Angiotensin Receptor Neprilysin Inhibitor

Introduction

- Angiotensin receptor neprilysin inhibitor is a new class of medicine using in patient with HFrEF.
- Valsartan/sacubitril (LCZ 696 or Entresto®) is the first and currently only medication in this class.

Mechanism of action

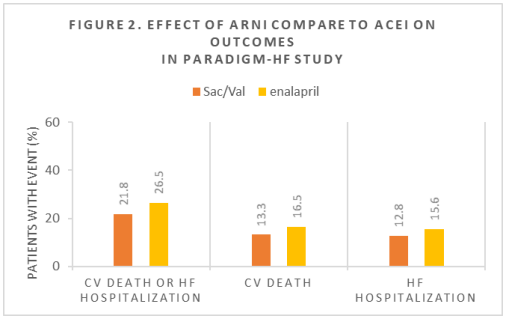
- Val/Sac has 2 main mechanisms
  1. Valsartan – an angiotensin 1 receptor blocker
  2. Sacbritil – a neprilysin inhibitor
     - Neprilysin (aka neutral endopeptidase – NEP) is an enzyme that degrades many peptides including natriuretic peptides (NP)
     - Inhibiting neprilysin results in elevated ANP, BNP and many peptide
- Overall effect is vasodilatation, ↓RAAS activation ↓ Na retention (clinical significant?)

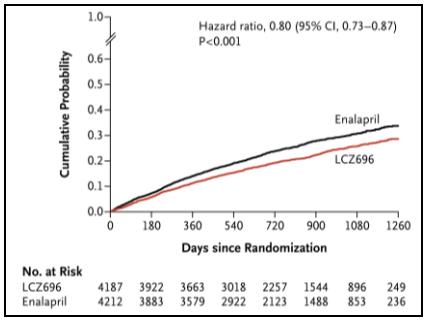
PARADISE-HF study (NEJM 2014)

- Design: Multicenter, randomized, double-blind, active-controlled, event-driven trial.
- Study Pop: Adult, stable HFrEF, EF < 35%, NYHA II-IV, elevated NP level, tolerate enalapril 10 mg/d (or equivalence of ACEI/ARB)
- N 8442 patients (63 yo, 80% male, EF 29%, 70% NYHA II, 60% ischemic)
- Intervention: 2 run-in periods prior to randomize, then
  - Valsartan/sacubitril 200 mg bid or
  - Enalapril 20 mg bid
- Background rx: 93% BB, 54% MRA
- Follow up: mean of 27 months
- Result: Significantly reduced composite endpoint of CV death or HF-rehospitalization
- (figure) Significantly reduced composite endpoint of CV death
  Significantly reduced composite endpoint of HF-rehospitalization
- Adverse effect Symptomatic hypotension (14%), Cr > 3 (1.5%), K > 6 (4%)

Table 1 Minimum required pre-study daily doses of commonly prescribed angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

ACE inhibitors	Minimum daily dose	ARBs	Minimum daily dose
Enalapril	10 mg	Candesartan	16 mg
Captopril	100 mg	Eprosartan	400 mg
Cilazapril	2.5 mg	Irbesartan	150 mg
Fosinopril	20 mg	Losartan	50 mg
Lisinopril	10 mg	Olmesartan	10 mg
Moexipril	7.5 mg	Telmisartan	40 mg
Perindopril	4 mg	Valsartan	160 mg
Quinapril	20 mg		
Ramipril	5 mg		
Trandolapril	2 mg		
Zofenopril	30 mg		





Other results from PARADIGM-HF

- Val/Sac is associated with more hypotension, but less AKI or hyperkalemia compared to enalapril
- Maybe more benefit in NYHA II compared to NYHA III-IV (p for interaction = 0.03)
- The same efficacy regardless of with or without MRA.
- The same efficacy regardless of starting BP, EF, or age group within PARADIGM-HF study.
- Improve quality of life by MCCQ.

Concerns and unknown

- Run-in period design may exaggerate reported benefits when compare to real world practice.
- Run-in period design may underestimate reported S/E compare to real world practice.
- There is only 1 RCT of Val/Sac i.e. PARADIGM-HF, but a very low p value. It is unlikely to have a 2nd trial in HFrEF.
- In patient with HFrEF, unknown benefits/adverse effect in
  - ACEI/ARB naïve patient
  - "Adding MRA" or "switching ACEI/ARB to ARNI" first is better.
  - NYHA I
  - Unstable AHF e.g. recent admission
- Unknown benefit in HFpEF
- ARNI also increase many other peptides which may result in adverse effect (angiotensin, endothelin, bradykinin, Beta-amyloid).
- Unknown effect on LV remodeling e.g. LVEF, LEVEDD.
- Cost effective? ICER = $45,000 (JAMA Cardiol. 2016;1(6):666-672.)

Guideline Statement

Society	Statement	COR	LOE
ACC/AHA 2017	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality	I	B-R
ESC 2016	Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA	I	B

Using ARNI

- Use in patient with adequate BP (SBP > 100), GFR > 30 and K < 5.2.
- Replacing ACEI/ARB (not adding).
- Starting dose at 100 mg bid, in patient who use to tolerate ACEI/ARB.
- Consider lower starting dose (25-50 mg bid) if ACEI/ARB naïve or was on low dose of ACEI/ARB.
- "36-hour wash out period" when switching from ACEI to ARNI
- Up titrate q 2 weeks to 200 mg bid.
- S/E include othostatic symptoms, hypotension, ↑Cr or ↑K, If having S/E consider ↓diuretics, ↓other BP meds, ↓K supplement, or ↓ARNI.
- BNP level in patient who is on ARNI is unreliable, use NT-proBNP level.
- Contraindicate in pregnancy or try to be pregnant.

Recommend reading

- McMurray JJV, et al. "Angiotensin-neprilysin inhibition versus enalapril in heart failure". NEJM 2014. 371(11):993-1004.