

Patient and Physician Reported Outcomes

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PARADIGM-HF: Pre-specified endpoints

- **Primary: Cardiovascular death or heart failure hospitalization**
 - Cardiovascular death
 - Heart failure hospitalization
- **Secondary:**
 - Death from any cause
 - **KCCQ (CSS - symptoms and physical limitations)**
 - New onset atrial fibrillation
 - Decline in renal function

Background:

Health-related quality of life in heart failure

- Health-related quality of life (HQoL) refers to the subjective perception of health
- Patients with heart failure have a significantly poorer HQoL than patients with many other common chronic conditions

Background: HQoL in heart failure

- Current treatment goals in heart failure are to improve both survival and HQoL
- Recommended therapies that have survival benefits have a modest positive effect (ACEIs) or no impact (BBs) on HQoL
- Some therapies that improve HQoL (eg, inotropic agents) do not improve survival

KCCQ

- Disease specific, 23 items, ranging from 0 to 100 (higher score = better HQoL)
 - physical limitation
 - symptoms (frequency, burden)
 - quality of life
 - social interference
 - self-efficacy
- Clinical Summary Score (CSS):
Mean of the physical limitation and total symptom domains scores
- Overall Summary Score (OSS):
CSS + quality of life and social limitation scores

PARADIGM-HF: Effect of LCZ696 vs. enalapril on other secondary endpoints

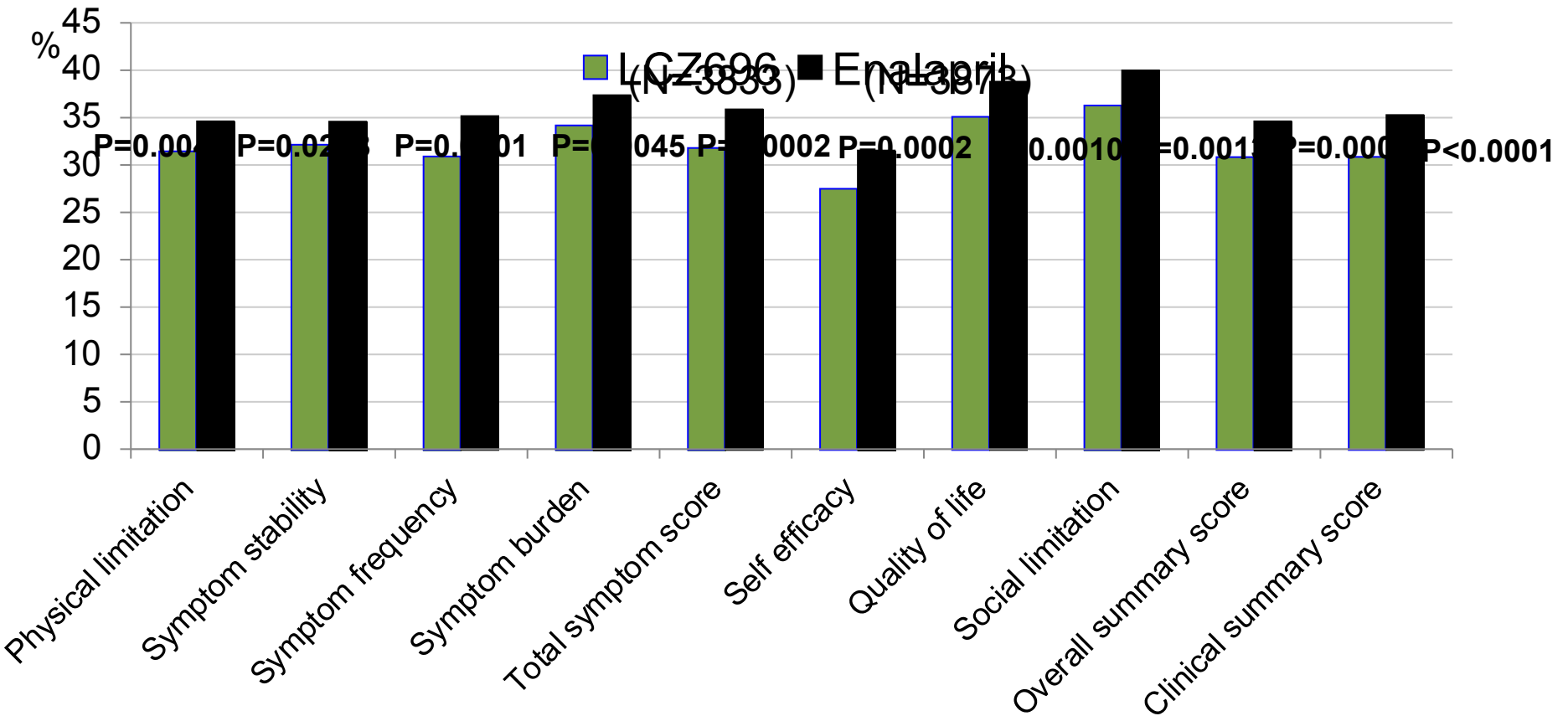
	LCZ696 (n=4187)	Enalapril (n=4212)	Treatment effect	P Value
KCCQ clinical summary score at 8 months	- 2.99 ± 0.36	- 4.63 ± 0.36	1.64 (0.63, 2.65)	0.001
New onset atrial fibrillation	84/2670 (3.2%)	83/2638 (3.2%)	Hazard ratio 0.97 (0.72, 1.31)	0.84
Protocol-defined decline in renal function*	94/4187 (2.3%)	108/4212 (2.6%)	Hazard ratio 0.86 (0.65, 1.13)	0.28

KCCQ: Treatment effect on OSS/CSS in recent large double-blind RCTs

Trial	Patients	Follow-up (months)	Difference between treatments (points)
RED-HF	NYHA class II/III 35/65%. Anaemia. Placebo vs. darbepoetin.	6	2.2
SHIFT	NYHA class II/III 59/40%. Placebo vs. ivabradine.	12	1.8
MADIT-CRT	NYHA class II/III 87/0%. ICD vs. ICD+CRT.	29*	1.3
PARADIGM-HF	NYHA class II/III 70/24%. Enalapril vs. LCZ696.	8	1.6

* Mean follow-up

PARADIGM-HF: Percentage of patients with at least 5 points deterioration in KCCQ scores at month 8



Clinical summary score based on the physical limitation and total symptom score domains. Death imputed as zero. The analysis included all patients with at least one KCCQ data point

KCCQ Clinical Summary Score

Change at 8 month from baseline

- Significant improvement in the clinical summary score for HF symptoms and physical limitations
- Consistent effect in all single domains

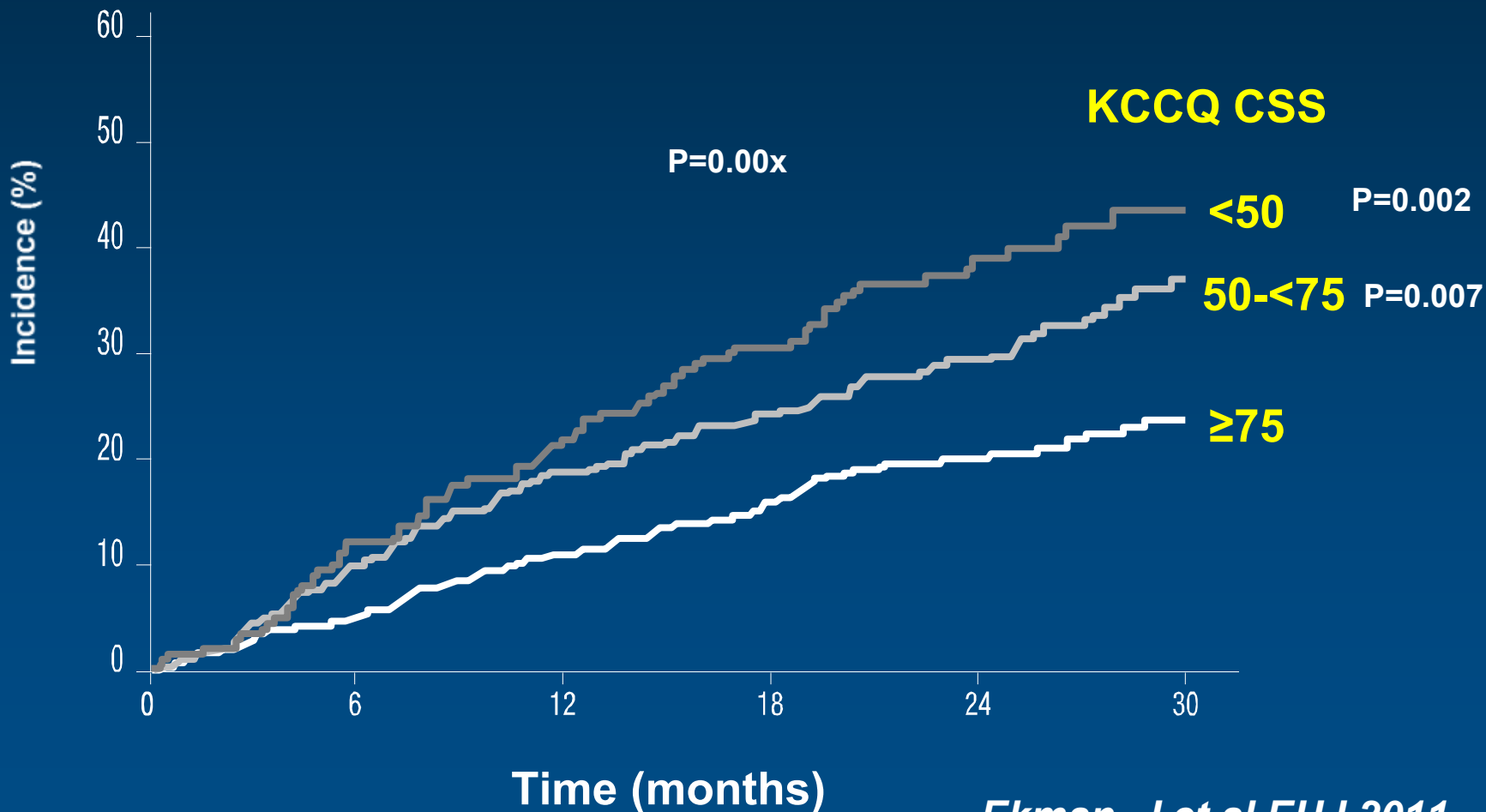
	LCZ696 (N=3833)		Enalapril (N=3873)		LSM of difference (95% CI)	P-value	
	n	LSM of CFB (SE)	n	LSM of CFB (SE)		2-sided	1-sided
Physical limitation*	3588	-2.59 (0.390)	3589	-4.13 (0.389)	1.54 (0.46, 2.62)	0.0052	
Symptom stability	3631	-6.10 (0.401)	3632	-7.92 (0.401)	1.82 (0.71, 2.93)	0.0014	
Symptom frequency	3637	-3.00 (0.402)	3632	-5.22 (0.402)	2.22 (1.10, 3.33)	0.0001	
Symptom burden	3640	-3.59 (0.400)	3635	-5.29 (0.400)	1.70 (0.59, 2.81)	0.0027	
Total symptom score*	3640	-3.32 (0.390)	3635	-5.23 (0.390)	1.91 (0.83, 2.99)	0.0005	
Self-efficacy	3638	-1.70 (0.404)	3632	-3.11 (0.404)	1.41 (0.29, 2.53)	0.0138	
Quality of life	3635	-1.11 (0.390)	3632	-3.23 (0.390)	2.11 (1.03, 3.20)	0.0001	
Social limitation	3448	-2.06 (0.434)	3454	-4.62 (0.433)	2.56 (1.36, 3.76)	0.0000	
Overall summary score	3643	-2.35 (0.358)	3638	-4.27 (0.357)	1.91 (0.92, 2.91)	0.0002	
Clinical summary score	3643	-2.99 (0.364)	3638	-4.63 (0.364)	1.64 (0.63, 2.65)	0.0014	0.0007

*Clinical summary score based on the physical limitation and total symptom score domains

Death imputed as zero



Incidence of CV mortality and HF worsening by class of KCCQ clinical score

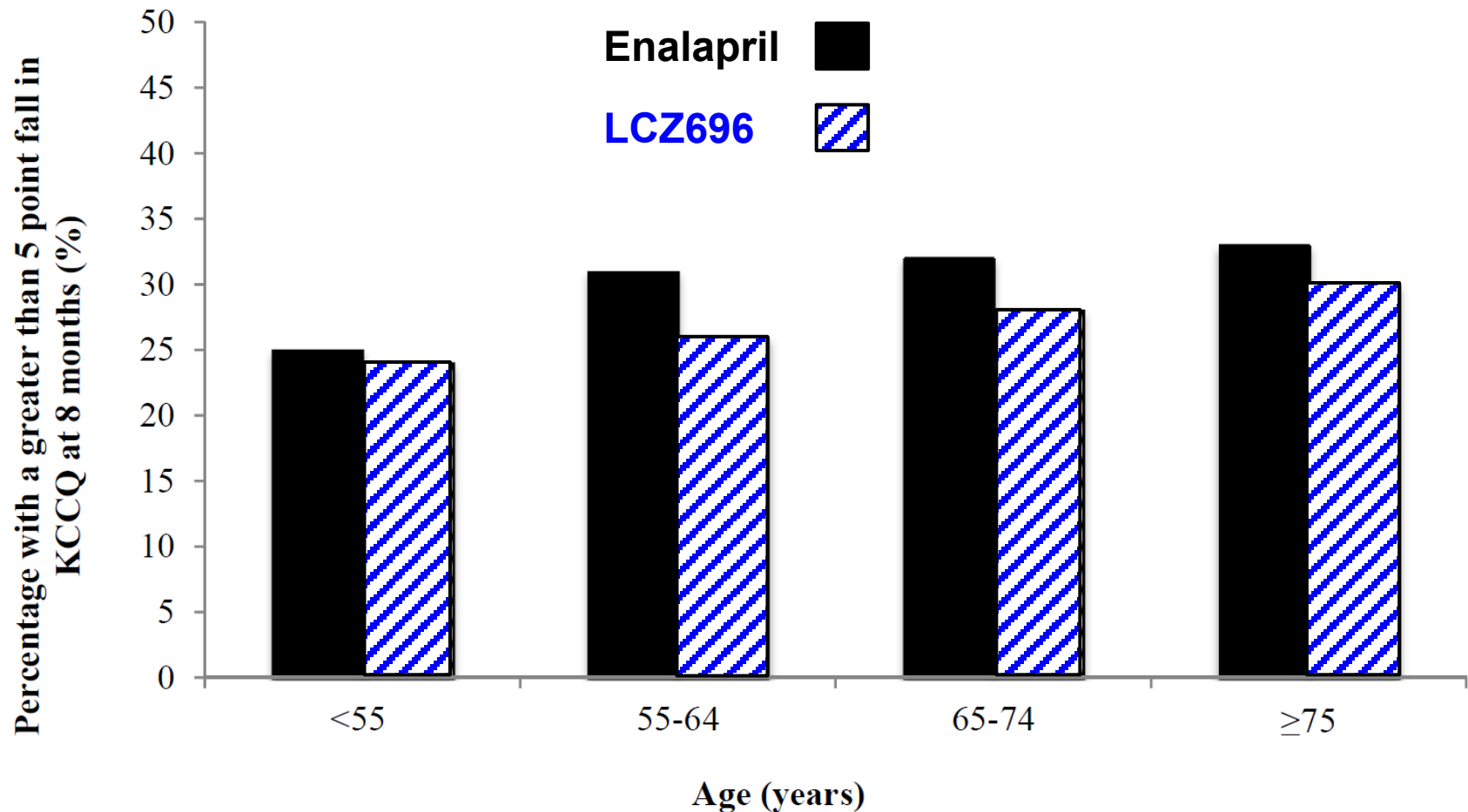


Effect of LCZ696 on the primary endpoint according to baseline KCCQ score (tertiles)

	Tertile (KCCQ score)	LCZ696 n/m (%)	Enalapril n/m (%)	Hazard ratio (95% CI) LCZ696 vs. Enalapril	P-value
KCCQ CSS*	<T1 (70)	318/1091 (29%)	353/1146 (31%)	0.94 (0.81-1.09)	0.41
	T1 ≤, <T2 (70-88)	211/1104 (19%)	344/1186 (29%)	0.61 (0.51-0.73)	<0.001
	≥ T2 (89)	204/1162 (18%)	205/1027 (20%)	0.88 (0.73-1.07)	0.21

PARADIGM-HF: Effect of LCZ696 according to age category

Proportion of patients with ≥ 5 points fall (deterioration) in Kansas City Cardiomyopathy Questionnaire at 8 months



EQ-5D

	LCZ696 N=4187		Enalapril N=4212		LCZ696 vs. Enalapril	
Visit	n	LSM of CFB (SE)	n	LSM of CFB (SE)	LSM of difference (95% CI)	P-value (2-sided)
Visit 9	3876	2.21 (0.24)	3858	1.29 (0.24)	0.91 (0.24, 1.58)	0.0075*
Visit 10	3740	2.55 (0.25)	3684	1.74 (0.26)	0.81 (0.10, 1.52)	0.0245*
Visit 11	3598	2.41 (0.26)	3527	2.29 (0.26)	0.13 (-0.59, 0.85)	0.7312
Visit 14	2557	2.73 (0.30)	2463	1.63 (0.30)	1.10 (0.27, 1.93)	0.0094*
Visit 17	1205	3.62 (0.42)	1193	1.96 (0.42)	1.66 (0.49, 2.83)	0.0055*
Overall	3948	2.54 (0.19)	3930	1.75 (0.19)	0.92 (0.36, 1.48)	0.0012*

The analysis is performed with a repeated measures ANCOVA model including treatment, region, visit, and treatment-by-visit interaction as fixed effect factors and baseline EQ-5D value as a covariate, with a common unstructured covariance for each treatment group.

PARADIGM-HF: Physician assessment

**Change in NYHA functional class
from baseline to month 8 (*pre-specified time-point*)**

	LCZ696 N=3833* n (%)	Enalapril N=3825* n (%)	P-value
Improved	639 (16.7)	569 (14.9)	0.0015
Unchanged	2989 (78.0)	2990 (78.2)	
Worse	205 (5.4)	266 (7.0)	

*Surviving patients with data (deaths excluded)

Change in NYHA Functional Class

Greater improvement with LCZ696 compared with enalapril

Death imputed as worse rank

	LCZ696 (N=4187) n (%)	Enalapril (N=4212) n (%)	P value
Improved	639 (15.8)	569 (14.0)	.0003
Unchanged	2989 (74.1)	2990 (73.6)	
Worse	407 (10.1)	504 (12.4)	

Death: LOCF

	LCZ696 (N=4187) n (%)	Enalapril (N=4212) n (%)	P value
Improved	660 (16.4)	582 (14.5)	0.0007
Unchanged	3132 (78.0)	3135 (78.3)	
Worse	224 (5.6)	289 (7.2)	

Summary

- **In addition to improvements in mortality and morbidity, there were significant improvements in HRQoL by LCZ696 compared with enalapril.**
- **Similar improvements were also recorded for EQ-5D and in NYHA-class assessments.**