

# 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

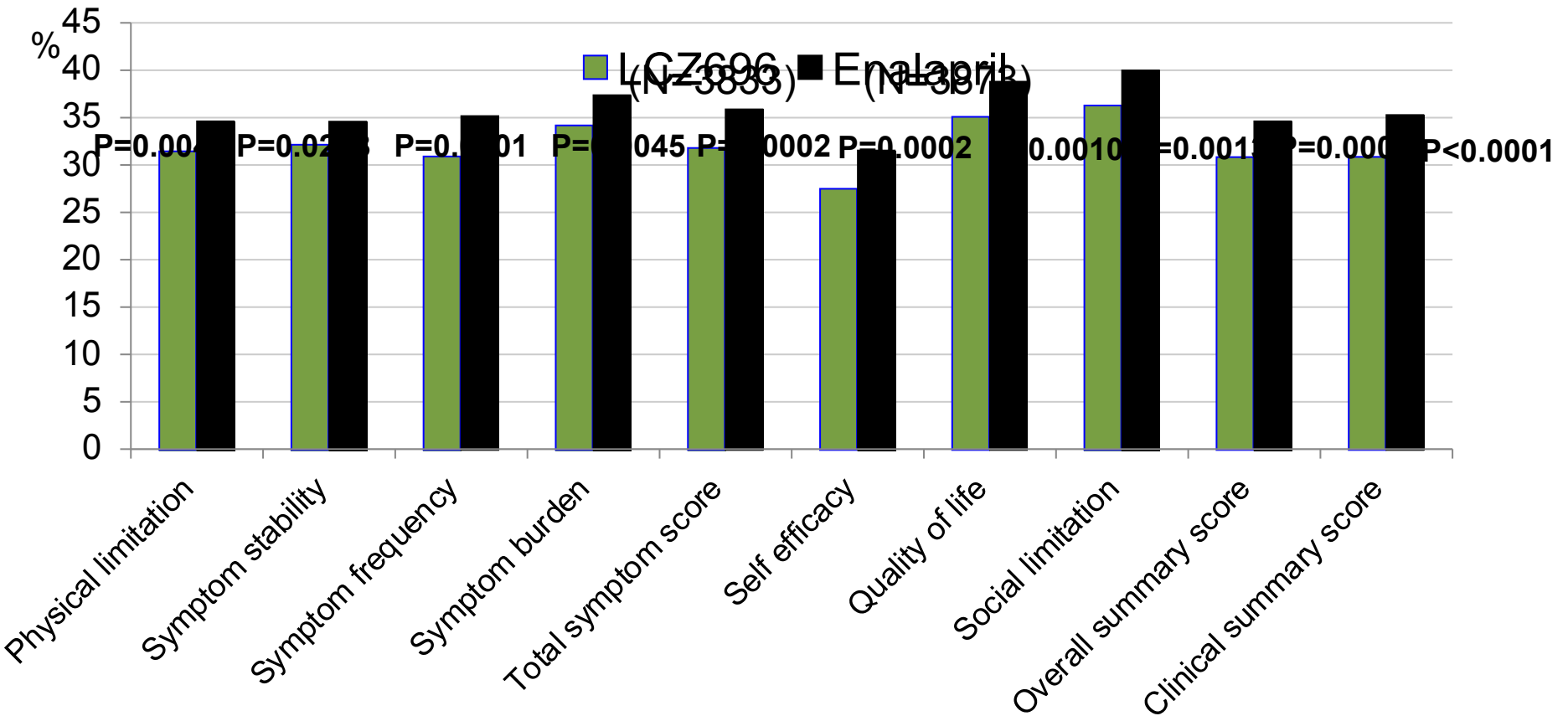
	<b>LCZ696 (n=4187)</b>	<b>Enalapril (n=4212)</b>	Treatment effect	P Value
KCCQ clinical summary score at 8 months	<b>- 2.99 ± 0.36</b>	<b>- 4.63 ± 0.36</b>	1.64 (0.63, 2.65)	<b>0.001</b>
New onset atrial fibrillation	<b>84/2670 (3.2%)</b>	<b>83/2638 (3.2%)</b>	Hazard ratio 0.97 (0.72, 1.31)	0.84
Protocol-defined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

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

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

*\* 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

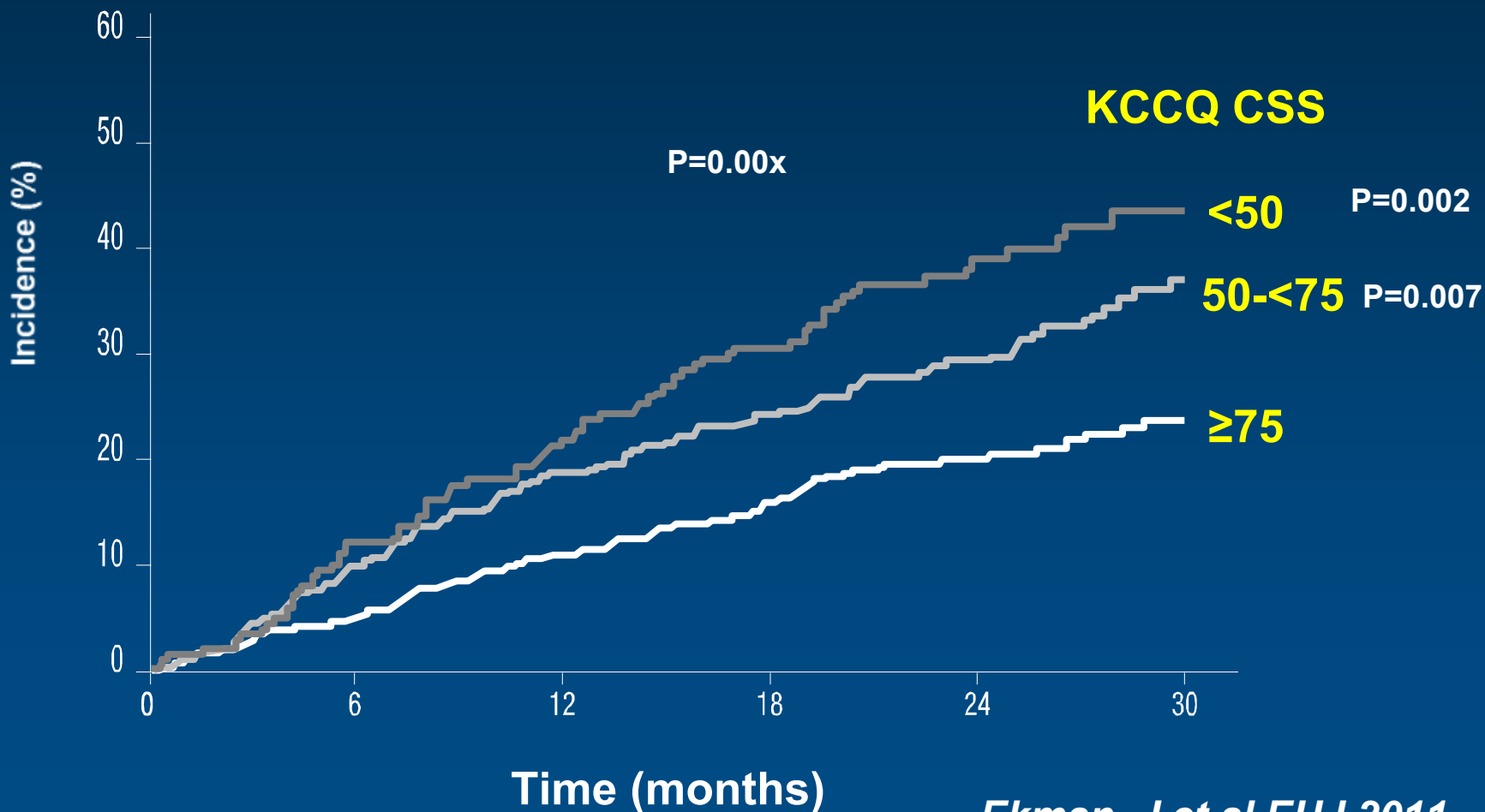
	LCZ696 (N=3833)		Enalapril (N=3873)		LSM of difference (95% CI)	P-value	
	n	LSM of CFB (SE)	n	LSM of CFB (SE)		2-sided	1-sided
<b>Physical limitation*</b>	<b>3588</b>	<b>-2.59 (0.390)</b>	<b>3589</b>	<b>-4.13 (0.389)</b>	<b>1.54 (0.46, 2.62)</b>	<b>0.0052</b>	
Symptom stability	3631	-6.10 (0.401)	3632	-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	
<b>Total symptom score*</b>	<b>3640</b>	<b>-3.32 (0.390)</b>	<b>3635</b>	<b>-5.23 (0.390)</b>	<b>1.91 (0.83, 2.99)</b>	<b>0.0005</b>	
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	
<b>Clinical summary score</b>	<b>3643</b>	<b>-2.99 (0.364)</b>	<b>3638</b>	<b>-4.63 (0.364)</b>	<b>1.64 (0.63, 2.65)</b>	<b>0.0014</b>	<b>0.0007</b>

\*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

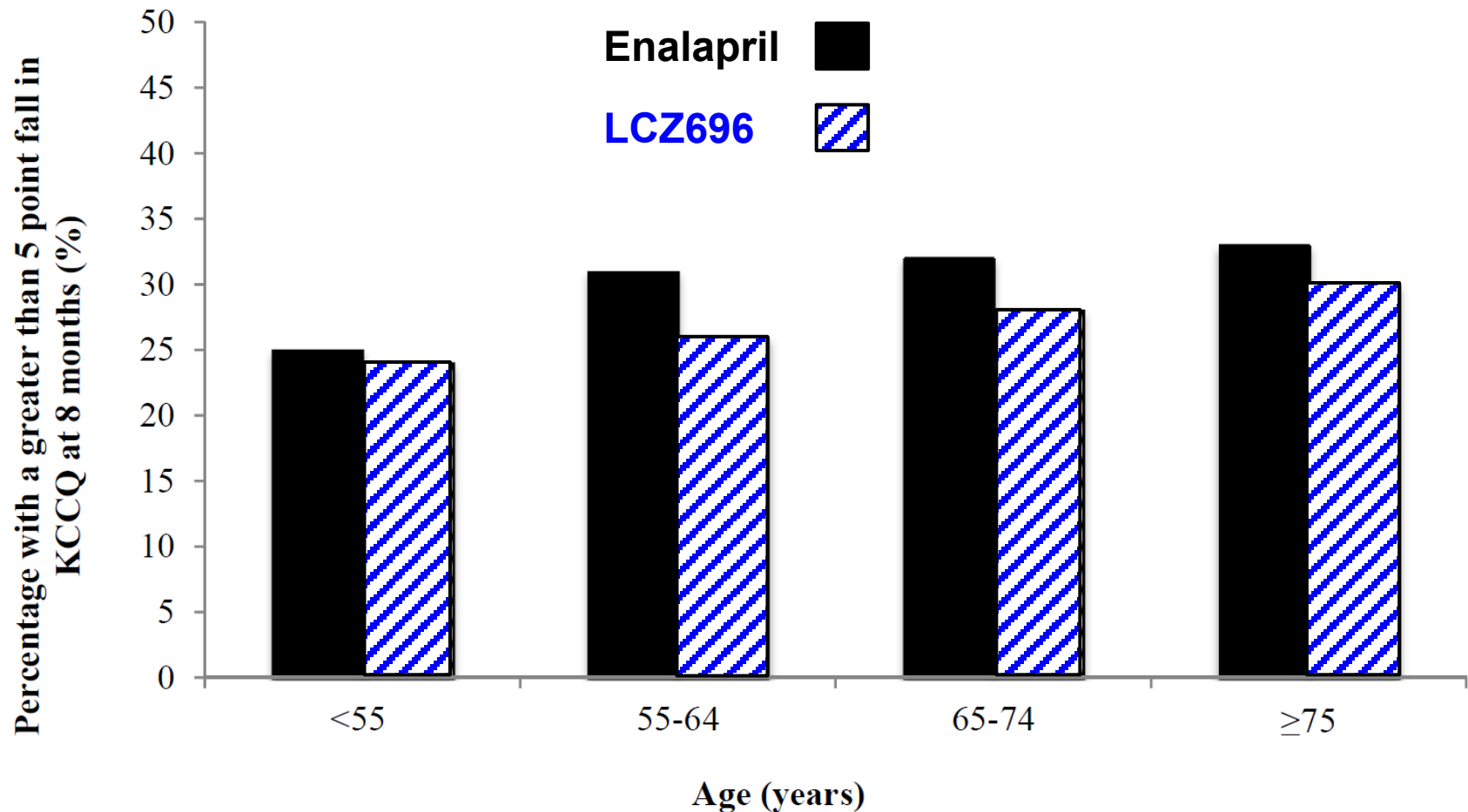


# Effect of LCZ696 on the primary endpoint according to baseline KCCQ score (tertiles)

	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  $\geq 5$  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*)**

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

\*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.**