

**Influence of Ejection Fraction on Cause-specific mortality in Heart Failure with preserved
Ejection Fraction**

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Abbreviations

LVEF: left ventricular ejection fraction

CV: cardiovascular

HFpEF: heart failure with preserved ejection fraction

TOPCAT: treatment of preserved cardiac function heart failure with an aldosterone antagonist

HFrEF: heart failure with reduced ejection fraction

SCD: sudden cardiac death

Short Title: Influence of LVEF on mortality in HFpEF patients

Left ventricular ejection fraction (LVEF) is an important predictor of cardiovascular mortality in patients with heart failure (HF) and cause of death varies with ejection fraction.¹⁻³ Nevertheless, the influence of LVEF on cause-specific death in HF with preserved ejection fraction (HFpEF) patients is not well described.

We evaluated the influence of LVEF on cardiovascular (CV) and non-CV deaths in the Treatment of Preserved Cardiac function with an Aldosterone antagonist (TOPCAT) study. The TOPCAT trial enrolled HFpEF patients with LVEF \geq 45% and assessed the effect of spironolactone on a composite outcome of CV death, aborted cardiac arrest and hospitalization for HF management, over a median follow-up of 42 months.⁴ LVEF was determined at each site by echocardiography (96.7%), radionuclide ventriculography (2.3%) or angiography (1%).

All endpoints were adjudicated centrally by a blinded clinical endpoint committee. Deaths were classified into three categories: CV, non-CV, and unknown. CV deaths were further classified as sudden cardiac death (SCD), and death due to myocardial infarction (MI), pump failure, stroke, or another CV cause. Death was considered non-CV if an unequivocal and documented non-CV cause could be established as primary cause of death. Cause of death was considered unknown when there was insufficient data available to determine the reason to be CV or non-CV.⁵ We divided the range of LVEFs across the entire TOPCAT trial into four separate categories: \leq 47%, 48% to 52%, 53% to 57%, and \geq 58%. Each of these categories was centered around a multiple of 5, as we observed a substantial “digit preference” for LVEF values in multiples of 5 which has been seen in previous trials.² Baseline characteristics were summarized

for each group, and compared using trend tests. Unadjusted and age/sex adjusted incidence rates of cause-specific mortality were calculated across LVEF categories using Poisson regression models. The incident rates and proportions of cause-specific death were compared between lowest LVEF category versus others. All these analyses were conducted in the Americas (n = 1,767) owing to previously noted substantial regional differences in patient demographics, outcomes, and response to spironolactone in the TOPCAT trial.⁶

Among patients enrolled in Americas LVEF ranged from 44 to 85% (mean 58%, median 58%, 25th-75th percentile [53, 61%]). Baseline characteristics varied considerably by LVEF. Patients in higher LVEF categories were older, more likely to be female and have a history of hypertension, and less likely to be current smokers or have a history of MI, percutaneous coronary intervention, coronary artery bypass graft surgery or be on beta-blocker, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, than those with lower LVEFs (all $p < 0.05$). The crude and age/sex adjusted annualized rates of all-cause mortality, CV mortality and SCD were highest in the lowest LVEF category as compared to other categories ($p < 0.001$ for all components). Crude and age/sex adjusted annualized rates of pump failure, MI related, stroke related, non-CV death and unexplained death did not vary across LVEF categories (Figure). However, compared to patients with LVEF ≥ 48 , the proportion of SCD deaths in the lowest LVEF category was significantly higher (33% vs 17%, $p = 0.007$) and numerically higher for CV death (69% vs 56%, $p = 0.11$) and lower for non-CV death (22% vs 33%, $p = 0.13$).

The cause specific breakdown of CV and non-CV death was not reported by earlier smaller RCTs among (DIG-ancillary and PEP-CHF) HFpEF patients, the more recent RCTs including TOPCAT and I-PRESERVE have report these details on the mode of death among enrolled patients. Most of the HFpEF patients in these RCTs die of CV causes (60-70%) but none of the recent RCTs have evaluated the influence of LVEF on cause specific deaths. We have shown that rates of cause specific mortality in HFpEF patients vary by LVEF. The differences in cause of death across the LVEF spectrum in this HFpEF population may in part be explained by substantial variation in baseline characteristics across LVEF categories. HFpEF patients with lower LVEF had a higher proportion of coronary artery disease history and behaved more like HFrEF patients, perhaps accounting for higher rates of CV death and SCD rates in lower-LVEF HFpEF patients. On the other hand, patients in the higher LVEF categories had a lower burden of cardiovascular morbidities, thus explaining the higher proportion of non-CV deaths in these individuals. The proportion of deaths attributable to pump failure were quite low, while not unexpected, have potential implications for future investigation of non-heart failure therapies among these patients.

Our analyses have several limitations; LVEFs were measured at the sites in TOPCAT and verified on a fraction of enrolled subjects (27%) by the core laboratory. The core lab LVEFs were significantly greater by ~1.6 units than site reported LVEFs. There is substantial geographic variation in baseline characteristics and event rates in TOPCAT among patients

enrolled in Russia and the Republic of Georgia as compared to the Americas.^{6,7} Therefore, we have restricted these analyses to the Americas, in which we are more certain of the diagnosis of HF.

In summary, we found that baseline characteristics and event rates of cause-specific mortality in HFpEF vary by LVEF. These findings may have implications for future trials in HFpEF as the burden of disease modifiable by specific therapies may vary by LVEF.

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Figure Legend:

Figure: Age and sex adjusted annualized incidence of components of death by left ventricular ejection fraction in TOPCAT-Americas.

