



Targeting transthyretin (TTR) stability for amyloid cardiomyopathy: a landmark shift in heart failure therapy

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Transthyretin amyloid cardiomyopathy (ATTR-CM) is now being increasingly recognized as a previously underdiagnosed cause of heart failure in later life, occurring in two forms – hereditary (ATTRv-CM) and wild type (ATTRwt-CM), both with poor prognoses and a median survival rate of 2–6 years. ATTR-CM is the consequence of extracellular deposition of misfolded transthyretin (TTR) protein in the myocardium, progressively leading to restrictive cardiomyopathy, diastolic dysfunction, and heart failure. However, the introduction of a TTR stabilizer, based on the ATTR-ACT trial, is expected to be a turning point in disease-specific treatment for ATTR-CM. The recently conducted ATTR-ACT trial has proven that TTR stabilizers reduce mortality by 30% and cardiovascular-related hospitalizations by 32% over placebo. This means that patients treated with TTR stabilizers had a significantly lower risk of death and fewer hospital visits due to heart-related issues, with excellent treatment adherence (97.2% for TTR stabilizer). These outcomes were particularly evident in NYHA class I–II symptom patients, though further investigations continue to define its role in class III heart failure^[1]. Tafamidis is one of the substantial drugs among TTR kinetic stabilizers that bind to the thyroxine-binding sites on TTR and inhibit tetramer dissociation, the rate-limiting step in amyloid fibril formation^[2,3].

Shah *et al* further reported tafamidis's (80 mg) role in stabilizing left ventricular ejection fraction (LVEF), with marked echocardiographic improvements in left ventricular (LV) stroke volume, global longitudinal strain, and E/e' ratios^[4]. Drachma *et al* substantiated long-term efficacy, finding enhanced survival with a 47% decrease in the risk of mortality and improved quality of life after 60 months (approximately 5 years) in patients with baseline

LVEF <50% and ≥50%^[5]. Despite promising trial studies, several measures should be taken to overcome diagnostic delays and ensure the timely administration of TTR stabilizers. There is a need for clinical education on red-flag signs, such as unexplained LV hypertrophy, bilateral carpal tunnel syndrome, or atrial arrhythmias in elderly patients^[3]. Screening should be given priority in patients with heart failure symptoms, particularly decreased or preserved LVEF^[4]. Encouraging advanced imaging, such as bone scintigraphy, which can detect amyloid deposits in the heart, and genetic testing, which can identify the specific mutation causing ATTR-CM, can facilitate early detection of the disease and enable the initiation of TTR stabilizers before irreversible cardiac damage^[1,2]. We seek to highlight the therapeutic potential of TTR stabilizers as an effective treatment option for ATTR-CM by reflecting its role in improving survival, cardiovascular-related outcomes, and quality of life in the eligible population.

However, the affordability and availability of such treatment options are still significant problems, particularly in low- and middle-income countries. Nevertheless, future research to evaluate safety and effectiveness and comparative trials with other new therapies, such as gene silencers and CRISPR-based therapies, may establish the accurate position of TTR stabilizers in the dynamic treatment strategy.

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MK conceptualized the article, critically evaluated the literature. TKD drafted the manuscript. GSR supervised the final revision. SGR made the essential editing and participated in the final review. All authors read and approved the final manuscript.

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