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Editorial

The First Korean Clinical Evidence With Tafamidis in ATTR-CM

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▸ See the article "Real-World Efficacy of Tafamidis in Korean ATTR-CM Patients: A Retrospective Observational Strain Analysis" in volume 56 on page 232.

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Transthyretin amyloid cardiomyopathy (ATTR-CM) was once considered a rare and irreversible cause of heart failure, characterized by progressive myocardial infiltration of transthyretin amyloid fibrils leading to cardiac stiffness and dysfunction.[1] However, with the introduction of disease-modifying therapies, it has gained increasing recognition within the cardiology community.[2] The transthyretin stabilizer tafamidis demonstrated significant reductions in mortality and morbidity in the ATTR-ACT trial.[3] Nevertheless, although several studies from Japan have described the clinical experience and treatment outcomes with tafamidis,[4] evidence specific to Koreans remains limited.

In this issue of the *Korean Circulation Journal*, Shin et al.[5] report the first Korean experience with tafamidis therapy in patients with ATTR-CM. The investigators categorized patients into three groups: those not receiving tafamidis, those treated with 20 mg, and those treated with 80 mg daily. They evaluated serial echocardiographic and laboratory parameters over a 12–24-month follow-up. They also assessed the composite endpoint of all-cause mortality and worsening heart failure requiring hospitalization or urgent visits. This study provides important real-world evidence showing that tafamidis-treated patients experienced lower rates of adverse clinical events compared with untreated patients, with consistent findings across both dose groups. These results align with observations from the ATTR-ACT trial[3] and provide valuable region-specific evidence from Korea.

Beyond clinical outcomes, the authors contribute novel echocardiographic data. Comprehensive strain analysis demonstrated slower functional decline in the left ventricle (LV), left atrium (LA), and right ventricle (RV) among tafamidis-treated patients. Particularly, the LA stiffness index and RV-pulmonary circulation coupling index appeared more sensitive to disease progression than conventional LV ejection fraction or LV global longitudinal strain. These findings highlight the utility of multi-chamber strain parameters as more dynamic and sensitive complementary measures for monitoring therapeutic response of ATTR-CM. However, these parameters, while physiologically appealing, require prospective validation in larger cohorts before their prognostic and therapeutic implications can be applied in routine clinical practice.

The inclusion of an untreated group strengthens the interpretation of the results by allowing direct comparison with the natural course of the disease. Event rates were highest in

Data Sharing Statement

The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions

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untreated patients (all-cause mortality 50%, worsening heart failure 46.7%), emphasizing the progressive nature and clinical burden of unmodified disease. Notably, baseline imbalances reflected real-world practice. Patients in the 80 mg group were generally older, had greater comorbidity burdens, and more advanced disease at baseline, reflecting reimbursement-driven selection of higher-risk patients. Even within this high-risk population, the tafamidis treatment was associated with a lower adjusted risk for the composite outcomes, although the dose-group comparison was constrained by the small sample size.

While this study adds meaningful real-world evidence, several limitations should be considered when interpreting these findings. The low proportion of wild-type ATTR-CM (7 of 47 treated patients) contrasts with global experience, where wild-type disease accounts for 80–90% of cases.[3)6)7)] This imbalance limits generalizability, as the current cohort mainly reflects hereditary rather than senile disease. Moreover, these findings warrant cautious interpretation and may not be directly applicable to predominantly wild-type populations, which account for the majority of ATTR-CM cases in Western cohorts. Broader inclusion of wild-type ATTR-CM in future real-world studies, particularly through post-marketing surveillance, will be essential to more accurately define the efficacy of tafamidis across the full disease spectrum.

The comparison between tafamidis 20 and 80 mg also warrants cautious interpretation. Given that all patients receiving 20 mg carried mutant transthyretin (TTR) genotypes, a meaningful comparison between the 2 doses is not feasible in this study. Consequently, the present findings should not be interpreted as validation of the superior efficacy of 80 mg reported in the ATTR-ACT trial. Although the Kaplan-Meier curves visually suggest greater benefit with 20 mg compared with 80 mg, this apparent difference likely reflects imbalance in baseline characteristics rather than true dose-dependent efficacy. In particular, patients receiving 20 mg were generally younger and initiated tafamidis at an earlier disease stage, which could have influenced the observed survival patterns. While N-terminal pro-B-type natriuretic peptide (NT-proBNP) served as a strong prognostic biomarker, tafamidis treatment did not appear to reduce NT-proBNP levels over time. Troponin, another key prognostic marker, was measured in only about half of the cohort (41 of 77 patients), limiting its clinical interpretation.[1)] Finally, the multivariable models did not adjust for concurrent heart failure therapies, including angiotensin receptor blockers, mineralocorticoid receptor antagonists or sodium-glucose cotransporter-2 inhibitors, which may have confounded the observed associations.

While tafamidis remains the established treatment of ATTR-CM, several next-generation disease-modifying agents,[8)] including the TTR stabilizer acoramidis (ATTRibute-CM trial),[6)] the TTR silencers vutrisiran (HELIOS-B trial),[7)] and the TTR depleting monoclonal antibody ALXN2220, currently being evaluated in an ongoing phase 3 study (DepleTTR-CM trial).[9)] However, these agents have not yet been approved or reimbursed in Korea, underscoring the need for regional validation. Despite the progress, key clinical questions remains in ATTR-CM, such as the optimal timing of treatment initiation (at diagnosis vs. disease progression), outcomes following treatment switch or combination therapy,[10)] and cost-effectiveness in older and high-risk wild type populations.

In summary, Shin et al.[5)] provide the first real-world analysis of tafamidis therapy in Korean patients with ATTR-CM and identify LASI and RV-PC coupling index as potential markers for clinical monitoring. While this two-center experience offers preliminary evidence of

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tafamidis efficacy in Korea, broader multi-center prospective studies incorporating genotype, biomarker, and imaging parameters are needed to refine patient selection and optimize the treatment strategies across the spectrum of ATTR-CM.

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