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REVIEW

Specific treatment of ATTR-CM in Germany—expert consensus of the German Society of Amyloid Diseases (DGAK) and German Cardiac Society (DGK)

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Abstract

Background Transthyretin amyloid cardiomyopathy (ATTR-CM) is an increasingly recognized cause of heart failure. Three disease-modifying agents are now approved for treatment in Germany: the transthyretin (TTR) stabilizers tafamidis and acoramidis, and the TTR gene silencer vutrisiran. In the absence of head-to-head trials, practical guidance for individual treatment decisions is lacking.

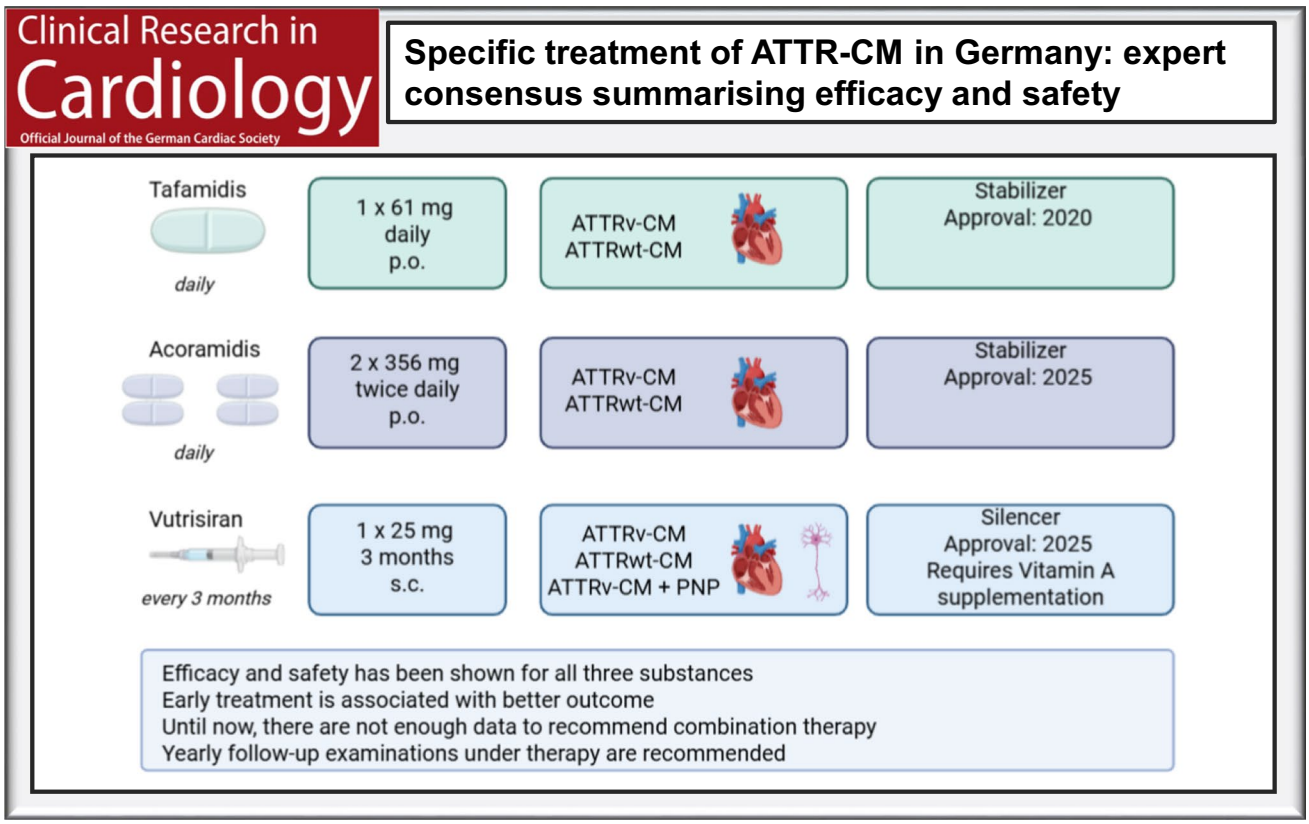
Methods A multidisciplinary expert panel appointed by the German Society of Amyloid Diseases (DGAK) and the German Cardiac Society (DGK) performed a comprehensive review of pivotal randomized controlled trials, open-label extension studies, real-world data, and the approved German summaries of product characteristics to develop evidence-based consensus recommendations.

Results All three agents have demonstrated significant reductions in all-cause mortality and cardiovascular hospitalizations in phase 3 trials with comparable efficacy and tolerability profiles. Due to the absence of direct comparative studies, the panel concludes that tafamidis, acoramidis, and vutrisiran, based on the current scientific data, are considered similarly effective for most patients with confirmed ATTR-CM. An exception applies to patients with hereditary ATTR-CM and a mixed phenotype (concurrent cardiomyopathy and polyneuropathy), for whom vutrisiran is recommended as first-line therapy. Combination therapy is safe but, lacking randomized data regarding efficacy, cannot be recommended at present. Treatment decisions should incorporate patient preferences, comorbidities, mode of administration, and local regulatory frameworks. Regular monitoring using clinical parameters, biomarkers including TTR serum levels, and cardiac imaging is recommended.

Conclusions This consensus provides a practical framework for the specific treatment of ATTR-CM in Germany, aiming for early treatment initiation. Local standards and shared decision-making remain essential for the establishment of ATTR-CM therapy in an individual patient.

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Graphical abstract



Keywords ATTR-CM · Amyloidosis · Tafamidis · Acoramidis · Vutrisiran

Introduction

Transthyretin (TTR) amyloid cardiomyopathy (ATTR-CM) is increasingly recognized as a cause of heart failure worldwide, reflecting heightened awareness and advances in diagnostic imaging and therapeutic strategies. To date, three agents from two drug classes (TTR stabilizers and TTR gene silencers) have been approved for treatment of ATTR-CM in Germany.

Stabilizers selectively bind to the unoccupied thyroid hormone-binding site of the native TTR tetramer, thereby preventing its dissociation—the rate-limiting step in amyloidogenesis. Currently, two stabilizers are available in Germany: tafamidis, approved in 2020 [1], and acoramidis, approved in 2025 [2]. In contrast, TTR gene silencers markedly reduce hepatic production of the TTR precursor protein. The small-interfering RNA (siRNA) vutrisiran was approved for the treatment of ATTR-CM in 2025 [3].

Efficacy and safety have been demonstrated for all agents in randomized, placebo-controlled trials. However, the absence of head-to-head studies precludes direct comparison, and differences in trial design and time of performance resulted in heterogeneous study populations [4]. Nevertheless, clinicians face the challenge of making individualized therapeutic decisions based on the available evidence.

This expert consensus summarizes the recommendations for the treatment of ATTR-CM based on a comprehensive review of current evidence on clinical outcomes, drug tolerability, and factors relevant to individualized treatment decisions in Germany. To ensure timely guidance, the authors included data from published manuscripts, peer-reviewed and published scientific abstracts, and officially approved German *summary of product characteristics*.

The panel of experts that developed this report was selected and appointed by the German Society of Amyloid Diseases (DGAK) and the German Cardiac Society (DGK).

Specific treatment of ATTR-CM: tafamidis

Efficacy

The clinical efficacy of tafamidis has been demonstrated in phase II studies, the pivotal phase III trial ATTR-ACT [1],

Table 1 Characteristics and phase III evidence of disease-modifying treatment options of ATTR-CM

		Tafamidis		Acoramidis		Vutrisiran	
Pivotal phase III trial		ATTR-ACT [1]		ATTRibute-CM [2]		HELIOS-B [3, 4]	
	Recruitment period	12/2013–08/2015		04/2019–10/2020		12/2019–08/2021	
	Randomization	Tafamidis 80 mg: tafamidis 20 mg: placebo = 2:1:2 Results are reported for the pooled tafamidis group		Acoramidis 2 × 800 mg: placebo = 2:1		Vutrisiran 25 mg: placebo = 1:1	
	N	441		Total: 632 Modified intention-to-treat population (exclusion of 21 pts. with stage 4 kidney disease): 611 Efficacy measures reported for *n* = 611 Safety measures reported for *n* = 632		654 (= overall population) Monotherapy population (patients who were not receiving tafamidis at baseline; *n* = 395)	
		Placebo	**Tafamidis**	**Placebo**	**Acoramidis**	**Placebo**	**Vutrisiran**
	Age (years)	74 ± 7	75 ± 7	77 ± 7	77 ± 7	76 (46–85)	77 (45–85)
	Male sex (%)	89	91	88	91	93	92
	NAC stage (%)			57	57	70	64
	1			33	32	27	31
	2			10	11	4	6
	3						
	NYHA functional class (%)	7	9	12	8	11	15
	1	57	61	70	77	79	77
	2	36	30	18	15	11	8
	3						
	NT-proBNP median (pg/mL)	3161	2996	2306	2326	1801	2021
	ATTRv (%)	24	24	10	10	12	11
	Tafamidis at baseline(%)	-	-	-	-	40	39
	Tafamidis drop-in (%)	-	-	23	15	13	13
	SGLT2i at baseline (%)	-	-	-	-	3	3
	SGLT2i drop-in (%)	-	-	-	-	35	31
	Inclusion criteria	• Age 18–90 years • Medical history of heart failure • IVS > 12 mm • NT-proBNP ≥ 600 pg/mL • 6MWD > 100 m • eGFR ≥ 25 ml/min • NYHA I–III		• Age 18–90 years • Clinical heart failure • IVS ≥ 12 mm • NT-proBNP ≥ 300 and < 8500 pg/mL • 6MWD ≥ 150 m • eGFR > 15 mL/min (patients with eGFR < 30 were excluded from the primary analysis) • NYHA I-III • not on TTR stabilizer		• Age 18–85 years • Clinical heart failure • IVS > 12 mm • NT-proBNP > 300 pg/ml (> 600 pg/mL in aFib) and < 8500 pg/ml • 6MWD ≥ 150 m • NYHA ≤ III (if NYHA III, then NAC stage < 3 required) • eGFR ≥ 30 mg/dl • On tafamidis or not planning to start tafamidis for 12 months	

Table 1 (continued)

	Tafamidis	Acoramidis	Vutrisiran
Study duration (months)	30	30	36 42 months for mortality (incl. first 6 months of OLE)
Primary endpoint	All-cause mortality, frequency of cardiovascular-related hospitalizations win ratio 1.7 [95% CI, 1.26–2.29], $p < 0.001$	All-cause mortality, cumulative cardiovascular hospitalizations, change in NT-proBNP, and change in the 6MWD Win ratio 1.8 [95% CI, 1.4–2.2], $p < 0.001$	Composite of death from any cause and recurrent cardiovascular events (hospitalizations for CV causes or urgent visits for heart failure) Overall population HR: 0.72 [95% CI, 0.56–0.93], $p = 0.01$ Monotherapy population HR: 0.67 [95% CI, 0.49–0.93], $p = 0.02$
Statistical design (primary endpoint)	Win Ratio/Finkelstein-Schoenfeld	Win Ratio/Finkelstein-Schoenfeld	Modified Andersen–Gill model All end points assessed separately in the overall population and in the monotherapy population
All-cause death	30 months: Pooled tafamidis 29.5% Placebo 42.9% HR: 0.70 [95% CI, 0.51–0.96], $p = 0.026$ ARR = 0.13 NNT = 8	30 months [14]: HR: 0.77 [95% CI, 0.58–1.02] ARR = 0.06 NNT = 16 42 months (incl. 12 months of OLE, acoramidis vs. placebo-to-acoramidis): HR 0.64 [95% CI, 0.47–0.88] $p < 0.0001$ [14]	42 months (incl. 6 months of OLE): overall population HR: 0.69 [95% CI, 0.49–0.98], $p = 0.04$ ARR = 0.11 NNT = 10 Monotherapy population HR: 0.66 [95% CI, 0.44–0.97], $p = 0.045$ ARR = 0.07 NNT = 14
CV death	Pooled tafamidis over 30 months: 20.1% Placebo: 28.2% HR: 0.69 [95% CI, 0.49–0.98] [15]	CV mortality over 42 months [16] HR: 0.55 [95% CI, 0.39–0.79], $p = 0.0011$	CV mortality over 42 months Overall population; HR: 0.67 [95% CI, 0.47–0.96] [17] Monotherapy population: HR: 0.64 [95% CI, 0.41–0.98]
CV hospitalisation	Rate: tafamidis 0.48 Placebo 0.70 RRR = 0.68 [95% CI, 0.56–0.81], $p < 0.001$ [15]	**First cardiovascular hospitalization**: HR: 0.60 [95% CI, 0.45–0.80], $p = 0.0005$) [18] **Recurrent cardiovascular hospitalizations**: RRR = 0.50 [95% CI, 0.36–0.70], $p < 0.0001$	**Recurrent CV event** Overall population RR: 0.73 [95% CI, 0.61–0.88], $p = 0.001$ Monotherapy population RR: 0.68 [95% CI, 0.53–0.86], $p = 0.001$ **CV hospitalization** Overall population: RR: 0.75 [95% CI, 0.62–0.91], $p < 0.01$ [17] Monotherapy population RR: 0.66 [95% CI, 0.51–0.86], $p < 0.01$ [17]

Table 1 (continued)

	Tafamidis	Acoramidis	Vutrisiran
HF hospitalisation	Tafamidis: 43% Placebo: 50% RRR = 0.65 [95% CI, 0.52–0.81] [15]	RR: 0.57 [95% CI 0.42–0.77], $p < 0.0003$ [19] Outpatient worsening heart failure event: HR: 0.59 [95%CI, 0.46–0.75], nominal $p < 0.0001$ [20]	**HF hospitalization:** Overall population RR: 0.67 [95% CI, 0.52–0.86], $p < 0.01$ Monotherapy population RR: 0.62 [95% CI, 0.45–0.86], $p < 0.01$ [17] **Urgent HF visits:** Overall population RR: 0.54 [95% CI, 0.30–0.98], $p = 0.04$ [17] Monotherapy population RR: 0.76 [95% CI, 0.40–1.42], $p = 0.39$ [17]
6MWD (meters difference to placebo)	+76 $p < 0.001$	+39.6 [95% CI, 21.1–58.2], $p \leq 0.001$	Overall population +26.5 [95% CI, 13.4–39.6], $p < 0.001$ Monotherapy population +32.1 [95% CI, 14.0–50.2], $p < 0.001$
		Increase > 35 m: acoramidis: 15.4% placebo: 8.4% [21] OR 2.0 [95% CI, 1.1–3.5], $p = 0.02$	Vutrisiran vs. placebo at month 30: Increase > 7 m [49.6% vs 33.2%] Increase > 15 m [55.5% vs 38.6%] Increase > 35 m [68.5% vs 51.6%]; all $p < 0.001$ [22]
KCCQ (points, difference to placebo)	+14 $p < 0.001$ [1]	+9.9 [95% CI, 5.97–13.91], $p < 0.001$ [2]	Overall population +5.8 [95% CI, 2.4–9.2], $p < 0.001$ Monotherapy population +8.7 [95% CI, 4.0—13.4], p < 0.001 [3]
	Tafamidis vs. placebo at month 30: Improvement or no worsening of KCCQ-OS: 42% vs. 21% [24]	Acoramidis vs. placebo at moth 30 [23]: "Alive and Not Worse" (KCCQ-OS < 5 and < 10-point decrease from baseline) 171 (47%) vs. 56 (30%) OR: 2.1 [95% CI, 1.4–3.1], $p < 0.001$ "Alive and Well" (KCCQ-OS > 60 and < 10-point decrease from baseline) 168 (46%) vs. 59 (31%) OR 1.9 [95% CI, 1.3–2.8], $p = 0.001$ "Alive and Better" (KCCQ-OS > 5 and > 10-point increase from baseline) 93 (25%) vs. 26 (14%) OR: 2.1 [95% CI, 1.3–3.4], $p = 0.0017$	Vutrisiran vs. placebo at month 30 [22]: improvement in KCCQ-OS > 5 points: 63.5% vs. 46.6%; $p < 0.001$ > 10 points: 74.6% vs. 60.7%; $p < 0.01$

Table 1 (continued)

		Tafamidis	Acoramidis	Vutrisiran
	NT-proBNP	Least-squares mean difference, −735.14 pg/mL [95% CI, −1249.16–−221.13] at 12 months and −2180.54 pg/mL [95% CI, −3326.14–−1034.95] at 30 months	**Decrease of > 700 pg/ml and > 30%:** acoramidis: 10% placebo: 1.5% OR: 7.4 [95% CI, 2.3–24.2], $p < 0.001$ [21] Acoramidis mono ($n = 232$) vs. placebo mono ($n = 98$) [25]: Median (Q1, Q3) change from baseline at month 30 was 436 (−431, 617) pg/mL vs. 2532 (440, 2634) pg/mL	Geometric mean fold-change ratios (vutrisiran/placebo) at month 30 [22]: 0.68 [95% CI, 0.61–0.76] Median change at month 30: vutrisiran: 118 pg/mL (Q1–Q3: −419 to 911 pg/mL) Placebo: 753 pg/mL (Q1–Q3: −8 to 2,573 pg/mL
	eGFR	least squares mean difference = 3.99 mL/min/1.73 m^2 [95% CI, 1.31–6.68[, $p = 0.004$) [26]		≥ 40% decline in eGFR in double blind period [27]: Vutrisiran 12.7% Placebo 21.2%
	Serious adverse events	Patients with ≥ 1 treatment emergent SAE: Tafamidis 75.4% Palcebo 79.1%	Patients with ≥ 1 treatment emergent SAE: Acormidis 54.6% Placebo 64.9%	≥ 1 SAE: Vutrisiran: 62% Placebo: 67%
	Discontinuation of study drug	Dose reduced due to a TEAE: Tafamidis 0.8% Placebo 2.3% [28] Discontinued treatment due to a TEAE: tafamidis 21.2% Placebo 28.8% In the long-term extension study proportion of patients who discontinued treatment tafamidis 80 mg vs. 20 mg (17.6% and 20.0%)	TEAE leading to discontinuation: Acoramidis 9.3% Placebo 8.5%	Vutrisiran 3% Placebo 4%
	Gastrointestinal events	Tafamidis: 51.1% Placebo: 56.5% Generally mild to moderate, mainly diarrhea, obstipation, nausea	Acoramidis 52.5% Placebo 46.4% Mild to moderate gastrointestinal events such as diarrhea (11.6% vs. 7.6%) as well as nausea, vomiting, dyspepsia, and abdominal pain	Gastrointestinal AEs vutrisiran vs. placebo in the double blind phase [29]: overall population: RR: 0.58 Monotherapy population: RR: 0.63 Tafamidis subpopulation RR: 0.51
Open lable extension		Up to 90 months; efficacy tafamidis vs. placebo-tafamidis **all-cause death** [30]**:** HR: 0.59; $p < 0.001$	all-cause-mortality (42 months) [31] ATTRwt-CM: HR: 0.70 [95% CI, 0.50–0.98], $p = 0.04$ ATTRv-CM: HR: 0.41 [95% CI, 0.19–0.93], $p = 0.03$	1 year OLE, overall population: [32] all-cause mortality or first CV event: HR: 0.63 [95% CI, 0.51–0.79] all-cause-mortality: HR: 0.63 [95% CI, 0.46–0.84]

Table 1 (continued)

		Tafamidis	Acoramidis	Vutrisiran
TTR levels		72 patients on tafamidis for 3–12 months: increase from 21.81 ± 0.70 to 29.33 ± 0.76 ml/dL [33]	ATTRibute: mean: + 9.1 +/− 0.3 mg/dL after 28 days + 5 mg/dL TTR = 31.6% reduction in the risk for all-cause mortality	Reduction of TTR level at month 30: mean (overall population) 81.0% [95% CI, 79.0–83.0]
	TTR stabilisation **Major methodological differences in in vitro experiments make comparisons challenging** **Yet undefined: what minimal reduction in rate of TTR tetramer dissociation is needed to achieve maximal clinical benefit**	**In vitro:** • ≥ 96% [10] **In vivo**: > 90% (method: HPLC analysis) [34]	**In vitro**: • up to twofold higher stabilization in samples from ATTRv patients when compared to tafamidis [35] • 4 times longer residence time for acoramidis bound to TTR compared with tafamidis [36], • 4 times higher affinity of acoramidis for purified TTR when compared to tafamidis [36] • higher TTR stabilization against acidic denaturation (≥ 90%) than tafamidis or diflunisal [36] Blinded potency comparison using subunit exchange method [10]: at 10 µM Acoramidis (kex = 0.0007) slightly more potent as a kinetic stabilizer compared to tolcaptone (kex = 0.0045) and tafamidis (kex = 0.0020), which are substantially more potent than diflunisal (kex = 0.0126) [10] **In vivo**: • > 90% [37, 38] (method: Flourescent Probe Exclusion and Western Blot) • 99% at month 45 (OLE) [39] (method: Flourescent Probe Exclusion)	
Physiologic TTR function	**Thyroxin**	Potential asymptomatic reduction in thyroxin serum levels [40]	Potential asymptomatic reduction in thyroxin serum levels [41]	no signal regarding hypothyreosis [42]
	Vitamin A			Under vitamin A supplementation no signal regarding ocular vitamin A deficit events [42]
Pharmacokinetics/-dynamics	**Half life**	**49 h** [43, 44]	**25 h** [44, 45]	**5.2h** [46]
	Elimination	59% liver/biliodigestive system 22% kidneys [10, 11]	32% liver/biliodigestive system 86% kidneys	

Table 1 (continued)

		Tafamidis	Acoramidis	Vutrisiran
	Potential interactions	Drugs that are breast cancer resistance protein (BCRP) substrates may be increased in serum levels (e.g., methotrexate, rosuvastatin, imatinib) Drugs that are organic Anionic transportes (OAT 1 and OAT 3) substrates may be increased in serum levels (e.g., NSAID, Bumetanid, Furosemid, Lamivudin, Methotrexat, Oseltamivir, Tenofovir, Ganciclovir, Adefovir, Cidofovir, Zidovudin, Zalcitabin) Post-market AE of Tafamidis based on FDA AE reporting system: Risk of ear and labyrinth disorder and urinary tract infection [47]	CYP2C9-substrates may be increased in serum levels (e.g., warfarin, NSAIDs, Phenytoin, Losartan)	Minimal and likely not relevant [46]
Special patient subgroups	**Advanced age**	**Efficacy vs. placebo in patients ≥ 80 years** [48]**:** **all-cause mortality** HR: 0.6828 ($p = 0.15$) **CV-related hospitalizations per year** RR: 0.89 ($p = 0.57$) **6MWD** + 84.6 m ($p < 0.01$) **NT-proBNP** 0.6 fold ($p < 0.01$) **KCCQ-OS** + 13.6 points ($p < 0.05$)	**Efficacy vs. placebo in patients ≥ 78 years** [49]**:** **all-cause mortality or first CV event within 42 months** HR: 0.62 [95% CI, 0.45–0.85], $p = 0.003$ **all-cause mortality within 42 months** HR: 0.83 [95% CI, 0.54–1.27], $p = 0.396$	**Efficacy vs. placebo in patients ≥ 75 years** [3]**:** PE (composite of death from any cause and recurrent cardiovascular events) Overall populaiton HR: 0.81 [95% CI, 0.58–1.11] Monotherapy population HR: 0.72 [95% CI, 0.47–1.10]
	Comorbidity burden			Vutrisiran consistently improved clinical outcomes across the spectrum of Charlson Comorbidity Index for the primary endpoint (p interaction = 0.14) and death from any cause alone ($p$interaction = 0.54) [50].
	Impaired systolic function	**Efficacy tafamidis vs. placebo-tafamidis** [51]**: all-cause mortality (after 60 months)** **LVEF < 50%** HR: 0.53 [95% CI, 0.37–0.76)], $p < 0.001$ **LVEF ≥ 50%** HR: 0.53 [95% CI, 0.34–0.82], $p < 0.01$		
	Impaired renal function	Limited data for eGFR ≤ 30 ml/min No data for patients on dialysis Expert experience with a small number of patients with severely impaired renal function/on dialysis did not reveal any safety issues; there is no data regarding efficacy in these patients	**eGFR < 45 ml/min** [49] **All-cause mortality or first CV event within 42 months** HR: 0.66 [95% CI, 0.39–1.13]	**CKD stage 4 patients** [27]**:** **All-cause mortality and CV events in double blind period (33–36 months)** **Overall population:** HR: 0.47 [95% CI, 0.26–0.85] **Monotherapy population** HR: 0.53 [95% CI, 0.25–1.13]

Table 1 (continued)

		Tafamidis	Acoramidis	Vutrisiran
	Advanced disease	**Efficacy tafamidis vs. placebo** [52]: **All-cause mortality until end of study (median 52–64 months)** **NAC I** HR: 0.43, $p < 0.001$ **NAC II** HR: 0.51, $p = 0.003$ **NAC III** HR: 0.75, $p = 0.298$ No significant interaction between treatment and NAC stage at the end of study (p for interaction = 0.575), at month 60 (p for interaction = 0.442), and at month 30 (p for interaction = 0.530)	**Efficacy acoramidis vs. placebo** [49, 53]: **all-cause mortality or first CV hospitalization within 30 months** **NYHA III** HR: 0.84 [95% CI, 0.42–1.65], $p = 0.610$ **NYHA I/II** HR: 0.57 [95% CI, 0.43–0.76], $p < 0.0001$ **NYHA I/II no aFib** HR: 0.55 [95% CI, 0.34–0.89], $p = 0.0145$ **NYHA I/II with aFib** HR: 0.58 [95% CI, 0.41–0.81], $p = 0.0018$ **All-cause mortality within 42 months** **NYHA III** HR: 0.98 [95% CI, 0.47–2.04], $p = 0.959$ **NYHA I/II** HR: 0.58 [95% CI, 0.41–0.83], $p = 0.0025$ **NYHA I/II no aFib** HR: 0.37 [95% CI, 0.19–0.71], $p = 0.0031$ **NYHA I/II with aFib** HR: 0.69 [95% CI, 0.45–1.06], $p = 0.0871$ **NAC I** HR: 0.60 [95% CI, 0.37–0.98], $p = 0.041$ **NAC II** HR: 0.60 [95% CI, 0.37–0.97], $p = 0.038$ **NAC III** HR: 0.94 [95% CI, 0.41–2.16], $p = 0.877$	**Efficacy vutrisiran vs. placebo all-cause mortality and recurrent CV events (36 months)** [54] **Overall population** NYHA I HR: 0.54 [95% CI, 0.27–1.10] NYHA II HR: 0.77 [95% CI, 0.57–1.03] NYHA II HR: 0.68 [95% CI, 0.33–1.41] **Monotherapy population** NYHA I HR: 0.32 [95% CI, 0.12–0.87] NYHA II HR: 0.79 [95% CI, 0.55–1.12] NYHA II HR: 0.31 [95% CI 0.09–1.02] **All-cause mortality (42 months)** **Overall population** NYHA I HR: 0.32 [95% CI, 0.11–0.94] NYHA II HR: 0.73 [95% CI, 0.50–1.06] NYHA II HR: 0.58 [95% CI, 0.20–1.69] **Monotherapy population** NYHA I HR: 0.43 [95% CI, 0.10–1.82] NYHA II HR: 0.73 [95% CI, 0.48–1.12] NYHA II HR: 0.19 [95% CI, 0.02–1.63]

Table 1 (continued)

		Tafamidis	Acoramidis	Vutrisiran
	Atrial fibrillation	**Tafamidis vs. Placebo:** Risk of all-cause mortality was 45% lower in patients without aFib/aFlutter HR: 0.550 [95% CI, 0.368–0.821] [55]	**Acoramidis vs. placebo** [56]: **All-cause mortality or first CV hospitalization within 30 months** **aFib** Acoramidis 40.4% Placebo 50.4%, $p=0.0248$ **No aFib** Acoramidis 28.6% Placebo 50.7% $p=0.0075$ **6MWD** **aFib** Acoramidis vs. placebo + 27.0 m, $p=0.0224$ **No aFib** Acoramidis vs. placebo + 61.9 m, $p<0.0001$ **KCCQ-OS** **aFib** Acoramidis vs. placebo + 8.2 points, $p=0.0011$ **No aFib** Acoramidis vs. placebo + 12.6 points, $p=0.0002$	**Vutrisiran vs. placebo: primary end point** **No aFib/aFlutter** RR: 0.76 [95% CI, 0.49–1.17]) **aFib/aFlutter** RR: 0.67 [95% CI, 0.49–0.93], P-interaction = 0.62 Treatment effect of vutrisiran similar for secondary end points regardless of aFib/aFlutter status (P-interaction > 0.20 for all) [57]

TTR transthyretin, *NAC* National Amyloidosis Center, *NYHA* New York Heart Association, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *ATTRv* Transthyretin Amyloidosis due to variant TTR, *SGLT2i* Sodium Glucose Transporter 2 inhibitor, *IVS* interventricular septum, *6MWD* six-minute walk distance, *eGFR* estimated glomerular filtration rate, *OLE* open label extension study, *CI* confidence interval, *CV* cardiovascular, *HR* hazard datio, *ARR* absolute risk ratio, *NNT* number needed to treat, *RRR* relative risk ratio, *HF* heart failure, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *OS* overall summary score, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event, *AE* adverse event, *ATTRwt* transthyretin amyloidosis due to wild-type TTR, *NSAID* non-steroidal anti-inflammatory drug, *CYP* cytrochrome P, *LVEF* left ventricular ejection fraction, *CKD* chronic kidney disease, *aFib* atrial fibrillation

long-term open-label extension (OLE) analyses, and several real-world observations [5–8] up to 7.5 years [9].

Tafamidis reaches a peak concentration of 26—35 mM in serum, with a half-life of 49 h [10–12]. Tafamidis is glucuronidized and eliminated by the liver/biliodigestive system (59%) and kidneys (22%) [12]. In early 12-month phase II studies, tafamidis achieved high plasma TTR stabilization in vivo. Although not powered for mortality, these preclinical trials suggested disease stabilization with reduced progression of left ventricular (LV) wall thickness and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels compared with the expected natural course [13].

The ATTR-ACT trial [1] randomized 441 patients (90% men, 74 (7) years, 76% ATTRwt; Table 1) to tafamidis-meglumin (20 mg or 80 mg pooled) vs. placebo in addition to standard therapy (predominantly diuretics at that time). Tafamidis significantly reduced the primary endpoint, which hierarchically assessed all-cause mortality followed by the frequency of cardiovascular-related hospitalizations as well as its components (Table 1). The absolute reduction of all-cause mortality was 13.4%, resulting in a number needed to treat (NNT) of 8 over a trial duration of 30 months. The key secondary endpoints, six-minute walk distance (6MWD) and Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (Table 1), were also improved by tafamidis treatment.

Across pre-specified subgroups, including those based on TTR genotype (ATTRwt vs. ATTRv) and New York Heart Association (NYHA) functional class (I or II vs. III), the incidence in all-cause mortality as well as of cardiovascular hospitalizations was in favor of tafamidis over placebo, except for patients with NYHA class III at baseline, among whom the rates of cardiovascular hospitalizations were higher in patients treated with tafamidis than in those treated with placebo [1].

OLE and long-term extension data [30] (patients on tafamidis continued tafamidis, patients on placebo started tafamidis at months 30) confirmed a sustained survival benefit beyond 5 years in patients initially randomized to tafamidis compared to patients initially randomized to placebo and delayed initiation of tafamidis, highlighting the importance of early therapy initiation.

The favorable findings of tafamidis therapy were consistent in post-hoc analyses [8, 52] and confirmed for other subgroups like, e.g., octogenarians [6, 48] or patients with reduced LV ejection fraction (Table 1).

Safety

The evidence regarding the long-term safety of tafamidis in patients with ATTR-CM demonstrates that tafamidis is well tolerated over extended periods, with a safety profile comparable to placebo and no dose-related safety concerns [28]. Across the pivotal ATTR-ACT trial and its OLE, adverse events were generally mild to moderate.

Diarrhea and constipation were the most frequently reported adverse events, with other events such as urinary tract infections and ear/labyrinth disorders being less common and not clearly increased in frequency when comparing tafamidis to placebo [1, 47]. Permanent discontinuation due to adverse events was rare (0.8% for tafamidis vs. 2.3% for placebo).

Tafamidis may lead to an asymptomatic reduction in thyroxine serum levels. Clinically relevant drug interactions are rare, but inhibition of the breast cancer resistance protein (BCRP) transporter can increase exposure to substrates such as rosuvastatin; no major CYP450 interactions have been demonstrated [58].

There are limited data for eGFR $\leq$ 30 ml/min and no data for patients on dialysis. The real-world experience of the authors with a small number of patients with severely impaired renal function or patients on dialysis did not reveal any safety issues. Nevertheless, there is no data regarding efficacy of tafamidis in these patients (Table 1).

Extracardiac effects

Tafamidis is associated with stabilization or slowed progression of neuropathy and autonomic dysfunction in ATTRv patients with polyneuropathy (ATTR-PN), with the greatest benefit when treated early in the course of the disease. Tafamidis-meglumin 20 mg has shown efficacy in ATTR-PN stage I [59, 60], leading to approval for treatment of ATTR-PN stage I in 2011 in some countries [5, 61, 62]. Evidence for effects on potential neuropathy in ATTRwt patients does not exist. GI-specific endpoints in ATTR-CM trials are limited. However, real-world and long-term data reinforce that tafamidis does not worsen gastrointestinal dysfunction in ATTR-CM patients beyond what was observed in clinical trials [5, 63].

A post-hoc analysis further revealed attenuated deterioration of renal function in patients on tafamidis vs. placebo [26].

In a small cohort of patients with ATTRv who were exposed to tafamidis (20 mg), the authors were able to detect tafamidis in the cerebrospinal fluid (CSF) and the vitreous body [64]. These data suggest that tafamidis can cross the CSF-blood and eye-blood barriers, reaching a ratio of TTR tetramer to tafamidis which might induce moderate kinetic stabilization of TTR in the CSF. However, there is not enough scientific evidence to recommend tafamidis for central nervous system manifestations.

Specific treatment of ATTR-CM: acoramidis

Efficacy

Acoramidis mimics the characteristics of the super-stabilizing, disease-protecting variant T119M; hence, superior stabilization abilities have been postulated. In vitro, acoramidis showed up to twofold higher stabilization abilities when compared to tafamidis in blood samples from ATTRv patients [35]. Further, kinetic studies showed a 4 times longer residence time for acoramidis bound to TTR compared with tafamidis, a 4 times higher affinity of acoramidis for purified TTR when compared to tafamidis, and a higher TTR stabilization against acidic denaturation (≥ 90%) than tafamidis or diflunisal [10, 36]. In contrast, using TTR subunit exchange methodology, investigators showed equal potency in preventing tetramer dissociation at plasma concentrations achieved via approved oral doses of tafamidis and acoramidis, respectively [65].

Key inclusion criteria of the ATTRibute-CM trial [2, 14, 16, 18, 21] included age ≤ 90 years, 6MWD ≥ 150 m, NT-proBNP < 8500 pg/mL, and estimated glomerular filtration rate (eGFR) > 15 mL/min/1.73 m^2. Background therapy with tafamidis was not permitted at the time of study entry; however, after 12 months of study participation, initiation of concomitant tafamidis therapy was allowed (11.2% in the acoramidis arm and 19.4% in the placebo arm). Follow-up of the main study was 30 months and extended by a 12-month open-label treatment during which all patients ($n = 389$) received acoramidis. In order to collect safety information, ATTRibute-CM also included patients with severe renal impairment (CKD stage 4). Assuming lack of benefit in individuals with advanced comorbid renal disease, the authors mutually agreed to exclude these individuals from the primary analysis for efficacy [2]. Hence, the modified intention-to-treat population comprises 611 patients with baseline eGFR ≥ 30 ml/min.

The primary endpoint was a four-step hierarchical composite consisting of all-cause mortality, cumulative cardiovascular hospitalizations, change in NT-proBNP, and change in the 6MWD. There was a significant benefit in favor of acoramidis with a win ratio of 1.8 (95% CI, 1.4–2.2, $p < 0.001$). Consistent effects were observed across several subgroups defined by TTR genotype, age, NT-proBNP, eGFR, NYHA functional class, and recruitment location [49]. The two- and three-step hierarchical endpoints consisting of all-cause mortality and cardiovascular hospitalization, as well as the change in 6MWD, were also significant, with win ratios of 1.4 (95% CI, 1.1–1.8) and 1.5 (95% CI, 1.1–2.0), respectively. Furthermore, significant treatment effects favoring acoramidis were observed for cardiovascular hospitalization frequency (occurring as early as 3 months after treatment initiation) and for changes in NT-proBNP, KCCQ score, TTR levels, and 6MWD when analyzed individually. The effect of acoramidis on all-cause mortality was not statistically significant at 30 months (HR 0.77; 95% CI, 0.54–1.10) but became significant in the long-term extension population after 42 months (HR 0.64; 95% CI, 0.47–0.88) [14, 18]. Again, the OLE confirmed a sustained survival benefit in patients initially randomized to verum compared to patients initially randomized to placebo, highlighting the beneficial effects on prognosis lost by delaying therapy [14].

Post-hoc analyses of the total intention-to-treat population ($n = 632$) [19] showed consistent favorable results across all subgroups studied, confirming the efficacy of acoramidis in the total sample of patients with ATTR-CM, including patients with severe kidney impairment.

In ATTRibute-CM, treatment with acoramidis resulted in an early increase in TTR serum levels (mean 9.1 mg/dL after 28 days), which was more pronounced in ATTRv than ATTRwt patients. The absolute increase in TTR levels was a strong and independent predictor of all-cause mortality: each increase of 5 mg/dL in TTR was associated with a 31.6% reduction in the risk of all-cause mortality. Statistically, the treatment effect of acoramidis on all-cause mortality was fully mediated by the change in TTR levels [66]. Entering the OLE phase meant transition to acoramidis therapy for all patients. Patients initiating acoramidis after treatment with tafamidis in the placebo group showed a significant increase in TTR serum levels, whereas there was no change in TTR serum levels in patients from the verum group, who had been on both acoramidis and tafamidis during the double-blind phase [14, 16].

ATTRibute-CM did not include serial echocardiograms; hence, there is limited information regarding functional changes under therapy. In a small MRI substudy of ATTRibute-CM patients from one center, after 30 months, 3 of 24 (12.5%) patients treated with acoramidis and none of the 4 placebo-treated patients showed a reduction in extracellular volume of > = 5% as a quantitative marker of amyloid deposition [67].

A post-hoc responder analysis from ATTRibute-CM showed a significantly higher frequency of clinically meaningful improvement in NT-proBNP (decrease of > 700 pg/ml and > 30%: 10% vs. 1.5%) and 6MWD (increase > 35 m: 15.4% vs. 8.4%) in the verum group [21].

Safety

The safety of acoramidis was investigated in the ATTRibute-CM study and its OLE [2, 14, 18].

The overall incidence of adverse events during the double-blind phase was comparable between the acoramidis group and the placebo group (98.1% vs. 97.6%, respectively).

Serious adverse events occurred less frequently with acoramidis than with placebo (54.6% vs. 64.9%), particularly cardiac failure (24.0% vs. 39.3%) and heart diseases such as atrial fibrillation. Treatment discontinuations due to adverse events occurred at similar rates in both groups (9.3% in the acoramidis group vs. 8.5% in the placebo group); likewise, there was no significant difference in the number of deaths.

Long-term data from the OLE demonstrated that no new safety concerns arose after 42 months. Safety was confirmed in both wild-type ATTR and hereditary ATTR-CM [16, 68].

With regard to side effects under acoramidis therapy, the ATTRibute-CM study showed a more frequent occurrence of mild to moderate gastrointestinal side effects such as diarrhea (11.6% vs. 7.6%), nausea, vomiting, dyspepsia, and abdominal pain compared to placebo, which were resolved after discontinuation of the study drug. Gout was also observed more frequently in the verum group (11.2% vs. 8.1%) [2].

In ATTRibute-CM, acoramidis treatment was associated with an early increase in serum creatinine and a decrease in eGFR, which stabilized within 4 weeks and was reversible after discontinuation of the study drug. After day 28, serum creatinine remained stable in the acoramidis group, while the placebo group showed a progressive increase in serum creatinine and decrease in eGFR from baseline to month 30 [68]. The pharmacokinetics of acoramidis are not clinically significantly affected by renal failure, and no dose adjustment is required in patients with impaired renal function. Concordantly, ATTRibute-CM showed no safety signals for patients with severe renal impairment (creatinine clearance < 30 ml/min). There are no data available for patients on dialysis.

There is insufficient data available on acoramidis use during pregnancy and breastfeeding [2]; animal studies have shown developmental toxicity at a dose that also caused maternal toxicity. The use of acoramidis during pregnancy and in women of childbearing age who are not using contraception is therefore not recommended. Acoramidis should also not be used during breastfeeding, as it is not known whether the substance and its metabolites pass into breast milk.

Extracardiac effects

The ATTRibute-CM study and subsequent analyses focused primarily on cardiac endpoints; data on possible effects on extracardiac organ manifestations of amyloidosis, e.g., on neuropathic, renal, or gastrointestinal endpoints, have not yet been systematically reported.

Specific treatment of ATTR-CM: vutrisiran

Efficacy

Vutrisiran is a double-stranded small interfering RNA (siRNA) that binds to the TTR mRNA in the liver. Single-dose administration showed rapid absorption (peak plasma concentration 3–5 h post dose), a short plasma half-life (4.2–7.5 h), and a potent and sustained TTR reduction (mean maximum TTR reduction of 57–97%, maintained for ≥ 90 days post dose) [69].

Vutrisiran demonstrated clinically meaningful benefits on outcomes, functional capacity, cardiac biomarkers, and health status in patients with ATTR-CM in the phase 3 HELIOS-B trial [3]. In a population of symptomatic ATTR-CM with follow-up for the primary outcome to approximately 33 months and for mortality to 42 months, vutrisiran significantly reduced the composite of all-cause mortality and recurrent cardiovascular events compared with placebo. The relative risk reduction for the composite endpoint was 25–30%, with an absolute reduction in events approaching 8–10% over the 33-month treatment period, and an approximate one-third reduction in all-cause mortality over 42 months. These effects were more pronounced in patients treated with vutrisiran as monotherapy and in those with less advanced disease at baseline, supporting a disease-modifying action when intervention occurs earlier in the disease course (Table 1).

Benefits in clinical events were paralleled by preservation of functional capacity as measured by the 6MWD. Over 30 months, patients receiving vutrisiran experienced substantially less decline in 6MWD than those on placebo, with between-group differences of 25–30 m in the overall cohort and > 30 m in the monotherapy subgroup at 30 months. These magnitudes are consistent with clinically relevant effects in heart failure and cardiomyopathy populations and were directionally similar across key clinical subgroups, including those defined by background tafamidis use and baseline disease severity. Importantly, the divergence in 6MWT trajectories emerged over time and remained sustained through the 30-month assessment, indicating a durable impact on functional capacity.

Vutrisiran also favorably influenced cardiac neurohormonal activation as reflected by reduction of NT-proBNP levels. Across 30 months of follow-up, placebo-treated patients showed substantial rises in NT-proBNP, whereas increases with vutrisiran were attenuated, translating into a relative reduction of about one-third in geometric mean NT-proBNP compared with placebo at 30 months. This

biomarker effect was detectable as early as 6 months, with progressive separation of treatment curves over time, and appeared more pronounced in patients not receiving concomitant tafamidis. Early NT-proBNP changes at 6 months correlated with subsequent risks of cardiovascular events and death, linking the observed biomarker modulation to downstream clinical benefit.

Consistent with these objective clinical and biomarker improvements, vutrisiran preserved health-related quality of life measured by the KCCQ-OS. Over 30 months, patients assigned to placebo experienced a clinically relevant deterioration in KCCQ-OS scores, whereas those treated with vutrisiran had significantly smaller declines, yielding significant between-group differences of about 6 points, with larger effects again observed in the monotherapy subgroup. These differences exceed commonly accepted thresholds for clinically meaningful change in heart failure populations and were directionally favorable across multiple subgroups, including patients with earlier stages of ATTR-CM.

In line with the respective results from the stabilizer trials, first data from the HELIOS-B OLE show a persistent benefit for patients initially and permanently treated with vutrisiran when compared to those initially treated with placebo and then switched to vutrisiran, again highlighting the importance of early initiation of therapy [32].

Taken together, the HELIOS-B data provide a coherent efficacy signal: long-term vutrisiran therapy in ATTR-CM reduces all-cause mortality and cardiovascular events up to 42 months, attenuates decline in 6MWD over 30 months, substantially mitigates the rise in NT-proBNP beginning at 6 months and sustained through 30 months, and preserves health status assessed by KCCQ-OS over the same 30-month interval. An association between the degree of TTR lowering and efficacy could not be demonstrated yet (Table 2).

Safety

In HELIOS-B, safety assessments included adverse events, clinical laboratory measures, and vital signs and were monitored by an independent data monitoring committee. Vutrisiran showed a favorable safety profile [3]: the incidence of adverse events, serious adverse events, and adverse events leading to discontinuation of the study drug was similar in the verum and the placebo group. Significant safety-relevant changes in laboratory parameters or vital signs were not observed in either group. In the HELIOS-B overall as well as in the monotherapy population, the safety profile of vutrisiran remained favorable across age categories [71], suggesting safety up to advanced ages. A pooled safety analysis [42] from HELIOS-B and HELIOS A (vutrisiran in patients with ATTRv and polyneuropathy) included 707 patients with a median duration of exposure to vutrisiran of 33.4 (0.0–57.8) months per patient. The most common AEs were COVID-19, cardiac failure, and atrial fibrillation; the most common SAEs were cardiac failure and atrial fibrillation, with an incidence similar to the placebo group. There was no important difference in the incidence of any AEs or SAEs in subgroups based on age, sex, race or ATTR type. Treatment-related injection-site reactions occurred in 2.1% of patients on vutrisiran and 2.4% in the placebo group, of whom none was considered serious, and all were transient. 1.5% of patients on vutrisiran developed postbaseline antidrug antibodies, which were all low in titer and transient, with no (S)AEs considered related to respective antibodies. Evaluation of (S)AEs by organ system did not point towards specific vutrisiran-related organ dysfunction. The most common (S)AEs were cardiac (S)AEs including cardiac failure and atrial fibrillation. Most common ocular (S)AEs were cataract and dry eye with numerically lower frequency in the vutrisiran group when compared to placebo. Further "drug-related hepatic disorders" as well as "acute renal failure" occurred in equal frequency in the verum and the placebo groups, respectively. Further, laboratory assessments revealed no safety signals in liver function tests, hematology, or renal function related to vutrisiran.

Extracardiac effects

The HELIOS-A trial established vutrisiran as an effective and safe therapeutic option for patients with ATTRv exhibiting polyneuropathy or a mixed phenotype of polyneuropathy and cardiomyopathy [72]. Detailed analyses demonstrated consistent therapeutic efficacy of vutrisiran, particularly in sensorimotor domains, and earlier treatment initiation relative to disease onset was associated with significantly better outcomes in ATTRv polyneuropathy [73]. Observational studies further suggest that patients with ATTRwt may also develop large- and small-fiber polyneuropathy, although the functional impact in this population appears to be limited [74]. At present, it remains unclear whether vutrisiran can modify the polyneuropathy occasionally observed in patients with ATTRwt and whether the therapy may also influence other extracardiac manifestations, including musculoskeletal involvement.

Gastrointestinal involvement in ATTR may lead to malnutrition and weight loss. In HELIOS-A, nutritional status was assessed as a secondary endpoint using the modified body mass index (mBMI), calculated as BMI multiplied by serum albumin concentration [g/l]. Lower mBMI values indicate worse nutritional status. This modification was chosen because malnutrition-related hypoalbuminemia can lead to fluid retention and edema, potentially masking weight loss when conventional BMI is used. Under vutrisiran therapy, a smaller decline in mBMI was observed compared with placebo [72].

Emerging evidence from the HELIOS-B trial also suggests beneficial effects of vutrisiran on gastrointestinal manifestations of ATTR. Vutrisiran reduced the burden of reported gastrointestinal events by more than 50% compared with placebo, with effects observed as early as 3 months after treatment initiation. These findings were consistent across all predefined subgroups and independent of concomitant tafamidis therapy [29].

In HELIOS-B, more than two thirds of patients had moderate renal impairment (KDIGO-eGFR stages G2–G3). A post-hoc analysis demonstrated a significantly smaller decline in eGFR in patients treated with vutrisiran, with fewer individuals experiencing a ≥ 40% eGFR reduction compared with placebo during the double-blind period [27].

Costs and prescription

In the treatment of ATTR-CM, there is a tension between the clinical efficacy of new therapies and their high costs. The differences in treatment costs between the substances have recently decreased, particularly since a 50% price reduction of vutrisiran at the end of 2025. Based on the pharmacy retail price, the current annual treatment costs in Germany are approximately 100.000–150.000€. These high costs lead to various challenges: (1) given the likely increase in ATTR-CM diagnoses with increasing disease awareness, the healthcare system will be under considerable strain due to high drug costs. (2) There is a strong reluctance to prescribe expensive medications, particularly among office-based physicians who are not specialized in amyloidosis. According to the authors´ experience, the prescription of TTR-targeting substances is almost exclusively performed by amyloidosis centers or a few specialized amyloidosis clinics in most regions of Germany. This fact makes these centers a bottleneck and contributes to longer waiting times, delayed diagnosis and treatment initiation, and subsequently, to patients´ worse prognosis. A substantial share of patients might even be completely prohibited from causal treatment due to these hurdles. 3) The median age at diagnosis—approximately 80 years in Germany—is close to the statistical life expectancy, or already exceeds it at the time of diagnosis. This raises ethical concerns, as the cost per quality-adjusted life year (QALY) massively exceeds the threshold of $100,000 [75, 76] in a situation where further life expectancy is limited. Consequently, cost-effectiveness analyses using so-called Health Benefit Price Benchmarks recommend a price reduction of approximately 90% for all substance classes (Institute for Clinical and Economic Review, *icer.org*) [75].

The recognition of high-cost medications as "practice-specific exceptions" (Praxisbesonderheit) is of central importance for the outpatient setting in Germany, alongside discount agreements (Rabattverträge) with health insurances. Prescribing high-cost medications may otherwise lead to a disproportionate impact on the (limited!) physician's prescribing budget during economic audits (Wirtschaftlichkeitsprüfung), potentially resulting in financial recourse. However, neither the designation as a practice-specific exception nor the existence of discount agreements protects against individual case reviews (Einzelfallprüfung). These factors contribute to a cautious prescribing behavior among office-based physicians in Germany, ultimately leading to an increased burden on specialized amyloidosis centers, as described above.

In order to improve ATTR-CM patient care in Germany, the authors aim for a joint patient care concept: establishment of the diagnosis as well as initiation and repeated evaluation of the specific therapy at specialized amyloidosis centers in close collaboration with decentralized office-based physicians who closely monitor the patients´ health condition and adopt regular drug prescriptions.

Other factors relevant for the individual treatment decision

Extracardiac manifestations

As detailed above, the specific treatment options differ regarding effects on extracardiac manifestations and comorbidities. Hence, initial clinical patient evaluation should include a respective screening (e.g., neuropathic, GI, musculo-sketetal, autonomic). Dedicated questions can be addressed in the physician–patient interview. Screening instruments regarding neural or autonomic manifestations (e.g., Neuropathic Pain Symptom Inventory, Inflammatory Neuropathy Cause and Treatment or Composite Autonomic Symptom Score 31) as well as structured questions regarding potential gastrointestinal manifestations (early satiety, loss of appetite, diarrhea, constipation, abdominal pain) might further support the identification of extracardiac manifestations. Regular monitoring of serum neurofilament levels can support the suspicion that polyneuropathy is progressing [77].

Kidney function

Impaired renal function is common in elderly patients and, based on the available study data, may lead to restrictions on the prescription of approved drugs. Although prescribing is not formally contraindicated in patients with an eGFR < 30 ml/min, data are limited for this patient subgroup. In this context, a recent subgroup analysis of the

Helios-B trial showed that vutrisiran is effective and well tolerated even in patients with ATTR-CM with declining renal function, including those developing CKD stage 4, and may slow eGFR decline in such patients [27].

None of the three substances (vutrisiran, tafamidis, acoramidis) have established safety or efficacy in dialysis patients, and their use in this population should be approached with caution and carefully supervised.

Administration and vitamin A supplementation

TTR stabilizers are orally administered and are generally easy to integrate into everyday life. Tafamidis is taken once daily, whereas acoramidis requires two film-coated tablets twice daily. As with any chronic oral therapy, adherence may be challenging, especially in patients with a high pill burden. The TTR gene silencer vutrisiran is administered subcutaneously every 3 months, which most likely improves adherence, but long-term therapy requires the supplementation of vitamin A (2500 I.U./per day), which usually is taken orally and has to be covered by the patients´ own expenses in Germany. Further challenges are a need for medically supervised drug administration for many patients and possible local reactions at the injection site.

Home care service

Home care services can support patients with ATTR-CM at home regarding symptom control, application of specific and heart failure therapy, particularly those with significant comorbidities. There are no scientific data regarding home care services in ATTR-CM management. Since patients with ATTR-CM suffer from high risk of worsening heart failure and arrhythmias as well as from a high burden of comorbidities, regular and systematic outpatient visits are mandatory [78]. Home care nurses for ATTR-CM should be particularly trained in amyloidosis and heart failure care and affiliated to the respective amyloidosis center or clinic to avoid loss of information. This concept may help to improve outpatient care in a raising number of patients, but scientific evaluation is required before dedicated recommendations can be given.

Initiation, withholding, and discontinuation of specific therapy

With respect to the available data, especially OLE data, the authors emphasize the importance of early therapy initiation (enabled by early diagnosis), what appears to be significantly more important than the actual choice of substance. OLE studies demonstrated that disease progression could not be restored after switch to verum, respectively delayed treatment, and led to reduced long-term outcomes.

Potential criteria against specific therapy

Patients > 90 years old [6], which are poorly represented in clinical studies, and those with advanced disease stage (NAC 3) are at high risk of futility from treatment with a transthyretin stabilizer [6, 18]. In patients with ATTR-CM and NYHA class III, effects of specific treatment on mortality or combined mortality and HF hospitalization were non-conclusive [1, 3, 18]. In a long-term extension study [8], tafamidis reduced mortality in patients with heart failure NYHA class III, but overall survival was poorer compared to NYHA class I/II patients. A post-hoc analysis of the HELIOS-B trial showed that patients in NYHA class III or with NT-proBNP > 2000 pg/ml numerically had fewer events with vutrisiran but without statistical significance [54]. Importantly, the power of these sub-analyses is limited, and the trials are overall positive for primary endpoint reduction. Thus, careful patient evaluation in advanced ATTR-CM, i.e., NAC stage 3 and NYHA class III, is recommended before the initiation of specific therapy, taking the extent of remodeling, biomarker elevation, symptoms, optimization of heart failure therapy, comorbidities, and frailty status into account. As a rule of thumb, specific therapy provides a significant prognostic benefit after 2–3 years; hence, patients with an estimated life expectancy of < 2 years are not likely to benefit, and one should focus on best supportive care in these individuals.

Discontinuation of therapy

There are few data about discontinuation of ATTR-CM treatment. Recent German registry data showed that physicians rarely stop specific therapy [79, 80]; affected patients usually show with advanced amyloid disease and/or comorbidities. The reasons for treatment discontinuation were frailty or poor mobility (61%), comorbidities or limited life expectancy (43%), progression of heart failure (36%), and palliative care (29%). Importantly, age was not a reason to stop treatment [80].

Specifically, the authors recommend to stop therapy in palliative settingsand in cases of clear-cut progression to persistent NYHA class IV. The rationale for withdrawing therapy differs from that for withholding treatment. A patient who deteriorates after being stable on therapy requires careful assessment to determine whether this reflects treatment failure, an advanced natural disease course, or an intercurrent non-ATTR condition, before therapy is discontinued. Decisions to withdraw therapy should therefore be made on

an individual basis, applying the same multimodal progression criteria outlined in the monitoring section. Ideally, this should be done in a multidisciplinary setting at an experienced amyloidosis centre, particularly when the indication for withdrawal remains uncertain.

Monitoring of therapy

TTR serum levels

TTR serum levels are increasingly used as a biomarker to assess treatment response. Considering the possibility of individual responses to treatment, it seems obvious that the effects of treatment should be identified at an early phase. In clinical practice, laboratory analyses in general measure circulating serum TTR tetramer levels. In the ATTRibute-CM trial, an early increase in TTR levels 28 days after acoramidis initiation was associated with improved survival, with a mean increase of 9.1 mg/dl increase at 28 days [66]. Similar observations have recently been reported for tafamidis therapy, showing a mean increase of 7.3 mg/dl after 1 month, with an early increase associated with reduced all-cause mortality [81]. Gene silencers, on the other hand, result in significantly reduced TTR levels, reaching a knockdown of 80–90% within 6 weeks following initiation of vutrisian therapy [82]. TTR levels must be interpreted with caution, as they can be influenced by several non-disease-related factors, including acute infection, systemic inflammation, nutritional status, frailty, and liver function [83]. Additionally, there is a lack of data on TTR reference values and their natural fluctuations. Overall, TTR levels may represent a reasonable additional parameter for monitoring treatment efficacy; they are a promising tool to quickly assess pharmacodynamic efficacy and potential long-term outcome for both TTR stabilizers and vutrisiran. However, until more evidence is available, they should be used as a complementary measure alongside clinical evaluation when considering treatment changes.

Imaging

Obviously, echocardiography is widely available and therefore a sine qua non first-line imaging modality for the diagnosis and longitudinal monitoring of patients with ATTR-CM. Cardiologists reading echocardiograms should be aware of typical signs of ATTR-CM including increased wall thickness, reduced longitudinal systolic function and impaired relaxation as well as reduced left atrial strain and increased atrial size. Echocardiography cannot directly visualize amyloid deposits, but may provide important information regarding cardiac structure and function. There is a body of evidence suggesting beneficial effects of TTR targeting therapy assessed by echocardiography; hence, quality-controlled echocardiography aiming for low measurement variability might be helpful regarding assessment of disease progression and response to therapy in patients with ATTR-CM [84].

Further non-invasive imaging methods such as cardiovascular magnetic resonance (CMR) and positron emission tomography (PET) play an increasingly important role regarding both diagnosis and longitudinal monitoring of ATTR-CM. CMR-based techniques such as late-gadolinium-enhancement (LGE) and T1-/T2-mapping allow both detection and quantification of amyloid deposits in the myocardium [85]. In particular, quantitative CMR parameters such as "native T1" or "extracellular volume fraction" (ECV) correlate with cardiac amyloid burden and may serve as imaging biomarkers for disease severity and progression, thereby enabling monitoring of treatment effects over time [86, 87].

PET-based approaches using amyloid-binding radiotracers (e.g., 124I-evuzamitide, 18F-florbetapir, 18F-florbetaben, 11C-Pittsburgh compound B) allow to visualize and directly quantify myocardial amyloid deposits [88], and first case reports regarding monitoring are promising [89]—but robust longitudinal PET data in ATTR-CM are missing.

SPECT-based bone scintigraphy is currently one of the most important non-invasive imaging methods for diagnosing ATTR-CM. An increasing number of studies are investigating its value in monitoring therapy, and although most of them demonstrate a reduction in myocardial tracer uptake in patients treated with amyloid-specific disease-modifying therapy [90–92], routine follow-up bone scintigraphy for monitoring purposes cannot be recommended so far since. Confirming studies have been unable to reproduce encouraging findings, so far, and results from serial SPECT showed poor correlation with numerous established biomarkers of ATTR-CM treatment response [93, 94].

Multimodal monitoring

Recently, an update on the recommendations on "Monitoring Disease Progression

in Patients With ATTR-CM" was published [84]. The authors present six parameters with respective thresholds and recommendations regarding frequency of monitoring. These include clinical parameters (HF-related hospitalization, outpatient diuretic intensification), biomarkers (NT-proBNP increase of > 700 pg/mL with a relative increase of > 30% or relative decrease of eGFR > 20%), and functional status (KCCQ > 5-point decrease; NYHA class increase); disease progression can be considered present if at least 2 criteria are met. In contrast to the criteria mentioned above, imaging-based parameters were not taken into

account. This decision was based on concerns regarding inter-observer variability, difficulties in interpreting changes over time in individual patients, limited data on imaging-based progression monitoring, and the limited feasibility of cardiac magnetic resonance imaging for routine monitoring. Nevertheless, serial echocardiography should at least remain part of standard follow-up care for heart failure and can still provide relevant information in clinical practice.

In summary, there are several parameters and domains indicating disease progression. Nevertheless, none of these parameters has been investigated in a prospective randomized setting and no data are available regarding clinical consequences of disease progression. Conceptually, treatment modification in the setting of disease progression may be considered. However, as progression itself remains insufficiently defined and prospective randomized data on switching strategies are lacking, such an approach currently remains guided by clinical judgment (including imaging/biomarkers/clinical status/change in concomitant therapy).

For the purpose of this consensus, "disease progression" is defined as clinically meaningful deterioration despite at least 12 months of specific therapy at an adequate dose, evidenced by fulfillment of ≥ 2 of the six multimodal criteria described above (HF-related hospitalization, outpatient diuretic intensification, NT-proBNP increase > 700 pg/mL with relative increase > 30%, eGFR decline > 20%, KCCQ decrease > 5 points, or NYHA class worsening), in the absence of an identifiable non-ATTR cause (e.g., intercurrent infection, new comorbidities, or non-adherence). In such cases, evaluation of a change in substance or substance class may be considered, while acknowledging that prospective randomized data to guide switching decisions are currently unavailable.

Future perspectives

Eplontersen

Eplontersen is an antisense oligonucleotide (GalNAc-conjugated) that reduces hepatic TTR production—similar to the second-generation siRNA vutrisiran. Use of eplontersen is based on subcutaneous injections of 45 mg eplontersen every 4 weeks. Eplontersen is approved for adult patients with stage I and II ATTRv PN. Importantly, eplontersen is not approved for the treatment of ATTR-CM yet. Nevertheless, promising subgroup analyses in patients with ATTRv-CM have been published based on echocardiographic data that were obtained during the approval NEURO TTRansform study [95, 96]: patients with ATTRv-PN and cardiac involvement (so-called mixed phenotype) showed subtle improvements in echocardiographic parameters such as LV stroke volume and LVEF. The dedicated CARDIO TTRansform study is currently ongoing and was designed to assess clinical outcomes in ATTR CM (both wild type and hereditary) with primary cardiovascular endpoints. The first results of this promising study are expected to be shared during the upcoming ESC congress 2026 and may expand the therapeutic spectrum for ATTR-CM.

Diflunisal

Diflunisal is not a novel compound when it comes to ATTR treatment, as it has been investigated in ATTRv for several years. Pharmacologically, Diflunisal is a non-steroid anti-inflammatory (NSAID) agent which also acts as a TTR stabilizer by inhibiting TTR tetramer dissociation. Diflunisal plasma concentrations of 250 µM reduced the TTR dissociation rate by 95% [97]. In ATTRv-PN, diflunisal reduced neurological progression and preserved quality of life over 2 years compared with placebo, suggesting potential therapeutic benefit [98]. Since 11/2025, diflunisal has been available in Germany for the treatment of ATTRv-PN stages 1 or 2. In ATTR-CM, randomized trials are lacking, but a recent meta-analysis including 12 studies and 539 ATTR-CM patients showed reduced mortality in patients treated with diflunisal accompanied by a significant increase in TTR levels. However, the diflunisal discontinuation rate was high (24%), mainly driven by renal (21%) and gastrointestinal (13%) adverse events [99].

CRISPR-CAS

CRISPR-Cas9-based gene therapy, specifically the investigational product nexiguran ziclumeran (nex-z or NTLA-2001), is a novel approach as a potential one-time, in vivo gene-editing treatment for ATTR [100]. It inactivates the TTR gene in the liver, leading to deep, durable, and rapid reduction of the toxic amyloid-forming protein. Phase 1 trials demonstrated that a single intravenous dose resulted in significant, long-lasting reduction of serum TTR levels. The MAGNITUDE trial (NCT06128629) is an international, randomized, placebo-controlled phase 3 trial evaluating nex-z in ATTR-CM, with a primary composite endpoint of cardiovascular mortality and cardiovascular events. After a temporary FDA clinical hold in late 2025, the hold was lifted in March 2026, and the study is continuing. It will also incorporate serial cardiac MRI to assess changes in structure, function, and extracellular volume.

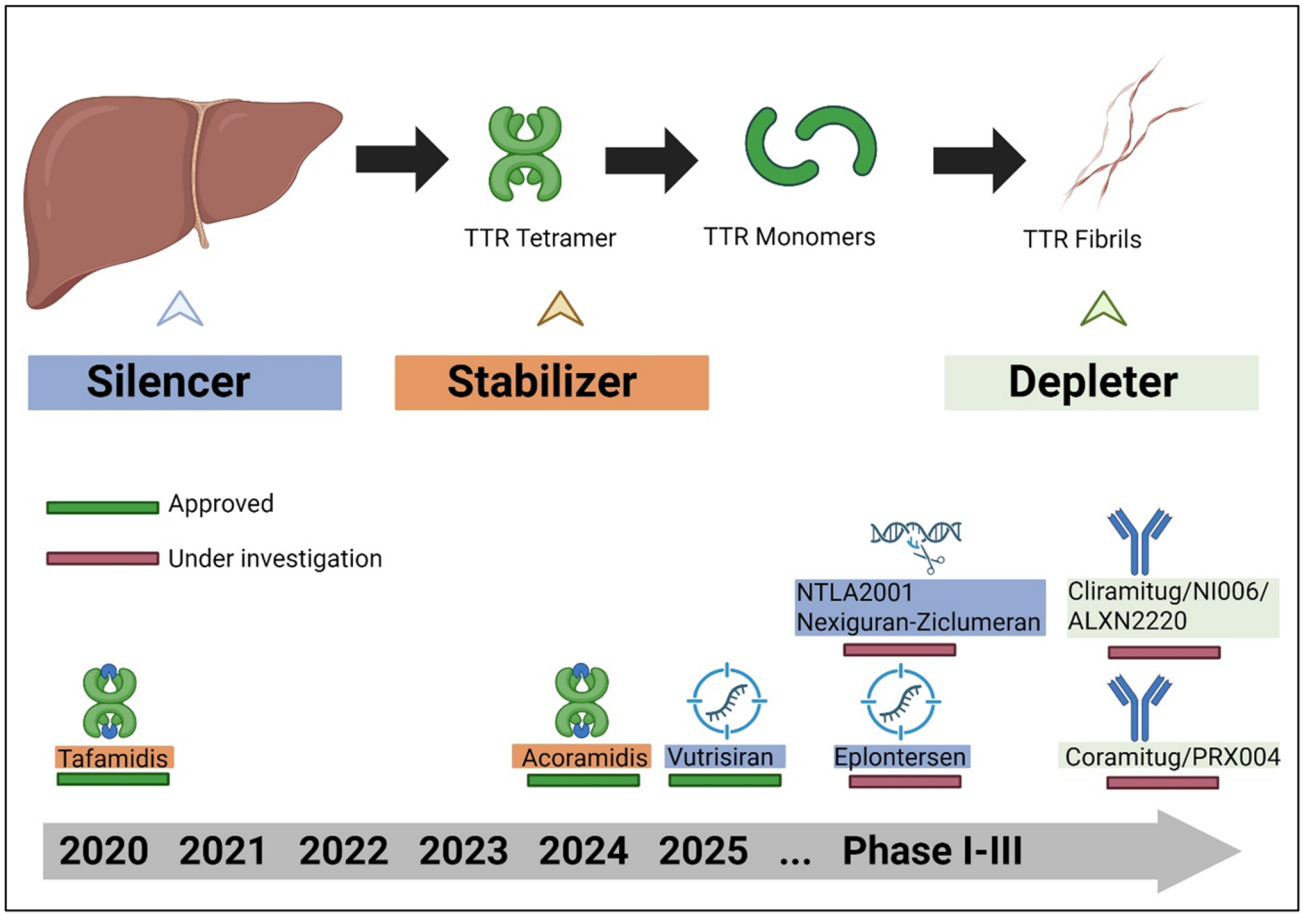


Fig. 1 Approved therapies and therapies under investigation

Depleter

NI006 (syn. ALXN2220, cliramitug) is a recombinant human anti-TTR antibody that binds to variant and wild-type misfolded TTR protein but not to physiological TTR. Antibody TTR binding activates phagocytic immune cells including macrophages, leading to removal of cardiac ATTR [101]. In a phase 1 clinical trial with 40 participants, cardiac amyloid load was reduced at 12 months, demonstrated in both cardiac MRI and bone scintigraphy [102]. NT-proBNP was also reduced. There were no safety issues and no antidrug antibodies detectable. The antibody NI006 must be applied by iv infusion every 4 weeks. A phase 3 clinical trial with NI006 vs. placebo in patients with advanced ATTR-CM (NT-proBNP > 2000 pg/mL at screening) has completed recruitment, and follow-up is ongoing (NCT06183931).

Another similar antibody, NNC6019-0001 (syn. PRX004, coramitug), showed good tolerability and significant NT-proBNP reduction over 12 months in a phase 2 trial [103], and is currently under investigation in a phase 3 clinical trial (NCT07207811; recruitment currently ongoing).

Since depleters aim to reduce myocardial amyloid burden, they are a promising treatment strategy for patients with advanced disease. A combined approach with eplontersen + NI006 vs. eplontersen + placebo will be tested in a clinical phase 2b trial starting soon (personal communication).

Expert recommendations

Table 2 Recommendations for the treatment of ATTR-CM

COR	LOE	Recommendations
1	**B-NR**	Establish correct diagnosis (cardiac imaging fulfilling criteria for amyloid cardiomyopathy + exclusion of monoclonal gammopathy + bone scintigraphy including SPECT or histopathologic confirmation)
1	**B-R**	Early diagnosis and early initiation of specific therapy to achieve best possible benefit
1	**B-R**	Screen for potential extracardiac manifestations and comorbidities
1	**B-R**	Patients with ATTR-CM should be treated with tafamidis, acoramidis or vutrisiran, but not with combinations
1	**B-R**	Patients with ATTRv with mixed phenotype should be treated with second-generation silencer preferably
2a	**C-LD**	Regular disease monitoring a) regular assessment of survival and general condition in association with new prescriptions b) Multimodal assessment according to disease stage and general condition at least once per year
2b	**C-EO**	Evaluation of change in substance or substance class in case of disproportionate disease progression
2a	**C-LD**	Evaluate discontinuation of specific therapy in case of lack of prognostic benefit due to severely advanced disease, competing comorbidities or general health status

ATTR transthyretin amyloidosis; *CM* cardiomyopathy; *COR* class of recommendation (range 1–3 [70]), *LOE* level of evidence (range A-C); *NR* non-randomized trial; *R* randomized trial; *LD* limited data; *EO* expert opinion; *SPECT* Single Photon Emission Computed Tomography; *v* variant

Summary

Three substances are available for treatment of ATTR-CM in Germany: tafamidis, acoramidis and vutrisiran.

The efficacy of all medications has been demonstrated in three separate randomized controlled studies; their safety and tolerability are comparable. Due to the lack of comparative studies, the authors conclude that, based on current evidence, the therapies are similarly effective to improve clinical outcomes, and all drugs may be prescribed once a diagnosis of ATTR-CM has been confirmed. It is not possible to establish strict decision-making criteria at this time, but local standards and patient preferences should be taken into account. Patients with ATTRv with mixed phenotype are an exception: based on the available data, treatment with second-generation silencer should be the first-line option in these cases. Combination therapies cannot be recommended at this time primarily due to the lack of evidence regarding their incremental benefit compared to monotherapy. Regular follow-up assessments are essential to monitor disease progression and to guide individualized decisions regarding treatment modification. Cardiac biomarkers, including TTR levels if available, and the assessment of clinical parameters—including quality of life—should be part of the assessment, as well as cardiac imaging. Depending on local conditions, echocardiography or MRI may be used, whereas serial PET and/or SPECT imaging is still the subject of current research (Fig. 1).

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