LCZ696: Innovation or Smoke and Mirrors

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Faculty/Presenter Disclosure

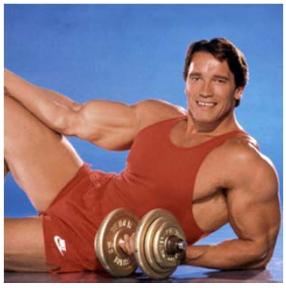
- **Faculty: Sheri Koshman**
- **Relationships with commercial interests:**
  Grants/Research Support: none
  Speakers Bureau/Honoraria: none
  Consulting Fees: none
  Other: none

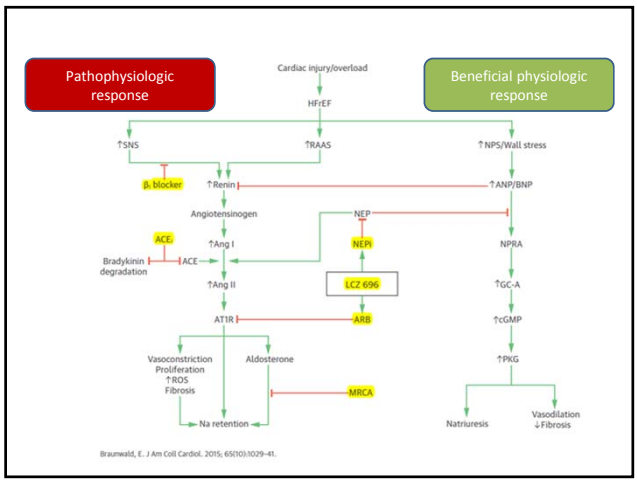
Objectives

- To describe the MOA of LCZ696
- To review the main findings of the PARADIGM-HF study
- To convince you that all patients with HFrEF should have their ACEi/ARB switched to LCZ696

Angiotensin Receptor / Neprilysin Inhibitor **(ARNI)**

- LCZ696 (Entresto™)
  - sacubitril
    - Neprilysin inhibitor
  - valsartan
    - Angiotensin II receptor blocker





LCZ696: PARADIGM-HF

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PARADIGM-HF

- P:
  - In patient with HFrRF (EF< 35-40%)
- I:
  - is LCZ696 200mg BID
- C:
  - better then enalapril 10mg BID
- O:
  - in decreasing CV death and HF hospitalizations?

N Engl J Med 2014;371:993-1004

PARADIGM-HF: Inclusion Criteria

- NYHA FC II–IV HF with LVEF ≤ 35-40%; protocol amendment in 2010 to 35%
- BNP (or NT-proBNP) levels as follows:
  - ≥150 (or ≥600 pg/mL), or
  - ≥100 (or ≥400 pg/mL) and a hospitalization for HFrEF within the last 12 months
- ≥4 weeks' stable treatment with an ACEI or an ARB (equivalent to enalapril 10mg/d), and a β-blocker
- Aldosterone antagonist should be considered for all patients (with treatment with a stable dose for ≥4 weeks, if given)

N Engl J Med 2014;371:993-1004

PARADIGM-HF: Exclusion criteria

- History of angioedema
- eGFR
  - <30 mL/min/1.73 m^2 at screening or randomization,
  - > 35% (amended from 25%) decrease in eGFR between screening and randomization
- Serum potassium
  - >5.2 mmol/L at screening
  - >5.4 mmol/L at the end of either run-in
- Symptomatic hypotension
  - SBP <100 mmHg at screening
  - SBP <95 mmHg at end of either run-in

N Engl J Med 2014;371:993-1004

PARADIGM-HF: Exclusion criteria

- Current acute decompensated HF
- History of severe pulmonary disease
- Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid, or other major CV surgery, PCI, or carotid angioplasty within the 3 months prior to screening
- Requirement for treatment with both ACEI and ARBs

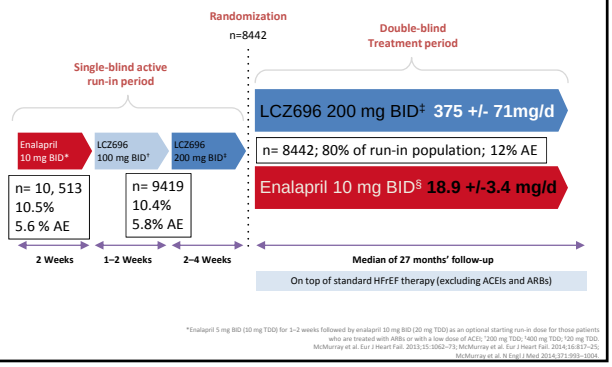
N Engl J Med 2014;371:993-1004

PARADIGM-HF: Objective

- Primary
  - To determine if LCZ696 is superior to enalapril in reducing CV death or HF hospitalization in HFrEF
- Secondary
  - Quality of life (KCCQ)
  - All cause mortality
  - Preventing new onset atrial fibrillation
  - Delaying renal dysfunction (ESRD, ↓eGFR 50%, ↓30-60mL/1.73m^2)
- "Exploratory":
  - NFMI, NFCVA, resuscitated SCD, hospitalizations, treatment failure, new onset DM, coronary revascularization, clinical composite score, decline in eGFR, biomarkers, pharmacokinetics, health resource utilization

N Engl J Med 2014;371:993-1004

PARADIGM-HF: Results



PARADIGM-HF: Results

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Age — yr	63.8±11.5	63.8±11.3
Female sex — no. (%)	879 (21.0)	953 (22.6)
Race or ethnic group — no. (%)†		
White	2763 (66.0)	2781 (66.0)
Black	213 (5.1)	215 (5.1)
Asian	759 (18.1)	750 (17.8)
Other	452 (10.8)	466 (11.1)
Region — no. (%)		
North America	310 (7.4)	292 (6.9)
Latin America	713 (17.0)	720 (17.1)
Western Europe and other‡	1026 (24.5)	1025 (24.3)
Central Europe	1393 (33.3)	1433 (34.0)
Asia–Pacific	745 (17.8)	742 (17.6)
Systolic blood pressure — mm Hg	122±15	121±15
Heart rate — beats/min	72±12	73±12
Body-mass index§	28.1±5.5	28.2±5.5
Serum creatinine — mg/dl	1.13±0.3	1.12±0.3

99 umol/L

N Engl J Med 2014;371:993-1004

PARADIGM-HF: Results

Clinical features of heart failure		
Ischemic cardiomyopathy — no. (%)	2506 (59.9)	2530 (60.1)
Left ventricular ejection fraction — %	29.6±6.1	29.4±6.3
Median B-type natriuretic peptide (IQR) — pg/ml	255 (155–474)	251 (153–465)
Median N-terminal pro–B-type natriuretic peptide (IQR) — pg/ml	1631 (885–3154)	1594 (886–3305)
NYHA functional class — no. (%)¶		
I	180 (4.3)	209 (5.0)
II	2998 (71.6)	2921 (69.3)
III	969 (23.1)	1049 (24.9)
IV	33 (0.8)	27 (0.6)
Missing data	7 (0.2)	6 (0.1)
Medical history — no. (%)		
Hypertension	2969 (70.9)	2971 (70.5)
Diabetes	1451 (34.7)	1456 (34.6)
Atrial fibrillation	1517 (36.2)	1574 (37.4)
Hospitalization for heart failure	2607 (62.3)	2667 (63.3)
Myocardial infarction	1818 (43.4)	1816 (43.1)
Stroke	355 (8.5)	370 (8.8)
Pretrial use of ACE inhibitor‖	3266 (78.0)	3266 (77.5)
Pretrial use of ARB‖	929 (22.2)	963 (22.9)

N Engl J Med 2014;371:993-1004

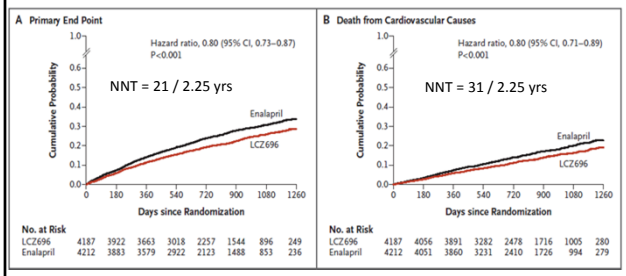
PARADIGM-HF: Results

Table 1. (Continued.)

Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Treatments at randomization — no. (%)		
Diuretic	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
Beta-blocker	3899 (93.1)	3912 (92.9)
Mineralocorticoid antagonist	2271 (54.2)	2400 (57.0)
Implantable cardioverter–defibrillator	623 (14.9)	620 (14.7)
Cardiac resynchronization therapy	292 (7.0)	282 (6.7)

N Engl J Med 2014;371:993-1004

Results: Enpoints



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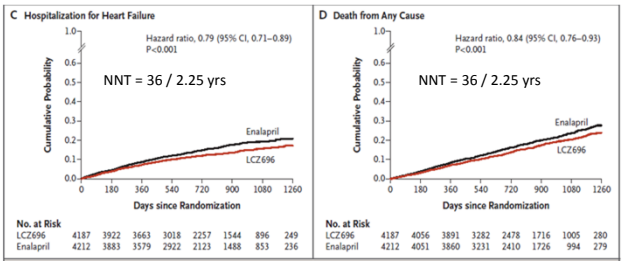
Results: Endpoints



N Engl J Med 2014;371:993-1004

Results: Adverse Events

Table 3. Adverse Events during Randomized Treatment.*

Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl (≥ 221 umol/L)	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl (≥ 265 umol/L)	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

NNH = 21
NNH = 77
NNT = 83
NNT = 77
NNT = 33

* Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the LCZ696 group and 29 (0.7%) in the enalapril group (P=0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (P=0.002); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (P=0.56).
† Angioedema was adjudicated in a blinded fashion by an expert committee.

N Engl J Med 2014;371:993-1004

Results: Adverse Events

	LCZ696	Enalapril	
Discontinuation (DC) rates	17.8%	19.8%	ARR = 2% NNT = 50
DC due to ADR	10.7%	12.3%	ARR = 1.6% NNT = 62
DC due to renal impairment	0.7%	1.4%	ARR = 0.7% NNT = 143

N Engl J Med 2014;371:993-1004

LCZ696: Innovation

Should all patients with HFrEF be switched to LCZ696?

YES

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Innovation

- **Simple definition of innovation**
  : a new idea, device, or method
  : the act or process of introducing new ideas, devices, or methods

Source: Merriam-Webster's Learner's Dictionary

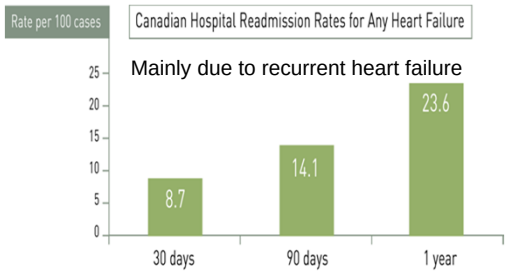
Innovation: Yes

- First in class drug
- Targets pathophysiologic AND beneficial physiological process
- Sizeable benefit shown in a large, well designed and conducted RCT
  - –superiority trial
  - –gold standard comparator at a comparable dose
  - –reflects contemporary practice
    - 93% B-blockers (50% on doses > 50% of target)
    - 55% on a MRA
- Not all patients fit into RCTs

Morbidity and Mortality in HF

HF=heart failure
†Data from European patients hospitalized for heart failure in the European Society of Cardiology Heart Failure (ESC-HF) Pilot study and EuroHeart Failure Survey (EHFS) II
‡Analysis of HF data from 1,282 incident cases of HF in the Atherosclerosis Risk in Communities (ARIC) population-based study of
n=15,792 individuals from four communities in the USA (1987–2002)
§Reported rates vary but some publications include rates up to 50%6–8
1.Maggioni et al. Eur J Heart Fail 2010;12:1076–84; 2. Nieminen et al. Eur Heart J 2006;27:2725–36;
3. Cleland et al. Eur Heart J 2003;24:442–636; 4. Loehr et al. Am J Cardiol 2008;101:1016–22;
5. Maggioni et al. Eur J Heart Fail 2013;15:808–17; 6. Roger et al. JAMA 2004;292:344–50;
7. Levy et al. N Engl J Med 2002;347:1397–402; 8. Askoxylakis et al. BMC Cancer 2010;10:105

HF Readmissions in Canada



Lee DS et al. *Can J Cardiol* 2004;20(6):599-607.

Hospitalizations by Volume

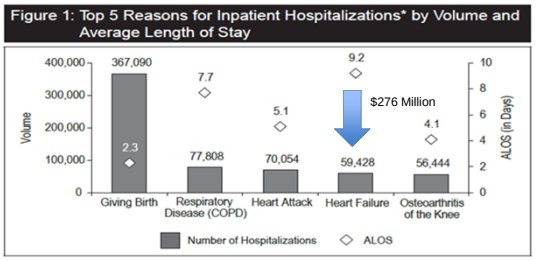
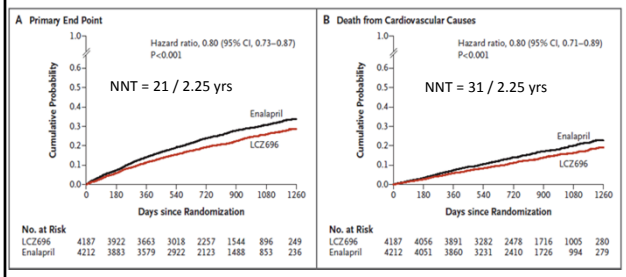


Figure 1: Top 5 Reasons for Inpatient Hospitalizations* by Volume and Average Length of Stay

Notes
* Figures exclude newborns and include obstetric records.
COPD: Chronic obstructive pulmonary disease.
ALOS: Average length of stay.
Sources
Hospital Morbidity Database and Ontario Mental Health Reporting System, 2013–2014, Canadian Institute for Health Information.

https://www.cihi.ca/en/types-of-care/hospital-care/acute-care/cihi-releases-top-10-reasons-for-hospitalization-and-surgery

Results: Enpoints



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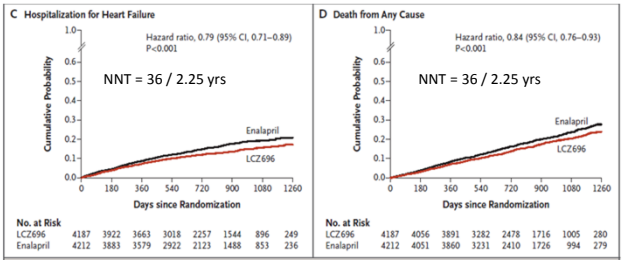

N Engl J Med 2014;371:993-1004

RAAS Comparison

Table 1 Key baseline characteristics of patients in trials compared

	SOLVD-T (*n* = 2569)	CHARM-Alternative (*n* = 2028)	PARADIGM-HF (*n* = 8399)
Age, years	61 (10)	67 (11)	64 (11)
Female sex, %	20	32	22
NYHA class, %			
I	11	0	5
II	57	48	70
III	30	49	24
IV	2	4	1
History			
MI	66	61	43
Hypertension	42	50	71
Diabetes mellitus	26	27	35
Systolic BP, mmHg	125 (18)	130 (19)	121 (19)
LVEF, %	25 (7)	30 (7.4)	29 (6.2)
Background therapy (%)			
Diuretic	85	85	80
Digoxin	67	45	30
Beta-blocker	8	55	93
MRA	NR	24	56

BP, blood pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NR = not reported.

Eur Heart J 2015;36:434-39

RAAS Comparison

Table 2 Number of events and event rates (per 100 patient-years) in trials compared

Outcome number (rate[a])	SOLVD-T		CHARM-Alternative		PARADIGM-HF	
	Placebo (*n* = 1284)	Enalapril (*n* = 1285)	Placebo (*n* = 1015)	Candesartan (*n* = 1013)	Enalapril (*n* = 4212)	LCZ696 (*n* = 4187)
CV death or HF hospitalization	707 (26.2)	573 (18.5)	406 (18.2)	334 (13.8)	1117 (13.2)	914 (10.5)
CV death	461 (13.7)	399 (11.2)	252 (9.8)	219 (8.2)	693 (7.5)	558 (6.0)
HF hospitalization	470 (17.2)	332 (10.9)	286 (12.8)	207 (8.6)	658 (7.7)	537 (6.2)
All-cause mortality	510 (15.1)	452 (12.8)	296 (11.5)	265 (10.0)	835 (9.0)	711 (7.6)

CV, cardiovascular; HF, heart failure.
[a]Rate per 100 patient-years.

Eur Heart J 2015;36:434-39

Indirect Comparison

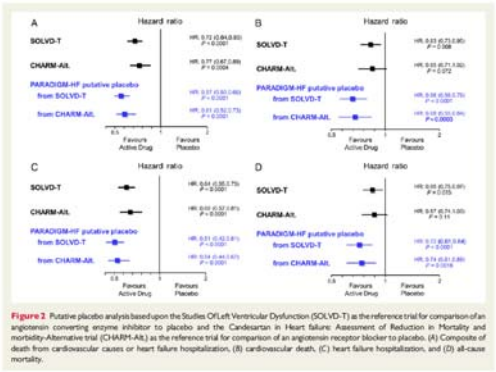

Figure 2 Putative placebo analysis based upon the Studies Of Left Ventricular Dysfunction (SOLVD-T) as the reference trial for comparison of an angiotensin converting enzyme inhibitor to placebo and the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity-Alternative trial (CHARM-Alt.) as the reference trial for comparison of an angiotensin receptor blocker to placebo. (A) Composite of death from cardiovascular causes or heart failure hospitalization, (B) cardiovascular death, (C) heart failure hospitalization, and (D) all-cause mortality.

Eur Heart J 2015;36:434-39

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PARADIGM-HF: Effect of dose

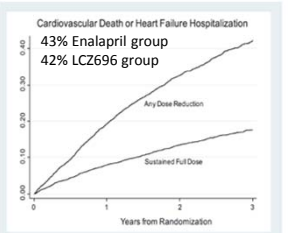


Figure 1 Kaplan–Meier curves showing primary outcome events by dose reduction status. Participants with a dose reduction had a higher risk of the primary event compared with those who remained on full study medication doses.

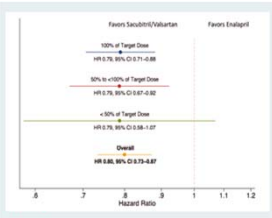


Figure 3 Hazard ratios (HR; sacubitril/valsartan relative to enalapril) of the primary outcome measure by time-updated mean dose post-randomization. Participants taking lower than target dose had a lower risk of the primary event compared with those taking lower than target doses of enalapril. CI, confidence interval.

Eur J Heart (2016) doi:10.1002/ejhf.580

Effect of Age

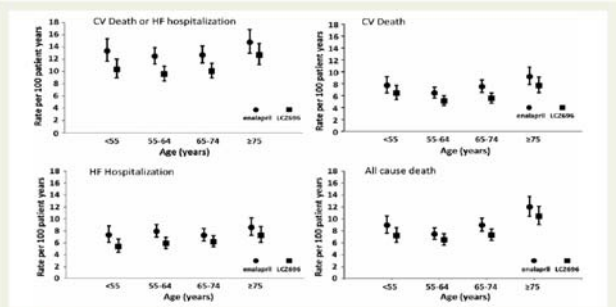


Figure 1 Clinical outcomes of cardiovascular death or heart failure hospitalization, cardiovascular death, heart failure hospitalization, and all-cause mortality by age category and treatment group. Rates are expressed as a rate per 100 patient-years of treatment (error bars are 95% confidence intervals).

Eur Heart J 2015;36:2576-84

Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

SACUBITRIL/VALSARTAN

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that sacubitril/valsartan be listed for the treatment of heart failure (HF) with reduced ejection fraction in patients with New York Heart Association (NYHA) class II or III HF to reduce the incidence of cardiovascular (CV) death and HF hospitalization, if all of the following clinical criteria are met:

Clinical Criteria:

- Reduced left ventricular ejection fraction (LVEF) (< 40%).
- Patient has NYHA class II to III symptoms despite at least four weeks of treatment with a stable dose of an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor antagonist (ARB) in combination with a beta blocker and other recommended therapies, including an aldosterone antagonist (if tolerable).
- Plasma B-type natriuretic peptide (BNP) ≥ 150 pg/mL or N-terminal prohormone B-type natriuretic peptide (NT-proBNP) ≥ 600 pg/mL; or plasma BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL levels if the patient has been hospitalized for HF within the past 12 months.

Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

SACUBITRIL/VALSARTAN

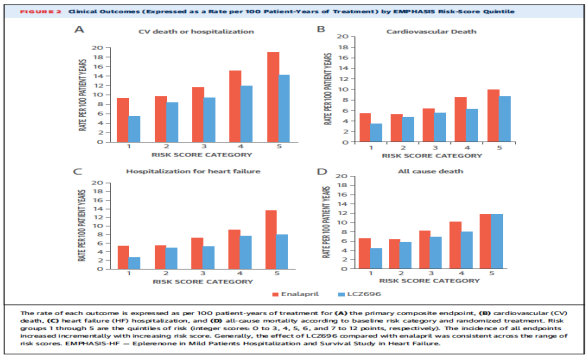
Reasons for the Recommendation:

1. One double-blind (DB), randomized controlled trial (RCT) (PARADIGM-HF; N = 8,442) demonstrated that treatment with sacubitril/valsartan reduced the risk of CV mortality or hospitalization for HF by 20% compared with enalapril (hazard ratio [HR] 0.80; 95% confidence interval [CI], 0.73 to 0.87).
2. At the submitted price ($3.62 per 50 mg, 100 mg, or 200 mg tablet), the CADTH Common Drug Review (CDR) estimated that sacubitril/valsartan is associated with an incremental cost-utility ratio (ICUR) of $42,787 per quality-adjusted life-year (QALY) compared with ramipril.
3. Patients enrolled in PARADIGM-HF were receiving stable doses of an ACEI or an ARB in combination with a beta blocker and often an aldosterone antagonist.

Cost Effective

- CDR
  - ICUR **$42,778** per QALY when compared with ACEI
- Gaziano TA, et al. (JAMA Cardiol doi:10.1001/jamacardio.2016.1747
  - ICUR **$45,017** per QALY
- Oilendorf DA, et al. (JAMA Intern Med 2016;176:249-50)
  - ICUR **$50,915** per QALY
- Sandhu AT, et al. (Ann Intern Med 2016; doi:10.7326/M16-0057)
  - ICUR **$47,053** per QALY (NYHA II - $44,531, NYHA III/IV - $58, 194)

Effect of Risk



JACC 2015;66:2059-71

Effect of other parameters….

- consistent effect across
  - LVEF
  - Age
  - Background therapy (medications, devices)
  - Dose

Eur J Heart (2016) doi:10.1002/ejhf.580
Eur Heart J 2015;36:2576-84
Circ Heart Fail 2016;9e002744
Circ Heart Fail 2016;9e00321

Conclusion

- Yes – all patients with HFrEF should be switched to LCZ696
- Sizeable benefit shown in important HF outcomes, in a large, well designed and conducted RCT
  - superiority trial
  - gold standard comparator at a comparable dose
  - reflects contemporary practice
- Hypotension is notable, but can be managed with careful initiation and titration and relative benefits seem to be maintained at less than target doses
- Cost effective
  - Likely to become more cost-effect as the acquisition cost of the drug decrease