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EDITORIAL COMMENT

Tafamidis Beyond the ATTR-ACT Trial

The Winner Takes It All*

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The fatal prognosis of patients suffering from transthyretin amyloid cardiomyopathy (ATTR-CM) has dramatically improved since the landmark results of the ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) published in 2018, which unveiled an entirely new therapeutic approach.[1] Tafamidis and its stabilizing effect on transthyretin tetramers were shown to reduce all-cause mortality and cardiovascular-related hospitalizations in affected patients and diminished the decline in functional capacity and quality of life compared with placebo. In this issue of *JACC: Advances*, Hanna et al[2] conducted a post hoc analysis to examine the proportion of ATTR-ACT patients who experienced improved efficacy measures throughout 30 months of the treatment with tafamidis (80 mg or 20 mg, n = 264) or placebo (n = 177). In addition to the key secondary end points of the ATTR-ACT trial, efficacy measures included assessment of longitudinal changes in serum N-terminal natriuretic peptide type B (NT-proBNP) concentration, patient global assessment of overall health, and New York Heart Association functional class in ATTR-ACT patients at distinct time points. The authors found that across all efficacy measures, treatment with tafamidis was associated with a higher likelihood of improvement than placebo at all time points. In detail, the odds ratio for improvement favored tafamidis ($P < 0.001$) at month 30 in the 6-minute walk test distance 4.9 (95% CI: 2.28-10.69), Kansas City Cardiomyopathy Questionnaire Overall Summary score 3.3 (95% CI: 1.85-5.78), serum NT-proBNP concentration 5.3 (95% CI: 2.66-10.73), and patient global assessment of overall health 2.9 (95% CI: 1.69-4.95). With this study, Hanna et al[2] expand the understanding of clinical expectation for tafamidis treatment and make an important contribution to the burgeoning knowledge on tafamidis, as several of these measures are also suggested to have prognostic value and add to the existing evidence of improved outcomes with tafamidis. In fact, a clear association between tafamidis treatment and a lower occurrence of cardiovascular outcomes in real life could be demonstrated.[3,4]

Further evidence of the clinical benefits of tafamidis in patients with ATTR-CM was provided by our own functional capacity study using serial cardiopulmonary exercise testing, showing improvement in physical performance in 54 ATTR-CM patients treated with tafamidis.[5] Based on emerging cardiac imaging evidence demonstrating potential treatment effects in ATTR-CM, clinical efficacy may be related to the beneficial impact of tafamidis on cardiac structure and function. In fact, data from recently published 2-dimensional speckle tracking echocardiography studies reported stabilizing effects on left ventricular (LV) functional parameters in patients treated with 61 mg of tafamidis compared to treatment-naïve ATTR-CM patients. Giblin et al[6] described a slower deterioration in LV global longitudinal strain, myocardial work index, and efficiency during 12 months of treatment with tafamidis compared with an untreated cohort. In line with this, we observed a slower deterioration of left atrial and LV longitudinal function when treating our patients with tafamidis, translating into significant clinical benefits compared with natural history.[7] These echocardiographic findings are further supported by cardiac magnetic resonance imaging studies, in which

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stabilization of late gadolinium enhancement and extracellular volume was observed in ATTR-CM patients treated with tafamidis, in contrast to a significant increase of late gadolinium enhancement and extracellular volume in the treatment-naive cohort.[8] Taken together, 4 years after the publication of the ATTR-ACT trial, which laid the grounds for market approval and broad use of tafamidis worldwide, there is ample evidence for its efficacy in all clinically relevant dimensions as well as for its beneficial effects on cardiac remodeling.

However, unlike under study conditions, there is no placebo group or untreated sibling in the real-world setting, and although tafamidis won against placebo in relevant endpoints, on an individual level, a majority of affected patients experience a decline in exercise capacity and quality of life and an increase in heart failure biomarkers. In fact, in the ATTR-ACT study, in absolute terms, both tafamidis- and placebo-treated patients showed progressive deterioration in health over time, in terms of 6-minute walk test distance as well as serum NT-proBNP levels. This lack in clinical improvement on an individual patient level is highly counterintuitive for clinicians practicing cardiovascular medicine and is contrasted by clinical benefits precepted by individual patients as well as structural and functional improvement of the heart, when applying pulmonary hypertension or heart failure treatments,[9,10] and monitoring a treatment effect that is beneficial only relative to an untreated comparison cohort, but not in absolute terms, can be challenging in clinical practice.

Taken together, there is consistent evidence of beneficial clinical effects of tafamidis compared with natural history. In particular, improvements in exercise capacity, quality of life, and cardiac health have been shown to be more likely in the treated cohort than those in untreated ATTR-CM patients, providing an important rationale for treatment decisions for both physicians and affected individuals.

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