Cleveland Clinic
Sydell and Arnold Miller Family
Heart, Vascular and Thoracic Institute

Tall Rounds®

Fast-paced, case-based online learning with the No. 1 hospital for heart care. Complimentary CME credit available.

clevelandclinic.org/tallrounds @TallRoundsTM

This activity has been approved for AMA PRA Category 1 Credit™.

The Rescue: Treating Confirmed ATTR

CLINICAL COMPANION TOOL

Key Concepts for Treatment

- Treatment combines supportive care for cardiac amyloidosis (CA), often in conjunction with other medical specialties to manage extracardiac manifestations, and disease-modifying/targeted therapies that are approved or in clinical trials[1]
- A multidisciplinary team and network approach to care ensures the best outcomes for patients
- Tafamidis is an FDA-approved transthyretin stabilizer to treat ATTR-CM
- The treatment paradigm is shifting from reduction to removal of amyloid deposits
- Several therapies are in development, including antibodies that can remove amyloid deposits, and your patient may benefit from participation in a clinical trial
- Earlier treatment initiation, combined with appropriate patient selection and expectations, ensures better outcomes

Cardiac Amyloidosis

Targets of therapy

	Block Protein Synthesis	Stabilize Tetramer	Remove Fibrils
Mechanism of Action	• Gene silencing using small interfering RNA (siRNA) or antisense oligonucleotides • Gene editing using CRISPR Cas 9	Stabilizes the tetramer, thereby reducing the availability of monomers for amyloidogenesis	Antibody-mediated phagocytosis removes ATTR amyloid deposits
Therapies: Approved and In Development	**siRNA** • Patisiran*[2] • Vutrisiran*[3] **Antisense** • Inotersen*[4] • Eplontersen*[5] **CRISPR Cas 9** • NTLA-2001[6]	• Tafamidis**[7] • Diflusinal[8] • Acoramidis[6]	• NNC6019[10] • NI1006 (ALXN2220)[11,12] • AT-02[13]

*FDA-approved for ATTR-PN; **FDA-approved for ATTR-CM

Current as of Jan. 24, 2024

Cleveland Clinic
Sydell and Arnold Miller Family
Heart, Vascular and Thoracic Institute

Tall Rounds®

Fast-paced, case-based online learning with the No. 1 hospital for heart care. Complimentary CME credit available.

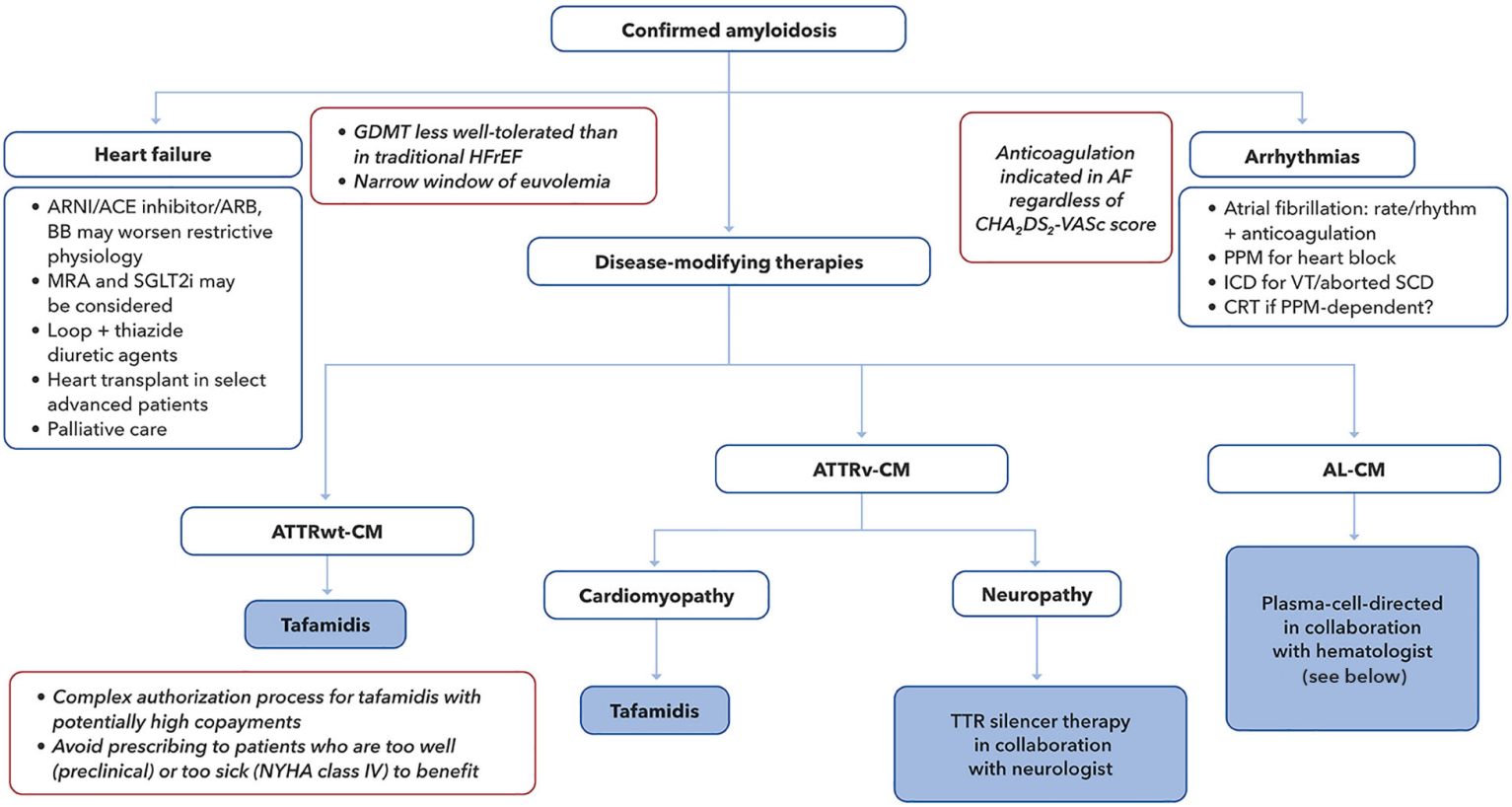
clevelandclinic.org/tallrounds @TallRoundsTM

This activity has been approved for AMA PRA Category 1 Credit™.

The Rescue: Treating Confirmed ATTR

CLINICAL COMPANION TOOL

Management algorithm[1]



AF, atrial fibrillation; ARNI/ACE inhibitor/ARB, renin-angiotensin system inhibitors; AL-CM, amyloid monoclonal immunoglobulin light chain; ATTR, amyloid transthyretin; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; BB, beta-blocker; CRT, cardiac resynchronization therapy; HFrEF, heart failure with reduced ejection fraction; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; PPM, permanent pacemaker; SCD, sudden cardiac death; SGLT2i, sodium glucose cotransporter 2 inhibitor; TTR, transthyretin; VT, ventricular tachycardia.

The Rescue: Treating Confirmed ATTR

CLINICAL COMPANION TOOL

AL Amyloidosis

Light chain amyloidosis (AL) most commonly results from clonal plasma cell disorder and, therefore, treatments include chemotherapy and immunotherapy agents similar to those used for myeloma.

Targets of therapy[14,15]

Therapies approved and in development:

Reduction in Light Chain Production	Inhibition of Amyloid Fibril Formation	Removal of Light Chain Amyloid Deposits
• Bortezomib • Carfilzomib • Daratumumab • Elotuzumab • Isatuximab • Ixazomib • Lenalidomide • Pomalidomide • Venetoclax	• Doxycycline	Anti-fibril antibodies • Anselamimab (CAEL-101) • Birtamimab

Current as of Jan. 24, 2024

Cleveland Clinic
Sydell and Arnold Miller Family
Heart, Vascular and Thoracic Institute

Tall Rounds®

Fast-paced, case-based online learning with the No. 1 hospital for heart care. Complimentary CME credit available.

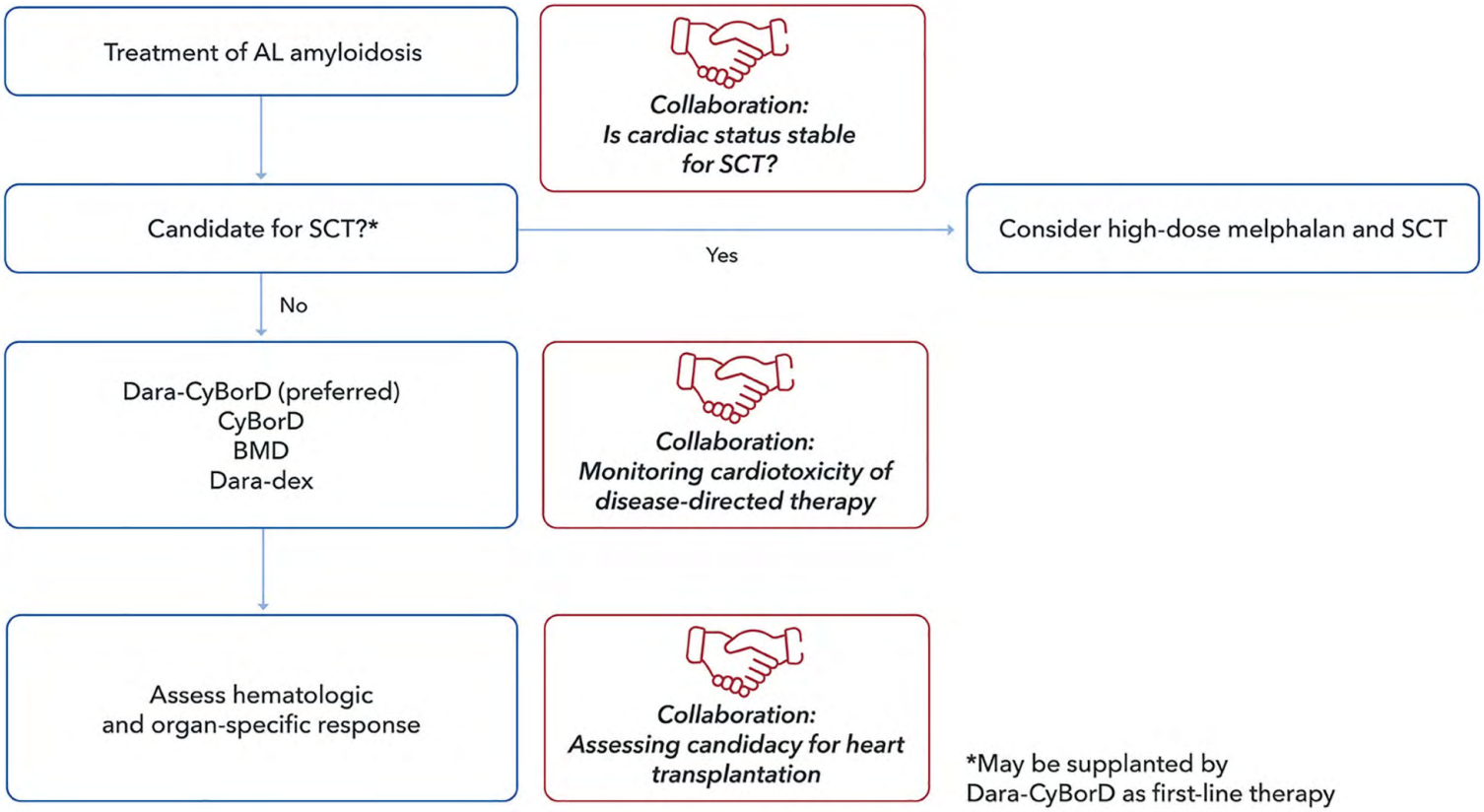
clevelandclinic.org/tallrounds @TallRoundsTM

This activity has been approved for AMA PRA Category 1 Credit™.

The Rescue: Treating Confirmed ATTR

CLINICAL COMPANION TOOL

Management algorithm[1]



AL, light-chain amyloidosis; BMD, bortezomib-melphalan-dexamethasone; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; Dara, daratumumab; dex, dexamethasone; SCT, stem cell transplantation

The Rescue: Treating Confirmed ATTR

CLINICAL COMPANION TOOL

References

1. Writing Committee, Kittleson MM, Ruberg FL, et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis: A Report of the American College of Cardiology Solution Set Oversight Committee [published correction appears in *J Am Coll Cardiol*. 2023 Mar 21;81(11):1135]. *J Am Coll Cardiol*. 2023;81(11):1076-1126.
2. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11-21.
3. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*. 2023;30(1):1-9.
4. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):22-31.
5. Coelho T, Marques W Jr, Dasgupta NR, et al. Eplontersen for hereditary transthyretin amyloidosis with polyneuropathy. *JAMA*. 2023;330(15):1448-1458.
6. Gillmore JD, Gane E, Taubel J, et al. CRISPR-Cas9 in vivo gene editing for transthyretin amyloidosis. *N Engl J Med*. 2021;385(6):493-502.
7. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379(11):1007-1016.
8. Siddiqi OK, Mints YY, Berk JL, et al. Diflunisal treatment is associated with improved survival for patients with early stage wild-type transthyretin (ATTR) amyloid cardiomyopathy: the Boston University Amyloidosis Center experience. *Amyloid*. 2022;29(2):71-78.
9. Gillmore JD, Judge DP, Cappelli F, et al. Efficacy and safety of acoramidis in transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2024;390(2):132-142.
10. A research study to look at how a new medicine called NNC6019-001 works and how safe it is for people who have heart disease due to transthyretin (TTR) amyloidosis. NCT05442047.
11. Garcia-Pavia P, Aus dem Siepen F, Donal E, et al. Phase 1 trial of antibody NI006 for depletion of cardiac transthyretin amyloid. *N Engl J Med*. 2023;389(3):239-250.
12. Study of ALXN2220 versus placebo in adults with ATTR-CM (DepleTTR-CM). NCT06183931.
13. A study of AT-02 in subjects with systemic amyloidosis. NCT05951049.
14. Zhang KW, Stockerl-Goldstein KE, Lenihan DJ. Emerging therapeutics for the treatment of light chain and transthyretin amyloidosis. *JACC Basic Transl Sci*. 2019;4(3):438-448.
15. Mahadevia H, Ponvilawan B, Sharma P, et al. Advancements and future trends of immunotherapy in light-chain amyloidosis. *Crit Rev Oncol Hematol*. 2023;183:103917.