noted over the follow-up period. Side effects including hyperkalemia and hypotension were similar.

Sacubitril is a neprilysin inhibitor and the combination with valsartan (renin-angiotensin-system [RAS] inhibitor) was noted to have significant benefit among ambulatory patients with HF compared with the use of RAS blocker alone. This trial extends these findings to an inpatient setting, albeit using NT-proBNP as a surrogate. A larger trial powered for clinical endpoints is warranted.

Switching patients from enalapril to sacubitril/valsartan at 8 weeks after randomization led to a greater reduction in NT-proBNP in patients with HF and reduced EF and a recent hospitalization for ADHF.

References:

Presented by Dr. Adam DeVore at the American College of Cardiology Annual Scientific Session (ACC 2019), New Orleans, LA, March 16, 2019.

Velazquez EJ, Morrow DA, DeVore AD, et al., on behalf of the PIONEER-HF Investigators. Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure. **2019;380:539-48**.

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Presented by Dr. Eric J. Velazquez at the American Heart Association Annual Scientific Sessions (AHA 2018), Chicago, IL, November 11, 2018.

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