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KILLIP CLASS AS A PREDICTOR OF SUDDEN CARDIAC DEATH: POST HOC ANALYSIS OF EPHESUS TRIAL DATA

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Background

- Patients with heart failure (HF) are especially susceptible to sudden cardiac death (SCD) after acute myocardial infarction (AMI).
- The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) previously demonstrated that in post-AMI patients with HF, aldosterone blockade with eplerenone in comparison to placebo decreased:
  - All-cause mortality by 15% (hazard ratio [HR]: 0.85; 95% confidence interval [CI], 0.75-0.96; $P = 0.008$).
  - Cardiovascular mortality by 17% (HR: 0.83; CI, 0.72-0.94; $P = 0.005$).
  - SCD by 21% (HR: 0.79; CI, 0.64-0.97; $P = 0.03$) over a mean follow-up of 16 months.[1]
- The effect on mortality, especially SCD, was profound within 30 days post-AMI (SCD, 37% reduction; 95% CI, 0.40-1.00; $P = 0.051$).[2]
- Inclusion/exclusion criteria for EPHESUS are shown in **Table 1**.
- Killip classification captures the presence and severity of HF in patients with AMI (**Table 2**). Since its development in 1967,[3] it has been validated as a predictor of mortality in patients with ST elevation MI (STEMI) treated with thrombolytic agents or percutaneous coronary intervention[4] as well as in patients with non-ST elevation MI (NSTEMI).[5]

Table 1. Inclusion and Exclusion Criteria in EPHESUS

Inclusion criteria	Clinically stable 3 to 14 days after AMI
	LVEF ≤ 40%
	Clinical evidence of CHF (pulmonary rales, pulmonary venous congestion on chest x-ray, presence of S3) or diabetes mellitus
Exclusion criteria	CHF of valvular or congenital etiology
	Unstable post-infarct angina
	Serum potassium > 5.0 mEq/L
	Serum creatinine > 2.5 mg/dL

AMI, acute myocardial infarction; CHF, congestive heart failure; LVEF, left ventricular ejection fraction.

Table 2. Killip Classification

Killip Class	Description	Diagnostic Criteria	Hospital Mortality Rate[a] in Original Series,[3] %
I	No HF	No clinical signs of cardiac compensation	6
II	HF	Pulmonary rales	
		S2 gallop	
		Pulmonary venous congestion	17
III	Severe HF	Frank pulmonary edema	38
IV	Cardiogenic shock (usually in patients with HF, often with pulmonary edema)	Systolic pressure ≤ 90 mm Hg	81
		Peripheral vasoconstriction	
		Oligouria	
		Cyanosis	
		Diaphoresis	

HF, heart failure.
[a]30-day rate.

Objective

- This post hoc analysis of the EPHESUS trial data examined the risk of SCD according to Killip class and/or left ventricular ejection fraction (LVEF) at baseline.

Methods

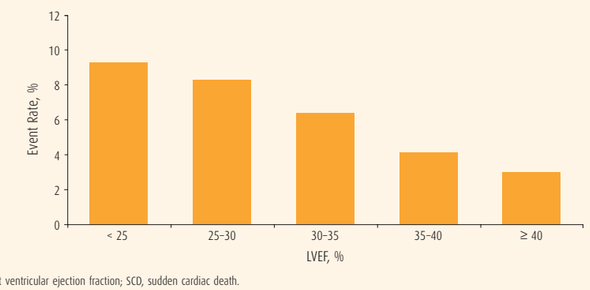
- 6632 patients were randomized 3 to 14 days post-AMI to treatment with placebo or the selective aldosterone blocker eplerenone 25 to 50 mg/d in addition to standard medical therapy.
- Data were collected through a mean follow-up of 16 months.
- A Cox regression model was used to analyze data. Covariates for treatment (eplerenone vs placebo), baseline Killip class (III/IV vs I/II), and baseline LVEF (< 30% vs ≥ 30%) were included in the model.
- Interaction between Killip class and LVEF was included in a separate model.

Table 3. Distribution of SCD by Killip Class and LVEF at Baseline

Subgroup			SCD
Killip Class	**LVEF**	**N**	**n (%)**
Class I/II	≥ 30	4263	163 (3.8)
	< 30	1015	78 (7.7)
Class III/IV	≥ 30	919	78 (8.5)
	< 30	379	42 (11.1)

LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

Figure 1. Lower LVEF was associated with higher rate of SCD.



LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

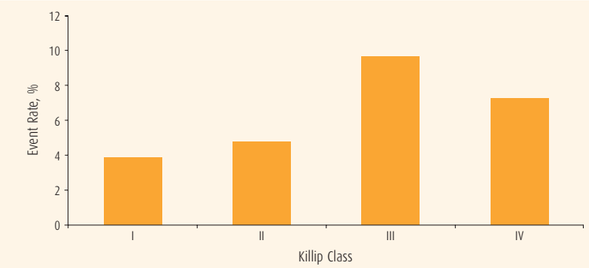
Table 4. SCD in Cox Proportional Hazards Model

Covariate	Hazard Ratio	95% CI	*P* Value
Treatment (eplerenone vs placebo)	0.78	(0.637, 0.965)	0.022
Killip class (III/IV vs I/II)	2.01	(1.615, 2.512)	< 0.001
LVEF (< 30 vs ≥ 30)	1.80	(1.442, 2.243)	< 0.001

The *P* value for testing interaction between Killip class and LVEF category was 0.052.

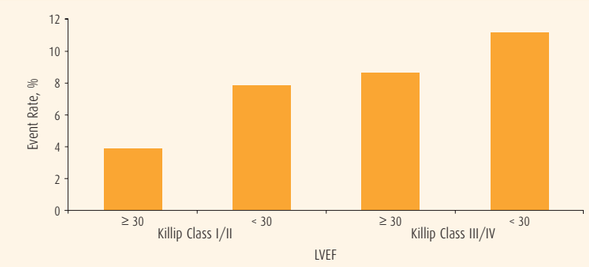
CI, confidence interval; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

Figure 2. Higher Killip class was associated with higher rate of SCD.



SCD, sudden cardiac death.

Figure 3. Rates of SCD by Killip class and LVEF.



LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

Results

- Distribution of patients and number (%) of SCD by Killip class and LVEF are shown in **Table 3**.
- Lower LVEF was associated with higher rates of SCD (**Figure 1**). After adjusting for treatment and Killip classes, risk of SCD was ~80% higher ($P < 0.001$) in subjects with LVEF < 30% compared with those with LVEF ≥ 30% (**Table 4**).
- High Killip classes were associated with higher rates of SCD (**Figure 2**). After adjusting for treatment and LVEF categories, risk of SCD was doubled ($P < 0.001$) in subjects with Killip class III/IV compared with those with Killip class I/II (**Table 4**).
- SCD occurred at higher rates in patients with LVEF < 30 when they were in Killip class I/II compared with those in Killip class III/IV (**Figure 3**). The interaction between Killip class and LVEF for SCD was significant ($P = 0.052$).

Discussion/Conclusion

- Killip class III/IV versus I/II was associated with a 2-fold increased risk of SCD.
- For patients in Killip class I/II, the risk of SCD was significantly higher when LVEF was < 30%.
- These results suggest the importance of determining Killip class and LVEF in efforts to predict the risk of SCD in post-AMI patients with HF.

References

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Acknowledgments

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