New foundational therapy in heart failure with reduced ejection fraction: should we keep following the 2016 European Society of Cardiology Heart Failure Guideline in 2021?

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Introduction: The 2016 European Society of Cardiology Heart Failure Guidelines (2016 HF GL) suggest sequential therapy initiation with angiotensinogen converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), beta-blocker (BB) and mineralocorticoid receptor antagonist (MRA) for patients with heart failure with reduced ejection fraction (HFrEF). Since their publication, major trials established the benefit of sacubitril/valsartan (ARNi) and SGLT2 in HFrEF, and ARNi are suggested to replace ACEi/ARB as first line therapy. So, with HFrEF foundational therapy evolvement, the 2016 HF GL sequential therapy initiation algorithm has been raised into question.

Purpose: To compare in the real-world practice, the effect on all-cause mortality of the simultaneous use of every pharmacological class currently included in the HFrEF foundational therapy with conventional sequential therapy.

Methods: A population of consecutive patients (pts) included in a post-discharge structured follow-up programin in a tertiary center was analyzed. Two groups were defined: 1) patients medicated with all pharmacological classes considered the HFrEF foundational therapy (ARNi, BB, MRA and SGLT2 inhibitor), independently of the dosages – "FT group"; 2) patients medicated with ACEi/ARB, BB and MRA on maximal tolerated doses – "2016 HF GL group". Pts under other therapeutical combinations were excluded. The study groups were compared with Chi-square and Mann-Whitney tests. Impact on all-cause mortality was established with Kaplan-Meier survival analysis and multivariate Cox regression after adjustment for age, sex and baseline creatinine, NYHA functional class and LVEF.

Results: From 2016 to February 2021, a total of 101 pts with HFrEF were included and followed for 25±16 months. 54 pts were included in the FT group and 47 in the 2016 HF GL. The study population (69.3% males, 64.6±11.4 years) were mainly in NYHA functional class II (48%) and III (48%). The most common HF aethiologies were ischemic heart disease (49.5%) and dilated cardiomyopathy (30.7%), median LVEF was 26% and 22% were under CRT. Baseline characteristics were similar between groups, except for diabetes (more common in FT group, 70 vs 22%, $p<0.001$). All-cause mortality rate during follow-up was significantly different between two groups: 1.9% in FT group and 17% in the HF GL group (p: 0.047) – Figure 1. The implementation of all foundational therapy classes was an independent protective factor for all-cause mortality (HR 0.41; IQR 0.004–0.468; P: 0.010) in multivariate Cox regression.

Conclusion: This real-world study suggests that conventional sequential therapy suggested by the 2016 HF GL may be less effective on reducing all-cause mortality in HFrEF than simultaneous use of all pharmacological classes that nowadays compose the foundation therapy. These results support the hypothesis of promoting early introduction of all therapy classes followed by a tailored uptitration may be beneficial.

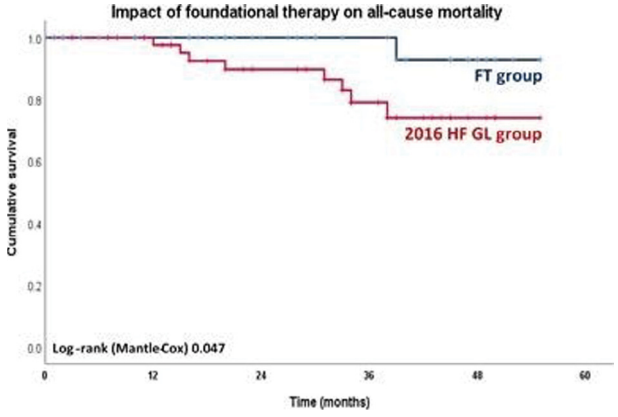

Figure 1