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Reply to 'Effects of tafamidis on heart failure hospitalization: The tale of the dog that did not bark'

We appreciate the comments from Aimo *et al.* on our recent publication describing all-cause survival among patients with New York Heart Association (NYHA) class III heart failure in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension (LTE) study.[1] We agree that further granularity on causation of hospitalization and mortality in patients with transthyretin amyloid cardiomyopathy (ATTR-CM) and severe heart failure symptoms would aid interpretation of tafamidis efficacy in this subgroup. The LTE study is ongoing and future analyses examining this may be possible after study completion.

As noted by Aimo *et al.*, the 30-month phase 3 ATTR-ACT was not designed or

powered to assess outcomes by NYHA class. Patients were randomized and the primary outcome was stratified by NYHA class, which showed a statistically significant reduction (30%) in all-cause mortality and a significantly lower (32%) relative risk of cardiovascular-related hospitalization with tafamidis treatment compared with placebo.[2] In NYHA class III patients specifically, a non-significant reduction (16%) in all-cause mortality and a significantly higher relative risk (41%) of cardiovascular-related hospitalizations were observed in patients treated with tafamidis compared with placebo.[2] Post-hoc analysis showed that this higher risk of cardiovascular hospitalizations was due to a confounding effect of lower mortality.[3] With adjustment for survival bias, tafamidis treatment was associated with a non-significantly lower (24%) risk of cardiovascular-related hospitalization versus placebo in patients who were NYHA class III at baseline and survived to the end of the study.[3]

Patients who completed ATTR-ACT were eligible to receive tafamidis in the LTE study, which remains ongoing. Those who received placebo in ATTR-ACT now receive tafamidis, and all patients have switched to the approved dose. Serial interim findings from the LTE study have shown a ~35% reduction in mortality among patients who were NYHA class III at baseline and treated with continuous tafamidis at the approved dose (in both the ATTR-ACT and the LTE study) compared with delayed tafamidis treatment (placebo in ATTR-ACT and tafamidis in the LTE study) after ~5 years of follow-up.[1,4] These analyses underestimate the treatment effect because the control group also receives tafamidis in the LTE study, and their median survival is longer than would be expected with continued placebo treatment.[1,4]

Findings from ATTR-ACT and the ongoing LTE study have demonstrated that tafamidis is associated with an increase in survival in patients in the NYHA class III subgroup at the start of treatment in ATTR-ACT. Since these patients have severe disease and a limited life expectancy, these improvements may be of great importance to both them and their families, in spite of the potential for additional hospitalization costs. With respect to our colleagues, our paper is not, as they suggest, a 'dog that did not bark' or a meaningful absence of fact; it is a positive and consistent demonstration of the effect of tafamidis in patients with an otherwise lethal disease.

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