PARADIGM-HF: Valsartan 160mg po BID + Sacubitril (=LCZ696) ENTRESTO vs Enalapril VASOTEC 10mg po BID [1]

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality & morbidity in HF

BOTTOM LINE

- In **PARADIGM-HF**, clinically stable patients with heart failure (HF) (NYHA class I 5%, class II ~70%, class III 24%, class IV ~0.7%; mean LVEF 29.5%; median BNP 253pg/mL) on conventional HF therapy & who were treated with LCZ696 had:
  - a lower risk of cardiovascular death & 1st hospitalization for worsening HF (ARR 4.7%, NNT=22/2.25 years), but
  - more symptomatic hypotension (ARI 4.8%, NNH=21; SBP<90mmHg ARI 1.3%, NNH=77) & non-serious angioedema (n=19 vs 10, NS)
- Limitations with current data: no Phase II studies have been conducted to assess safety & over 2,000 patients withdrew from the study during the run-in phases; therefore, it is difficult to predict real-world tolerability of this new agent. There was low representation of Blacks in the study (only ~5%), & there is a higher risk of angioedema in this population.
- LCZ696's efficacy looks promising; however, post-marketing safety data will help determine its exact role in HF over the next several years. This new agent may be an option for HF patients who have tolerated standard therapy with an ACEI/ARB, + β-blocker, and are not experiencing symptomatic hypotension.
- Due to the ↑ risk of angioedema, patients who are switched from an ACEI to LCZ696 should wait ≥36 hours before starting the new therapy.
- CCS 2014 HF Guidelines recommends patients with mild to moderate HF, EF <40%, ↑ NP level or HF hospitalization in the past 12 months, K^+ <5.2mmol/L, eGFR ≥30mL/min & on appropriate doses of guideline-directed therapy should be treated with LCZ696 in place of an ACEI or ARB, with close surveillance of K^+ & SCr (conditional recommendation; high-quality evidence).[2]
- ENTRESTO was approved by both Health Canada Oct'15 & the FDA, but real-world experience is lacking. The cost is ~$240/month.

BACKGROUND

- The CCS HF 2012 Guidelines[3] recommend ACEI as first-line therapy for patients with HF & reduced ejection fraction. Enalapril VASOTEC was the first ACEI to show a reduction in mortality:
  - **CONSENSUS**:[4] enalapril 10mg po BID (mean dose 18.4mg/day) versus placebo in NYHA class IV, n=253. RRR 40%, ARR 18%, NNT=6/~6 months (trial stopped early due to benefit).
  - **SOLVD**:[5] enalapril 10mg po BID (mean dose 16.6mg/day) versus placebo in primarily NYHA class II & III (~90%), n=2569. RR 16%, ARR 4.5%, NNT=22/~3.5 years.
- ARBs have not been shown to be superior to ACEI, ELITE II, OPTIMAAL & as such, are reserved for individuals who cannot tolerate an ACEI (strong recommendation, high-quality evidence).[CCS HF 2012, 3]
- Neprilysin inhibitors are a new class of medications with a unique mechanism of action that are being evaluated for HF. Neprilysin breaks down endogenous vasoactive peptides (e.g. natriuretic peptides, bradykinin, adrenomedullin). When neprilysin is inhibited, these substances ↑ & offset the neurohormonal activation that leads to vasoconstriction, Na^+ retention & maladaptive remodelling.
- **PARADIGM-HF** compared a combination product, LCZ696 (sacubitril [neprilysin inhibitor] + valsartan [ARB]) to enalapril.
- Of note, omapatrilat, another neprilysin inhibitor, has been studied in patients with HF & HTN but was not released to market due to concerns of angioedema. Unlike **PARADIGM-HF**, the omapatrilat studies did not include a run-in phase to assess drug tolerability, which increases their real-world applicability.
  - **OVERTURE**:[6] enalapril 10mg po BID versus enalapril + omapatrilat 40mg po daily, n=5770 HF patients. 1˚ endpoint: death & hospitalization for HF requiring IV treatment: NS. Angioedema: omapatrilat 0.8% vs enalapril 0.5%.
  - **OCTAVE**:[7] enalapril 10-40mg po daily versus omapatrilat 20-80mg po daily, n=25,267 HTN patients. Angioedema: omapatrilat 2.17% versus enalapril 0.81%.

TRIAL OVERVIEW [1, 8]

DESIGN: randomized, double-blind, active control, event-driven, multicentre 47 countries, ITT trial with concealed allocation. Study was funded by Novartis. Enrolment period: December 2009 – January 2013. Trial stopped early due to benefit of LCZ696.

- **Study Phases:** 1) screening period, 2) a single-blind run-in period during which all patients received enalapril 10mg BID x 2 weeks, followed by a single-blind run-in period during which all patients received LCZ696 (100mg BID 1-2 weeks, then 200mg BID x 2-4 weeks) to ensure an acceptable side-effect profile of the study drugs are target doses, & 3) double-blind treatment

INTERVENTION: LCZ696 200mg (ARB component=valsartan 160mg) BID vs enalapril 10mg BID, in addition to recommended therapy

INCLUSION: age ≥18 years, NYHA class II, III, or IV symptoms at screening, ejection fraction ≤40% (amended to ≤35% December 15th, 2010), plasma B-type natriuretic peptide (BNP) ≥150pg/mL (or N-terminal pro-BNP [NT-proBNP] ≥600pg/mL) at screening **or** hospitalized for HF in the past year and BNP ≥100pg/mL (or NT-pro-BNP ≥400pg/mL). Treatment with a stable dose of an ACEI or ARB (equivalent to enalapril ≥10mg/day) and β-blocker (unless CI or not tolerated) for ≥4 weeks prior to screening was permitted. Use of an aldosterone antagonist ≥4 weeks prior to screening was encouraged.

EXCLUSION: symptomatic hypotension, SBP<100mmHg screening or <95mmHg randomization; eGFR <30mL/min/1.73m^2 or ↓ of >25% (amended to 35%) between screening & randomization; K^+ >5.2mmol/L screening or >5.4mmol/L randomization; history of angioedema or unacceptable ACEI or ARB side effects; acute coronary syndrome, stroke/TIA, cardiac/carotid/other major CV surgery, PCI or carotid angioplasty within 3 months prior to Visit 1; any conditions that could alter the pharmacokinetics of the study drugs (e.g. active IBD, active duodenal or gastric ulcers, hepatic disease, cholestyramine or colestipol resin use).

POPULATION at baseline: n=8399 (prior to run-in phase, n=10,513)

- Mean age 64 years (±11.4yrs),~78% ♂, 66% Caucasian, ~7% from North America
- Mean SBP 122mmHg (±15mmHg), HR 72bpm (±12bpm), BMI 28kg/m^2 (±5.5kg/m^2), SCr 99.9µmol/L (or SCr 1.13mg/dL ±0.3)
- Mean LVEF 29.5% (±6.2%), ischemic cardiomyopathy ~60%, median BNP 253pg/mL (IQR 153-474)
- Median NT-proBNP: LCZ696 1631pg/mL (IQR 885-3154) versus enalapril 1594pg/mL (IQR 886-3305)
- NYHA: class I ~5%, class II ~70.5%, III ~24%, IV ~0.7%. Note: classification at randomization exclusion of class I was applied at screening.
- HTN 70.5%, DM ~35%, AF ~37%, hospitalized for HF ~63%, MI ~43%, stroke ~8.5%
- Treatment at randomization: ACEI ~78%, ARB ~22.5%, diuretic ~80%, digoxin LCZ696 29.2% vs enalapril 31.2% (p=0.04), β-blocker ~93%, mineralcorticoid antagonist LCZ696 54.2% vs enalapril 57% (p=0.01), ICD ~15%, cardiac resynchronization therapy ~7%

RESULTS

follow-up: median 27 months/2.25 years

TABLE: EFFICACY & SAFETY DATA

CLINICAL ENDPOINTS	LCZ696 200MG BID (N=4187)	ENALAPRIL 10MG BID (N=4212)	HAZARD RATIO (95% CI)	ABSOLUTE RISK REDUCTION/INCREASE	NNT/NNH /2.25YRS
PRIMARY ENDPOINT					
Composite of CV death or 1st hospitalization for worsening HF	21.8% (n=914)	26.5% (n=1117)	0.80 (0.73-0.87) p<0.001	↓ 4.7%	22 (95% CI 15-35)
SECONDARY ENDPOINTS (see bottom of Table for KCCQ Score results)					
CV death	13.3% (n=558)	16.5% (n=693)	0.80 (0.71-0.89) p<0.001	↓ 3.2%	32
1st hospitalization for worsening HF	12.8% (n=537)	15.6% (n=658)	0.79 (0.71-0.89) p<0.001	↓ 2.8%	36
Death from any cause	17% (n=711)	19.8% (n=835)	0.84 (0.76-0.93) p<0.001	↓ 2.8%	36
New-onset AF	3.1% (n=84/2670)	3.1% (n=83/2638)	NS	-	-
Decline in renal function ‡	2.2% (n=94)	2.6% (n=108)	NS	-	-
SAFETY ENDPOINTS					
Symptomatic hypotension	14% (n=558)	9.2% (n=388)	<0.001	↑ 4.8%	21
Symptomatic hypotension & SBP <90mmHg	2.7% (n=112)	1.4% (n=59)	<0.001	↑ 1.3%	77
Elevated SCr ≥221µmol/L (≥2.5mg/dL)	3.3% (n=139)	4.5% (n=188)	0.007	↓ 1.2%	83
Elevated SCr ≥265µmol/L (≥3mg/dL)	1.5% (n=63)	2% (n=83)	NS	-	-
Elevated K+ >5.5mmol/L	16.1% (n=674)	17.3% (n=727)	NS	-	-
Elevated K+ >6mmol/L	4.3% (n=181)	5.6% (n=236)	0.007	↓ 1.3%	77
Cough	11.3% (n=474)	14.3% (n=601)	<0.001	↓ 3%	33
Angioedema	0.45% (n=19)	0.24% (n=10)	NS	-	-
Withdrawal During Run-in Phase	**10.5% (n=1102)**	**10.4% (n=977)**	NS	-	-
Discontinuation Rates	17.8% (n=746)	19.8% (n=833)	p=0.02	↓ 2%	50
Discontinuation due to an adverse event	10.7% (n=448)	12.3% (n=518)	p=0.03	↓ 1.6%	62
Discontinuation due to renal impairment	0.7% (n=29)	1.4% (n=59)	p=0.002	↓ 0.7%	143

KCCQ SCORE ENDPOINTS	LCZ696 200MG BID	ENALAPRIL 10MG BID	BETWEEN GROUP DIFFERENCES IN SCORE	COMMENTS
Mean change in KCCQ Score at 8 months †	-2.99±0.36	-4.63±0.36	1.64 (0.63-2.65) p=0.001	The mean change in KCCQ scores was statistically significant, but not clinically significant. A mean improvement of ≥5 points between groups & in individuals is considered the minimal clinically important difference.[9]
Mean change in KCCQ Score at 8 months † (deceased patients excluded)	"Improved" (data not reported)	"Declined" (data not reported)	0.95 (0.31-1.59) p=0.004	

‡ Decline in renal function = end-stage renal disease, ↓≥50% in baseline eGFR, or ↓ >30mL/min/1.73m^2 to <60mL/min/1.73m^2.
† KCCQ = Kansas City Cardiomyopathy Questionnaire (scale from 0 to 100, higher scores indicate fewer HF symptoms & physical limitations)

- **MEAN DAILY DOSAGES:** LCZ696 375±71mg (=valsartan 300±57mg/day), Enalapril 18.9±3.4mg
- **MEAN SBP AT 8 MONTHS:** LCZ696 3.2±0.4mmHg lower (p<0.001), but the authors stated this was not the reason for benefit when it was analyzed as a time-dependent covariate

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Important clinical endpoints (e.g. cardiovascular death, HF hospitalizations) with blinded adjudication of outcomes.
- Only 20 patients lost to follow-up (0.13%).

LIMITATIONS:

- No Phase II studies have been conducted in systolic heart failure to determine safety. The investigators bypassed Phase II trials by designing PARADIGM-HF with the run-in & washout periods.
- Two run-in phases were used to identify individuals who could not tolerate the target doses of the study drugs. Over 2,000 patients dropped out before randomization due to adverse events (i.e. hypotension, cough, hyperkalemia, renal dysfunction).
- Only ~7% of the participants were from North America.
- Doses of enalapril and valsartan were based on prior HF study target doses. The mean doses achieved in these studies were similar to the mean enalapril dose obtained in PARADIGM-HF; however, the mean valsartan dose achieved in PARADIGM-HF was quite a bit higher than what has been previous study. It is unknown how much of the LCZ696 benefit was due to neprilysn inhibition versus the higher dose of valsartan.
  - Enalapril target dose 10mg po BID (20mg/day): CONSENUS mean dose 18.4mg/day, SOLVD 16.6mg/day, PARADIGM-HF 18.9mg/day
  - Valsartan target dose 160mg po BID (320mg/day): ValHeFT[10] mean dose 254mg/day, VALIANT[11] mean dose 247mg/day in valsartan only arm, PARADIGM-HF 300mg/day (based on mean LCZ696 dose of 375mg/day [LCZ696 200mg=valsartan 160mg])

UNCERTAINITIES:

- Real-world & long-term safety unknown due to the large number of patients who withdrew from the study during the run-in phase & the trial was only 27 months in duration.
- Baseline HF medications were provided, but doses were not; therefore, it is unknown whether patients were at target doses of their other therapies (e.g. β-blockers) or if doses were reduced to offset hypotension caused by the study drugs. The type of β-blocker was also not reported; therefore, it is unknown if patients were on one of the recommended β-blockers for HF (i.e. bisoprolol, carvedilol, metoprolol).
- LCZ696 had approximately twice as many cases of angioedema (n=19 vs 10), however the difference between treatment arms was non-statistically significant. The majority of patients were on ACEI (78%) or ARB (22.5%) prior to enrolment, and patients with a history of angioedema were excluded. Omapatrilat was not released to market due to concerns of angioedema. The risk of angioedema in individuals who have not been on an ACEI or ARB is unknown.
  - Blacks are at greater risk of angioedema, and made up only ~5% of the study population.
- Theoretically, patients on LCZ696 could be at risk of Alzheimer disease as amyloid β is a substrate for neprilysin.
- Benefits or harms in patients with NYHA class III (24%) & IV (~0.7%) due to the small numbers of patients in the study.
- No evidence for the combination of sacubitril with an ACEI (1st line therapy)… see comments on page 1, re: omapatrilat.

References available online (www.rxfiles.ca)

RxFILES RELATED LINKS

- Heart Failure Treatment Overview http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Heart-Failure.pdf
- Furosemide Oral "Sliding Scale" in Heart Failure http://www.rxfiles.ca/rxfiles/uploads/documents/HF-FurosemideSlidingScale.pdf

ABBREVIATIONS & SYMBOLS

1°=primary ♂=male **ACEI**=angiotensin converting enzyme inhibitor **AF**=atrial fibrillation **ARB**=angiotensin receptor blocker **ARI**=absolute risk increase **ARNI**=angiotensin receptor-neprilysin inhibitor **ARR**=absolute risk reduction **β**=beta **BID**=twice daily **BMI**=body mass index **BNP**=B-type natriuretic peptide **bpm**=beats per minute **CCS**=Canadian Cardiovascular Society **CI**=confidence interval/contraindicated **CrCl**=creatinine clearance **CV**=cardiovascular **DM**=diabetes **eGFR**=estimated glomerular filtration rate **HF**=heart failure **HR**=heart rate **HTN**=hypertension **IBD**=inflammatory bowel disease **ICD**=implantable cardioverter defibrillator **IQR**=interquartile range **ITT**=intention-to-treat **IV**=intravenous **K^+**=potassium **KCCQ**=Kanas City Cardiomyopathy Questionnaire **LCZ696**=sacubitril + valsartan **LVEF**=left ventricular ejection fraction **MI**=myocardial infarction **n**=number **Na^+**=sodium **NNT**=number needed to treat **NNH**=number needed to harm **NS**=not statistically significant **NT-pro-BNP**=N-terminal pro-B-type natriuretic peptide **NYHA**=New York Heart Association **PCI**=percutaneous coronary intervention **RRR**=relative risk reduction **SBP**=systolic blood pressure **SCr**=serum creatinine **TIA**=transient ischemic attack **yrs**=years

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