Targetting transthyretin stability for amyloid cardiopathy

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The plasma protein transthyretin (TTR) transports retinol-binding protein and thyroxine.[1]Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive cause of heart failure caused by the deposition of misfolded TTR protein as amyloid fibrils in the myocardium, leading to impaired cardiac function.[1] As the disease progresses, supportive care alone has limited impact, which has prompting the development of disease-modifying therapies in recent years.

The most well-established therapy is tafamidis, approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). It binds to thyroxine-binding sites on TTR, preventing tetramer dissociation and thereby inhibiting amyloid formation. Numerous post-2020 real-world trials validate that tafamidis substantially prolongs survival, decreases cardiovascular hospitalizations, and provides the maximum benefit when started early.[2] Diflunisal, an off-label non-steroidal anti-inflammatory drug (NSAID), also stabilises TTR but is not commonly used because of its gastrointestinal and renal side effects. Novel gene-silencing therapies, such as patisiran and inotersen, reduce hepatic production of TTR, lowering circulating levels and preventing further amyloid deposition.[3]

The APOLLO-B trial demonstrated that patisiran improved the six-minute walk distance, quality of life, and reduced N-terminal pro-B-type natriuretic peptide (NT-proBNP), a marker of cardiac stress.[3] Similarly, long-term extension studies of tafamidis show improved survival even in advanced-symptom patients, with earlier treatment initiation yielding the greatest benefit.[4] These results reinforce that early recognition and prompt initiation of treatment are essential in altering the course of disease, enhancing outcomes, and maintaining quality of life.

Despite the therapeutic advances, the high cost and limited accessibility of tafamidis and gene silencing agents restrict their widespread use, particularly in low- and middle-income countries. Data from diverse populations are also lacking, underlining the need for broader clinical trials. Furthermore,there is growing interest in combination approaches, such as TTR stabilisers with silencers, which may offer synergistic benefit. Similarly, development of reliable biomarkers for early detection and monitoring of treatment response remains an unmet need.

In conclusion, while ATTR CM treatment has shifted from supportive care to disease-modifying options, early diagnosis, timely initiation of therapy, and wider access remain crucial. Addressing these gaps through dedicated research and cost-effective strategies is essential to improve survival and quality of life in affected patients.

DOI: https://doi.org/10.47391/JPMA.33036

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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Submission complete: 07-10-2025 **First Revision received:**29-10-2025
Acceptance: 14-01-2026 **Last Revision received:**13-01-2026

AUTHORS' CONTRIBUTIONS:
NA: Writing, drafting, reviewing and final approval.
RBT: Reviewing, minor editing and final approval.
SK: Drafting, added content, reviewing and final approval.