CO100

EQ-5D Utility Impact of Worsening NYHA Class and CV hospitalization (CVH) on Health-related Quality of Life (HRQoL) of Patients With ATTR-CM Based on the ATTRibute-CM Trial

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OBJECTIVE

- **To quantify the impact of disease progression, measured by worsening NYHA class and recent CVH, on the EQ-5D in patients with ATTR-CM.**

INTRODUCTION

- Transthyretin (trans-thy-re-tin) amyloid cardiomyopathy (ATTR-CM) is an underdiagnosed and potentially fatal disease of the heart muscle. In ATTR-CM, a protein called transthyretin (TTR) becomes unstable and builds up in the heart, nerves, and other organs.[1]
- ATTR-CM leads to progressive heart failure, indicated by worsening of the New York Heart Association (NYHA) class, increased cardiovascular hospitalizations (CVH), and impaired health-related quality of life (HRQoL).
- In ATTR-CM, maintaining HRQoL is one of the treatment goals alongside preventing mortality and progression of the disease. The impact of worsening of NYHA class and recurrent CVH in HRQoL have not been characterized.
- Decrements in EQ-5D associated with worsening of NYHA class and recurrent CVH can be used as quality-of-life weight to calculate quality-adjusted life years (QALYs) in cost-utility analysis.

METHOD

- Individual patient-level data from the Phase III, randomized, multicenter, parallel-group study ATTRibute-CM (NCT03860935) were analyzed.[2] EQ-5D-5L[3] was collected as an exploratory endpoint at baseline and months 6, 9, 12, 18, 24, and 30.
- The analysis focused on the modified intention to treat (mITT) population, which included participants with baseline estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m2 and at least one efficacy assessment and study dose (N=611).
- UK EQ-5D-3L age- and sex-adjusted scores were mapped using the function developed by the National Institute for Health and Care Excellence Decision Support Unit.[4]
- The mapped EQ-5D-3L scores were then analyzed using mixed-effects linear regression with random intercept for each participant adjusting for baseline and time-varying covariates.
- Baseline covariates included age, sex, TTR genotype (wild vs. variant), N terminal pro-B-type natriuretic peptide (NT-proBNP; ≤3,000 vs. >3,000 pg/mL), eGFR (≥45 vs. <45 mL/min/1.73 m2), centered baseline utility, and treatment. The baseline utility score was centered by subtracting the baseline mean of the overall mITT population (i.e., 0.770) from each participant's baseline utility score.
- Time-varying covariates were those that could change over participants' visits, such as NYHA class, experiencing a CVH, or initiating tafamidis as a concomitant medication.
- The proximity of the CVH to the EQ-5D measurement was initially categorized as <1, 1–2, 2–4, or 4–12 months vs. "≥12 months or no hospitalization" before the measurement.
- Univariate analyses were first conducted to assess the association of each covariate and EQ-5D score. Covariates with P value <0.1 at the univariate analysis were selected for inclusion into the multivariate model.
- The multivariate regression model was trimmed using backward selection with an exit P value of >0.05.
- Disutility values for worsening NYHA class, the immediate impact of CVH, and the time for HRQoL to recover to prehospitalization levels were estimated.

RESULTS

- Both worsening NYHA class and CVH showed significant decrements in EQ-5D utility, with the greatest impact observed for NYHA IV and hospitalizations within 1 month.
- The completion rate, defined as the number of participants in the mITT population with an evaluable EQ-5D health utility at a given visit over the number of participants in the mITT population who were expected to provide a patient-reported outcome assessment at that visit, was high (>93% at any visit) (**Table 1**).

Table 1. Completion Rate for the EQ-5D Health Utility, mITT

Visit	Placebo (N=202)	Acoramidis (N=409)	Total (N=611)
Baseline	202/202 (100.0%)	405/409 (99.0%)	607/611 (99.3%)
Month 6	193/198 (97.5%)	391/401 (97.5%)	584/599 (97.5%)
Month 9	178/188 (94.7%)	351/371 (94.6%)	529/559 (94.6%)
Month 12	171/180 (95.0%)	348/360 (96.7%)	519/540 (96.1%)
Month 18	161/171 (94.2%)	310/332 (93.4%)	471/503 (93.6%)
Month 24	144/149 (96.6%)	306/309 (99.0%)	450/458 (98.3%)
Month 30	136/137 (99.3%)	288/289 (99.7%)	424/426 (99.5%)

Abbreviations: mITT = modified intention to treat; The completion rate was defined as the number of participants in the mITT population with an evaluable EQ-5D health utility at a given visit over the number of participants in the mITT population who were expected to provide a patient-reported outcome assessment at that visit

- At baseline, mean (SD) for both treatments arms was similar: 0.773 (0.179) and 0.765 (0.199) for acoramidis and placebo, respectively.
- Statistically significant predictors of EQ-5D-5L at the univariate analyses (P<0.1) included centered baseline EQ-5D score, age, sex, NT-proBNP, eGFR, proximity of the CVH to the EQ-5D-5L measurement, receipt of concomitant tafamidis, and NYHA class.
- Statistically significant predictors of EQ-5D after backward stepwise selection in the multivariate analysis based on P<0.05 included baseline EQ-5D score, age, proximity of the CVH to the EQ-5D-5L measurement, concomitant tafamidis, and NYHA class (**Table 2**).

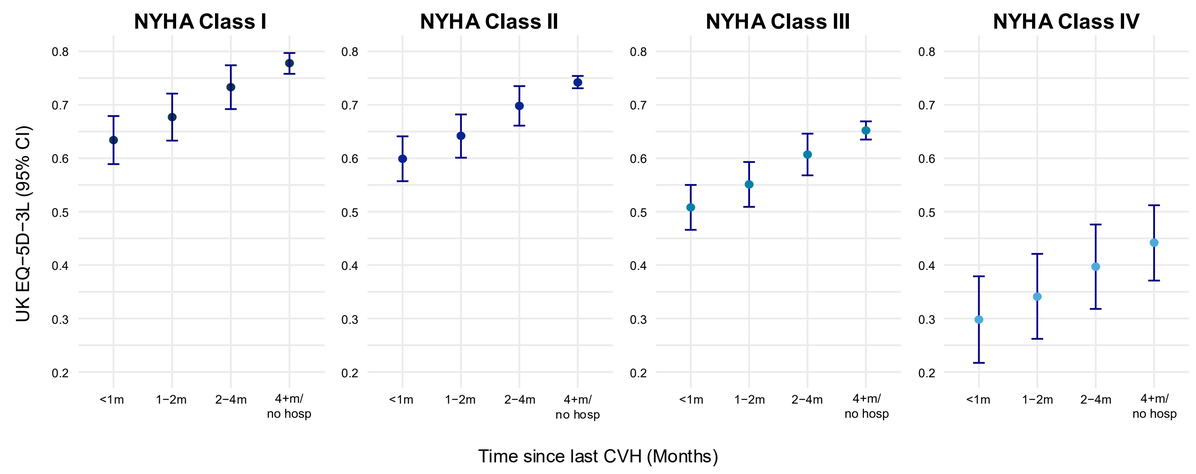
Table 2. Multivariate Models, mITT

Label	Multivariate Model 1				Multivariate Model 2			
	β	SE	95% CI	*P* value	β	SE	95% CI	*P* value
Intercept	0.9522	0.0616	(0.8315, 1.0730)	<0.001	0.942	0.0622	(0.8201, 1.0639)	<0.001
Centered baseline utility	0.6081	0.0286	(0.5520, 0.6643)	<0.001	0.6198	0.0288	(0.5634, 0.6762)	<0.001
Age (per year)	-0.0023	0.0008	(-0.0038, -0.0007)	0.005	-0.0025	0.0008	(-0.0041, -0.0009)	0.002
Proximity to CVH								
0–1 months vs. no hospitalization or ≥4 months before the visit	-0.1436	0.021	(-0.1848, -0.1024)	<0.001	-0.1451	0.021	(-0.1864, -0.1039)	<0.001
1–2 months vs. no hospitalization or ≥4 months before the visit	-0.1006	0.0202	(-0.1403, -0.0610)	<0.001	-0.1017	0.0202	(-0.1414, -0.0621)	<0.001
2–4 months vs. no hospitalization or ≥4 months before the visit	-0.0443	0.0186	(-0.0809, -0.0078)	0.017	-0.0464	0.0187	(-0.0829, -0.0098)	0.013
Concomitant tafamidis (yes vs. no)	-0.0263	0.0115	(-0.0488, -0.0039)	0.022	-0.0266	0.0115	(-0.0491, -0.0040)	0.021
NYHA class (Categorization 1)								
II vs. I	-0.0352	0.0099	(-0.0545, -0.0158)	<0.001	–	–	–	–
III vs. I	-0.126	0.0124	(-0.1503, -0.1016)	<0.001	–	–	–	–
IV vs. I	-0.3359	0.0373	(-0.4090, -0.2628)	<0.001	–	–	–	–
NYHA class (Categorization 2)								
III vs. I–II	–	–	–	–	-0.093	0.009	(-0.1100, -0.0767)	<0.001
IV vs. I–II	–	–	–	–	-0.303	0.036	(-0.3741, -0.2321)	<0.001

Abbreviations: CVH = cardiovascular hospitalization; mITT = modified intention to treat; NYHA = New York Heart Association

- Notably, NYHA III (591 observations) and NYHA IV (21 observations) were associated with reductions in EQ-5D-3L of 0.0933 (SE: 0.0085, P<0.001) and 0.3031 (SE: 0.0362, P<0.001), respectively, compared with NYHA I–II (2,342 observations).
- Difference in utilities between NYHA I and NYHA II were relatively small; thus, an additional model was investigated in which NYHA I and NYHA II were pooled.
- The coefficients on the variable for the proximity of the last CVH to the EQ-5D suggested that it can take up to 4 months for participants to recover from hospitalization, because the utility decrement for 4–12 months vs. "≥12 months or no CVH" appeared to be very small and not statistically significant. Therefore, the variable was recategorized as <1, 1–2, or 2–4 months vs. "no hospitalization or hospitalization ≥4 months."
- A CVH within the past month before the EQ-5D measurement (55/2954 observations) was associated with a decrement of 0.1451 (SE: 0.021, P<0.001), whereas a CVH within 1–2 months (56/2954 observations) or 2–4 months (64/2954 observations) was associated with a reduction in utility of 0.1017 (SE: 0.0202, P<0.001) and 0.0464 (SE: 0.0187, P<0.012), respectively, vs. "no hospitalization or hospitalization ≥4 months."
- Additionally, initiating and taking concomitant tafamidis was associated with a reduction in EQ-5D of 0.0266 (SE: 0.0115, P<0.021), suggesting that initiation of concomitant tafamidis may be triggered by potentially worsening health conditions in the trial's population.
- Marginal least squares mean utility estimates by NYHA class and proximity of the recent CVH estimated from **Model 1** are presented in **Figure 1**.

Figure 1. Mean Utility Estimates by NYHA Class, Multivariate Model 1



Abbreviations: CVH = cardiovascular hospitalization; NYHA = New York Heart Association; Note: Marginal means for each NYHA class were estimated assuming an average population with the following characteristics: mean age of 77.2 years and not using concomitant tafamidis.

Strengths and Limitations

- These utility decrements enable QALY estimation in cost-utility analyses of interventions that prevent hospitalizations or slow disease progression in ATTR-CM.
- The ATTRibute-CM study is representative of a large contemporary population of patients with ATTR-CM.
- The analyses were limited by the number of observations with NYHA class IV (only 21/2954 observations) and the small number of observations with CVH occurring within 4 months of the EQ-5D visit (176/2954 observations).

CONCLUSION

- **Results demonstrated that among ATTR-CM patients, worsening NYHA class and recent CVH were associated with significant negative impact on HRQoL as measured by the EQ-5D; this information is essential for researchers, patients and clinicians.**
- **Maintaining patients in a lower NYHA class and preventing CVH may result in significant HRQoL gains for patients with ATTR-CM.**
- **Additionally, the analysis suggested that it may take up to 4 months for HRQoL to gradually recover after hospitalization.**

References: 1. American Heart Association. Transthyretin amyloid cardiomyopathy (ATTR-CM). 2024. https://www.heart.org/en/health-topics/cardiomyopathy/what-is-cardiomyopathy-in-adults/transthyretin-amyloid-cardiomyopathy-attr-cm. **2.** Gillmore JD, et al. *N Engl J Med*. 2024;390(2):132-42. **3.** Rabin R, de Charro F. *Ann Med*. 2001;33(5):337-43. **4.** Hernandez-Alava M, Pudney S. *J Health Econ*. 2017;55:139-52.

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