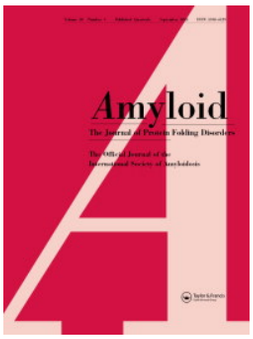

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ARTICLE

Patient-reported outcome measures for transthyretin cardiac amyloidosis: the ITALY study

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ABSTRACT

Background: Transthyretin cardiac amyloidosis (ATTR-CA) has a deep impact on the quality of life (QoL), yet no specific patient-reported outcome measures (PROMs) for ATTR-CA exist.

Methods: The ITALY study involved 5 Italian referral centres (Pisa, Pavia, Ferrara, Florence, Messina) enrolling consecutive outpatients with ATTR-CA.

Results: Two 30-item questionnaires were created for wild-type (wt) and variant (v) ATTR-CA. Scores ranged from 100 (best condition) to 0 (worst condition). Out of 140 patients enrolled (77% with ATTRwt-CA), 115 repeated the re-evaluation at 6 months. At baseline, only 30% of patients needed help to fill out the questionnaires. Among baseline variables, all KCCQ and SF-36 domains were univariate predictors of ITALY scores in ATTRwt-CA patients, with the KCCQ Symptom Summary score (beta coefficient 0.759), Social Limitations (0.781), and Overall summary score (0.786) being the strongest predictors. The SF-36 Emotional well-being score (0.608), the KCCQ Overall summary score (0.656), and the SF-36 Energy/fatigue score (0.669) were the strongest univariate predictors of ITALY scores in ATTRv-CA. Similar results were found at 6 months.

Conclusions: The ITALY questionnaires are the first specific PROMs for ATTRwt- and ATTRv-CA. Questionnaire completion is feasible. ITALY scores display close relationships with non-ATTR-specific measures of QoL.

Abbreviations: 6MWT: 6-min walking test; ATTR: amyloid transthyretin; CA: cardiac amyloidosis; HF: heart failure; KCCQ: Kansas City Cardiomyopathy Questionnaire; LV(EF): left ventricular (ejection fraction); NYHA: New York Heart Association; PROMs: patient-reported outcome measures; QoL: quality of life; SF-36: Short-Form 36; v: variant; wt: wild-type

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KEYWORDS
Amyloidosis; aTTR; PROMs; quality of life; questionnaires

Background

Systemic amyloidoses are infiltrative diseases caused by the accumulation of misfolded proteins as insoluble amyloid fibrils. Almost all cases of cardiac amyloidosis (CA) are caused by misfolding of monoclonal immunoglobulin light chains or transthyretin (TTR). TTR is a transport protein for thyroxine and retinol binding protein. TTR misfolding may occur despite a genetically normal (wild-type, wt) protein; this condition commonly affects elderly individuals, and cardiac involvement is usually isolated. Alternatively, ATTR may be caused by substitution or deletion mutations rendering TTR prone to misfolding; this form is known as variant ATTR (ATTRv) and may be characterised by isolated cardiac disease, isolated polyneuropathy, or both, and possibly by other manifestations such as gastrointestinal disturbances, ocular and renal involvement [1–5].

ATTR-CA has a severe impact on patients' health and quality of life (QoL) [6–9]. This may be related to the long time usually required to establish the diagnosis, the slow disease progression, the high frequency of multi-organ involvement (in particular dysautonomia and polyneuropathy) and age-related comorbidities, together with the limited therapeutic options. Furthermore, patients with

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ATTRv-CA often worry about disease transmission to offspring. Despite its relevance, there are currently no specific tools for QoL assessment in ATTR-CA, which nonetheless would be extremely useful to better characterise patients at baseline as well as to assess disease progression and the response to therapies [10]. Clinical trials on ATTR-CA have used several scales developed in other settings (such as the Kansas City Cardiomyopathy Questionnaire – KCCQ), adaptations of other scales (such as the modified Neuropathy Impairment Score + 7), or generic QoL measures (the Short Form 36 Health Survey – SF-36) [10].

The Impact of Transthyretin Amyloidosis on Life qualitY (ITALY) study aimed: (1) to create patient-reported outcome measures (PROMs) for ATTRv- and ATTRwt-CA; (2) to assess the feasibility of their administration; (3) to investigate the relationship between score values, clinical and laboratory findings, the KCCQ and SF-36 scores.

Methods

Questionnaire creation

The first study goal was to create 2 questionnaires exploring the QoL of patients with ATTRwt- or ATTRv-CA. Based on their clinical experience and an unstructured literature review, a multidisciplinary team including three clinical cardiologists, a neurologist, a clinical geneticist, research nurses, a physiatrist and a clinical geneticist, all with a specific expertise on ATTR-CA, identified the main topics (physical health, psychological health, disease awareness, and involvement in social activities), and the specific domains to be investigated (such as dyspnoea on effort, peripheral edoema, etc., to explore physical health). The investigators then formulated the questions related to each domain, and 5 answer options for each question. Each questionnaire included 30 questions. The questionnaires were circulated among study investigators from each participating centre besides Pisa (Pavia, Ferrara, Florence, and Messina). Study investigators were asked to compile a specific Delphi questionnaire assessing four points: (1) the relevance of each item in ATTRwt- or ATTRv-CA, (2) the need to include the item in the questionnaire, (3) the place of each item in the questionnaire, and (4) the clarity of wording. These points were evaluated on a scale from 1 (complete agreement) to 5 (complete disagreement). Four questions received a score $\geq$3 by at least one investigator with respect to the clarity of wording; these questions were revised according to the specific comments received. Two samples of 10 patients were then randomly selected from the Institutional databases of Pisa (ATTRwt-CA) and Florence (ATTRv-CA). During an in-person meeting, the patients received the questionnaire for their condition (either ATTRwt- or ATTRv-CA) and were asked to fill the same Delphi form used by study investigators, with the help of a psychologist who had not been involved in the development of the questionnaires. Two questions scored $\geq$3 again for the clarity of wording, and were revised together with the patients.

Questionnaire validation

Participation to the ITALY study was proposed to consecutive patients evaluated in dedicated outpatient clinics who: (1) had completed the diagnostic workup for ATTR-CA, including genetic testing, (2) had a definite diagnosis of ATTRwt- or ATTRv-CA, and (3) were clinically stable from at least 3 months, as adjudicated by study investigators. The exclusion criteria were: (1) unwillingness to provide the informed consent to study participation; (2) inability to read and understand Italian, and (3) cognitive decline or other medical conditions not allowing to complete the study procedures, with the exception of the 6-min walking test (6MWT).

During an outpatient visit, patients were asked to fill the questionnaire for ATTRwt- or ATTRv-CA as well as the KCCQ and SF-36 questionnaires. During the same visit, patients underwent blood sampling to measure N-terminal pro-B-type natriuretic peptide (NT-proBNP), BNP, or both (at the discretion of the participating centre), high-sensitivity troponin T and/or I (hs-TnT/I), full blood cell count and plasma creatinine (to calculate the estimated glomerular filtration rate through the Chronic Kidney Disease Epidemiology Collaboration equation), a transthoracic echocardiogram and a 6MWT. Furthermore, a study investigator blinded to questionnaire answers assessed the New York Heart Association (NYHA) class.

Patients and their caregivers were asked to report any admission to the Emergency Department or hospitalisation for heart failure (HF) occurring after enrolment. All patients were contacted by phone once a month to retrieve information on their health status; phone calls were made by a trained data manager unaware of the responses to the questionnaires. Patients were re-evaluated after 180 ± 7 days (Figure 1).

The ITALY study was registered on the ClinicalTrials.gov website (NCT04563286) and was approved by the Ethics Committees of all the Centres involved. All patients provided written informed consent to study participation.

Data collection

Data from each centre were deidentified and collected in a shared data repository. The anonymized questionnaires for ATTRwt- or ATTRv-CA, the KCCQ-23 and SF-36 questionnaires were sent to the coordinating centre (Pisa). The scores were then calculated by a study investigator (L.T.) blinded to all other data.

As for KCCQ-23, each item score ranges between 0 and 100, with lower scores for worse health status. Six domains are evaluated: physical limitation (average of the items 1–6), symptom stability (item 7), symptom frequency (average of items 8, 10, 12, 14), symptom burden (average of items 9, 11, 13), self-efficacy (average of items 15 and 16), QoL (average of items 17, 18, 19) and social limitations (average of items 20, 21, 22, 23). Four summary scores are derived by averaging the domain scores: total symptom score (symptom frequency and symptom burden), symptom summary score (physical limitation and total symptom score), clinical

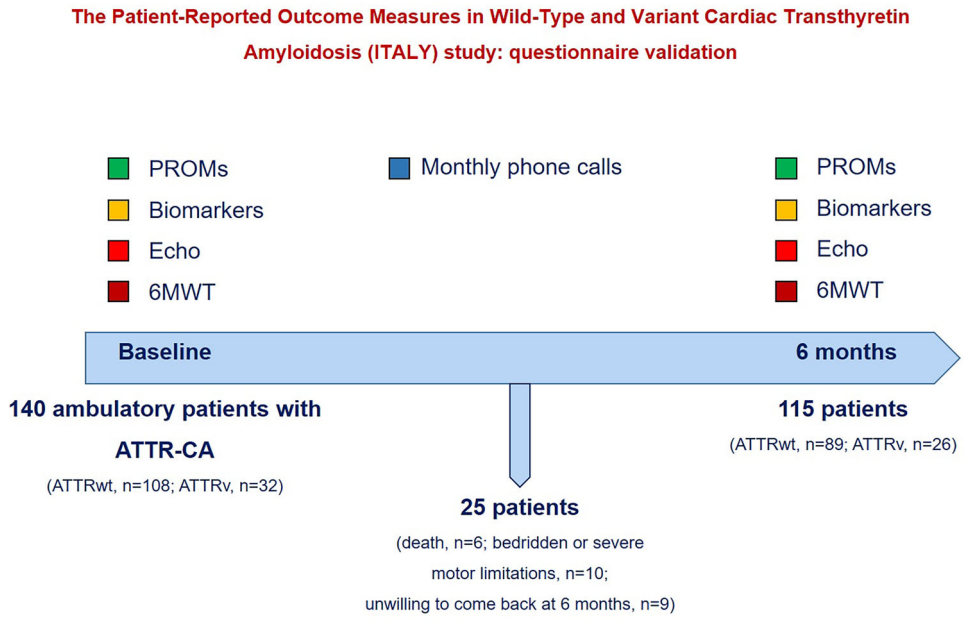

Figure 1. Protocol of the prospective validation of the ITALY questionnaires. See text for details. 6MWT, 6-min walking test; ATTR: amyloid transthyretin (v, variant; wt, wild-type); CA: cardiac amyloidosis; PROM: patient-reported outcome measures.

summary score (symptom summary and social limitation), overall score (physical limitation, total symptom, QoL, social limitation) [11].

The SF-36 Health Survey score was calculated according to the RAND Corporation model [12]. The score of each item ranges from 0 to 100, with lower scores denoting a worse health status. Eight domains are considered: physical functioning (average of items 3–12), role limitations due to physical health (13–16), role limitations due to emotional problems (17–19), energy/fatigue (23, 27, 29, 31), emotional well-being (24–26, 28, 30), social functioning (20, 32), pain (21, 22), and general health (1, 33–36) [13].

Statistical analysis

Normal distribution was assessed through the Shapiro-Wilk test; all variables had non-normal distribution and were expressed as median and interquartile range. Differences between groups were tested through the Mann-Whitney U test, and categorical variables were compared by the Chi-square test with Yates correction. Changes in continuous variables across repeated examinations were assessed through the Wilcoxon test for paired samples. Predictors of score values were searched through univariable linear regression analysis. Statistical analysis was performed using IBM SPSS Statistics (version 22, 2013).

Results

Patient characteristics at baseline

From March 2021 to July 2022, 140 patients with ATTR-CA were enrolled (Pisa, $n = 61$, 43%; Messina, $n = 34$, 24%; Pavia, $n = 26$, 19%; Ferrara, $n = 11$, 8%; Florence, $n = 8$, 6%). The majority of patients ($n = 108$, 77%) had ATTRwt-CA, while 32 had ATTRv-CA. The latter had the following mutations: Glu89Gln ($n = 15$), Ile68Leu ($n = 7$), Phe64Leu ($n = 2$), Ala36Pro ($n = 1$), Ala81Thr ($n = 1$), Gly47Ala ($n = 1$), Glu89Gln ($n = 1$), Thr49Ala ($n = 1$), Val94Leu ($n = 1$), Val122Ile ($n = 1$), Val30Met ($n = 1$).

Patients were mainly males (87%), and their median age was 77 years (IR 70–82). ATTRwt-CA patients were more often males and older than those with ATTRv-CA, had a worse renal function, and higher NT-proBNP values. Left ventricular (LV) systolic function was mildly depressed (median LV ejection fraction – LVEF – 51%), without significant differences between ATTRwt-CA and ATTRv-CA. Fifty-two patients (37%) were receiving disease-modifying therapy at baseline, most often tafamidis (ATTRwt-CA) or patisiran (ATTRv-CA). Two patients had been enrolled in phase 3 trials on acoramidis or patisiran (Table 1).

Re-evaluation at 6 months

Six patients (4%) died before the 6-month time-point; all these patients had ATTRwt-CA, and all deaths were adjudicated to be cardiovascular by referring clinicians. Other 10 patients became bedridden or developed severe motor limitations, and 9 were unwilling to return to the referral centre to undergo the follow-up examination. Patients not completing the follow-up had more often NYHA class III symptoms and higher NT-proBNP (Supplemental Table 1). Twelve patients (9%) died or were hospitalised at least once for HF.

Supplemental Table 2 provides a comparison between baseline and 6-month parameters for the 115 patients completing the 6-month follow-up. The main changes were an increase in NYHA class and NT-proBNP, a reduction in the 6-min walking distance, and an increase in relative wall thickness (an indicator of concentric remodeling). Thirty-three patients started tafamidis, and 20 were enrolled in phase 3 trials on acoramidis ($n = 18$) or patisiran ($n = 2$).

Table 1. Clinical and echocardiographic characteristics at baseline.

	ATTR-CA ($n = 140$)	ATTRwt-CA ($n = 108$)	ATTRv-CA ($n = 32$)	p
Male sex, *n* (%)	122 (87)	98 (91)	24 (75)	**.019**
Age (years)	77 (70–82)	79 (75–84)	65 (55–73)	**<.001**
Hypertension, *n* (%)	76 (54)	60 (55)	16 (50)	.580
Diabetes, *n* (%)	16 (11)	11 (10)	5 (16)	.396
Peripheral neuropathy, *n* (%)	35 (25)	13 (12)	22 (69)	**<.001**
NYHA class, *n* (%)				
I	15 (11)	8 (7)	7 (22)	.067
II	111 (78)	89 (82)	22 (69)	
III	14 (10)	11 (10)	3 (9)	
IV	0 (0)	0 (0)	0 (0)	
6-MWD (m)	358 (284–435)	342 (260–420)	399 (346–458)	.571
Laboratory parameters*				
NT-proBNP (ng/L)	1,822 (1,068–4,100)	2,244 (1,262–4,697)	1,345 (349–1,994)	**.027**
hs-TnT (ng/L)	44 (32–67)	45 (33–70)	29 (23–49)	.099
eGFR (mL/min/1.73 m^2)	61 (49–78)	59 (45–71)	83 (58–97)	**<.001**
Hemoglobin (g/dL)	13.9 (12.9–14.6)	13.9 (12.9–14.6)	13.6 (12.7–14.5)	.959
NAC stage I, II, III, *n* (%)**	75, 43, 14 (57, 33, 11)	51, 37, 14 (50, 36, 14)	24, 6, 0 (80, 20, 0)	**.008**
Transthoracic echocardiography				
LVEF (%)	51 (46–57)	50 (45–57)	52 (48–59)	.407
IVS (mm)	17 (15–20)	17 (16–20)	17 (14–20)	.132
PWT (mm)	15 (14–17)	15 (14–17)	15 (12–18)	.680
RWT	0.63 (0.54–0.78)	0.62 (0.56–0.79)	0.67 (0.44–0.77)	.517
LVEDVi (mL/m^2)	53 (43–64)	53 (42–63)	54 (46–69)	.423
LVESVi (mL/m^2)	25 (20–35)	25 (19–35)	27 (21–34)	.882
LVMI (g/m^2)	168 (141–202)	170 (138–202)	165 (147–211)	.844
E/e′	16 (13–21)	17 (13–21)	16 (10–22)	.286
LAVI (mL/m^2)	43 (34–51	44 (36–52)	37 (29–49)	**.035**
TAPSE (mm)	18 (14–20)	16 (13–19)	21 (18–24)	**<.001**
Systolic PAP (mmHg)	39 (30–47)	41 (35–49)	25 (21–35)	**<.001**
Disease-modifying therapies or enrolment in clinical trials				
Tafamidis, *n* (%)	29 (21)	22 (20)	7 (22)	**<.001**
Patisiran, *n* (%)	20 (14)	0 (0)	20 (63)	**<.001**
Doxycycline/TUDCA, *n* (%)	3 (2)	3 (3)	0 (0)	.075
Clinical trials				
Acoramidis or placebo, *n* (%)	1 (1)	1 (1)	0 (0)	.313
Patisiran or placebo, *n* (%)	1 (1)	1 (1)	0 (0)	.313

Significant p values are reported in bold. 6MWD: 6-min walking distance; ATTR-CA: cardiac transthyretin amyloidosis (v, variant; wt, wild-type); hs-TnT: high-sensitivity troponin T; IVS: interventricular septum; LAVI: left atrial volume index; LVEDVi: left ventricular end-diastolic volume index; LVESVi: left ventricular end-systolic volume index; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; NAC: National Amyloidosis Centre; NYHA: New York Heart Association; PWT: posterior wall thickness; RWT: relative wall thickness; TAPSE: tricuspid annular plane systolic excursion; PAP: pulmonary artery pressure. * NT-proBNP was available for 132 patients and hs-TnT for 79 patients. ** Available in 132 patients.

KCCQ and SF-36: baseline vs. 6-month assessment

At baseline, 136 patients completed the KCCQ questionnaire (97%; $n = 23$ with at least one missing answer), and 133 the SF-36 questionnaire (95%; $n = 41$ with at least one missing answer). At 6 months, 114 patients completed the KCCQ questionnaire (97% of those with available data; $n = 8$ with at least one missing answer), and 102 the SF-36 questionnaire (88%; $n = 28$ with at least one missing answer). Baseline KCCQ and SF-36 score values did not differ between patients completing vs. those not completing the follow-up (data not shown).

From baseline to 6 months, patients with ATTRwt-CA showed decreases in the KCCQ Physical Limitation and SF-36 Physical functioning scores, as well as KCCQ Symptom Summary and Clinical Summary and SF-36 and Emotional well-being scores. Differences in patients with ATTRv-CA were all not significant except for a small improvement in the KCCQ Overall summary score (Supplemental Table 3; Supplemental Figures 1 and 2).

ITALY scores

Two 30-item questionnaires were created and formatted for gender neutrality, clarity and interpretability. Each item had 5 answers graded from 4 (best option) to 0 (worst option). See for example question 7 of the ATTRwt-CA questionnaire:

How often have you woken up during the night with a feeling of lack of air?

Never	4
Less than twice a week	3
More than twice a week	2
Most days	1
Daily	0

For questions exploring the tolerance to different degrees of exercise, patients were asked to specify if they did not perform these activities and this answer was considered not evaluable, thus they were not scored (item 1 and 2). The global score was calculated as the sum of the scores for all questions divided by the maximum possible score to the answered questions, normalised on a 0–100 scale. For example, if the sum of scores for all questions was 72 and the patient had answered 29 questions, the score was calculated as follows: 72 points: (29 questions * 4 points for each question) = x: 100, from which x was calculated as 72 * 100/(29 * 4) = 62. The possible scores then ranged from

Table 2. ITALY score: 6-month vs. baseline assessment.

	ATTR-CA			ATTRwt-CA			ATTRv-CA		
	Baseline ($n = 115$)	6 months ($n = 115$)	p	Baseline ($n = 89$)	6 months ($n = 89$)	p	Baseline ($n = 26$)	6 months ($n = 26$)	p
Overall score	63 (54–73)	64 (54–73)	.670	63 (55–73)	65 (53–74)	.605	58 (52–72)	63 (55–73)	**.026**
Physical score	75 (55–83)	69 (54–82)	.173	75 (60–83)	69 (52–83)	.109	63 (52–80)	68 (54–78)	.581
Social score	60 (50–68)	59 (51–69)	.919	60 (51–69)	58 (49–70)	.321	59 (49–64)	60 (54–67)	.073

Significant p values are reported in bold. ATTR-CA: cardiac transthyretin amyloidosis (v, variant; wt, wild-type); ITALY: Impact of Transthyretin Amyloidosis on Life qualitY; KCCQ: Kansas City Cardiomyopathy Questionnaire; SF-36: Short Form-36.

100 (best possible health status) to 0 (worst possible health status). The items 1–12 and 13–30 were also evaluated separately as measures of physical and social health, respectively, and again normalised on a scale from 0 to 100.

Patients were also asked to specify if they completed the questionnaire alone or with help from others. The questionnaires are provided in the Supplemental material.

All patients undergoing the baseline evaluation ($n = 140$) and those repeating the analysis at 6 months ($n = 115$) completed the ITALY questionnaire for ATTRwt- or ATTRv-CA. Forty-one patients (30%) at baseline and 29 (25%) at 6 months filled the questionnaire with help. ATTRwt-CA patients needed more often help; the difference became significant at the sixth month ($p = .081$ and $p < .001$, respectively).

At baseline, 49 patients (35%) did not answer at least one question. At 6 months, 39 patients (34%) did not answer at least one question. Patients with ATTRwt-CA more often did not fully complete the questionnaire ($n = 43$ vs. 6 at baseline, $p = .004$; $n = 37$ vs. 2 at 6 months, $p = .007$). Question 2 of the ATTRwt-CA questionnaire ('How much shortness of breath have you experienced hurrying (as if to catch a bus) over the past 2 weeks?') was the one that most commonly did not have an answer or whose answer could not be evaluated: $n = 32$ at baseline and $n = 29$ at 6 months. The other questions with the highest numbers of no answers referred to dyspnoea during physical activities (climbing two flights of stairs or walking at a normal pace for 30 min without stopping).

At baseline, median ITALY overall score values were 64 (54–74) in ATTRwt-CA and 59 (51–71) in ATTRv-CA. Baseline score values did not differ significantly between patients completing vs. those not completing the 6-month follow-up (data not shown). When comparing baseline and 6-month score values in the other patients, significant changes in ITALY score values were found only in ATTRv-CA patients, who showed a small improvement in global scores ($p = .026$) (Table 2 and Figure 2).

ITALY vs. KCCQ and SF-36 scores at baseline

We then searched for predictors of ITALY score values at baseline, considering separately patients with ATTRwt-CA or ATTRv-CA. In patients with ATTRwt-CA, NYHA class, 6-min walking distance, NT-proBNP and hs-TnT and all KCCQ and SF-36 scores emerged as univariate predictors of the ITALY score. The KCCQ Symptom Summary score (beta coefficient 0.759), Social Limitations (0.781), and Overall summary score (0.786) were those most closely correlated with ITALY score values. Only some KCCQ and SF-36 scores were univariate predictors of ITALY score values in ATTRv-CA, the strongest predictors being the SF-36 Emotional well-being score (0.608), the KCCQ Overall summary score (0.656), and the SF-36 Energy/fatigue score (0.669) (Table 3). ITALY score values did not display a closer association with indicators of cardiac disease than the KCCQ and SF-36 scores (Table 3 and Supplemental Table 3). None of the scores predicted all-cause death at 6 months or the composite of death or HF hospitalisation at 6 months (data not shown).

ITALY vs. KCCQ and SF-36 scores at 6 months

We then searched for predictors of ITALY score values at 6 months among all variables collected at the same time-point. Among patients with ATTRwt-CA, all KCCQ and SF-36 score values predicted ITALY score values, most notably the KCCQ Symptom Burden (beta coefficient 0.809) and Overall summary score (0.820), and the SF-36 Overall score (0.823). In the ATTRv-CA subgroup, all SF-36 and many KCCQ score values emerged as significant univariate predictors of ITALY score values, the strongest being SF-36 Energy/fatigue (0.755), Physical functioning (0.838) and Overall score (0.855) (Table 4). Again, the ITALY scores did not display a closer association with indicators of cardiac disease than the KCCQ and SF-36 scores (Table 4 and Supplemental Table 4).

Discussion

The ITALY study led to the creation of the first specific PROMs for cardiac ATTRwt-CA and ATTRv-CA. It also validated them in comparison to non-specific PROMs often employed in ATTR-CA, namely the KCCQ and SF-36. Questionnaire completion proved feasible. ITALY scores displayed close relationships with non-ATTR-specific measures of QoL (KCCQ and SF-36).

QoL measures are emerging in modern medicine as valid end-points in trials and clinical studies. PROMs are much appreciated as they consider the disease from the patient's perspective, placing the patient and not the disease at the centre of health care. Furthermore, improving QoL is increasingly seen not only as a surrogate outcome measure, but also as an independent goal of treatment. Development and validation of PROMs is a challenging and time-consuming process that requires the involvement of patients as well as expert clinicians. Specific PROMs must explore as much as possible signs and symptoms of the investigated disease and they have to be short and easy to understand for

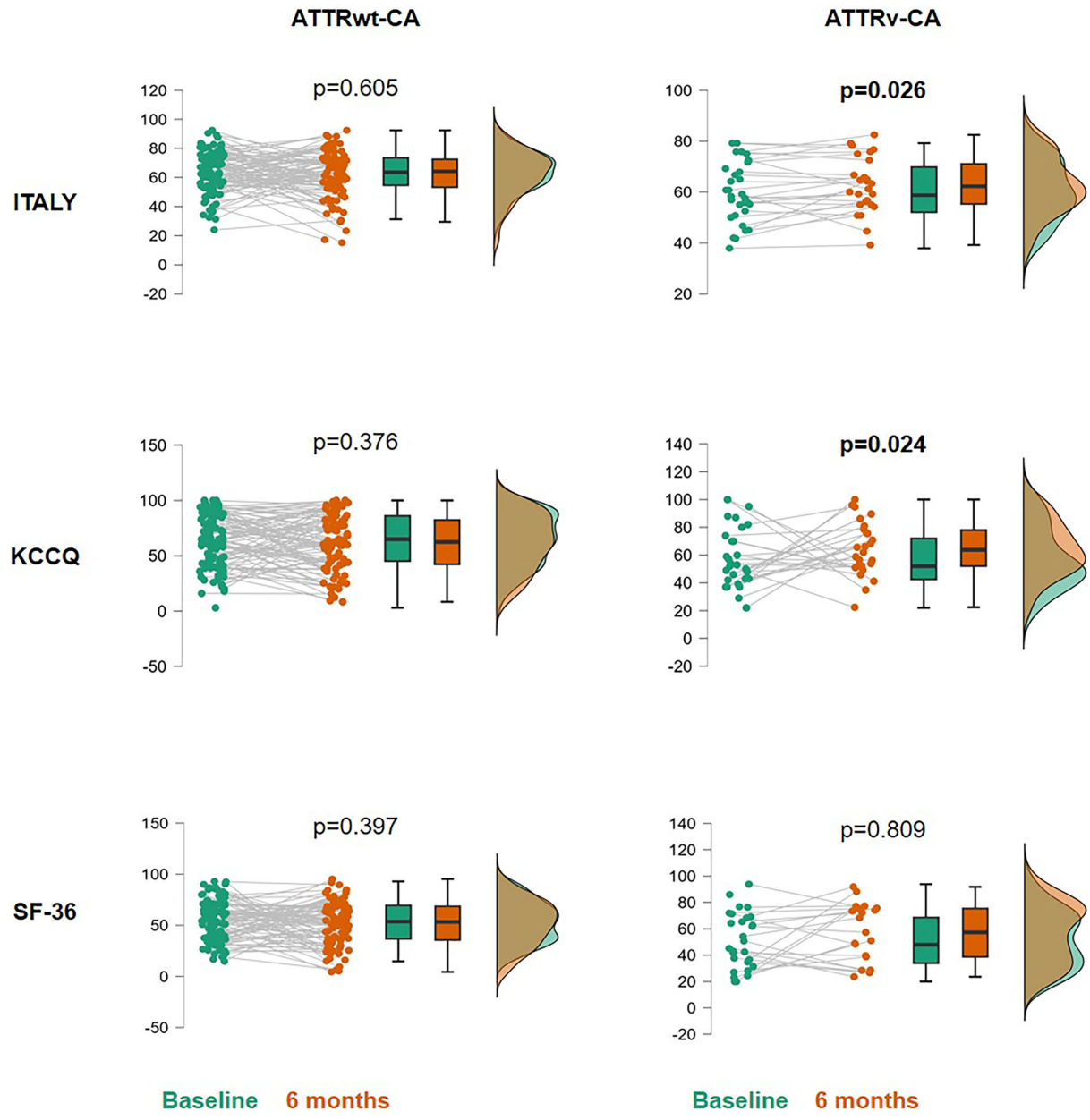

Figure 2. Changes in score values from baseline to 6 months. Significant *p* values are reported in bold. ATTR-CA: transthyretin cardiac amyloidosis (v, variant; wt, wild-type); ITALY: Impact of Transthyretin Amyloidosis on Life qualitY; KCCQ: Kansas City Cardiomyopathy Questionnaire; SF-36: Short-Form 36.

patients with different ages, gender, cultural or social backgrounds [14]. Additionally, PROMs should be validated in a large population that can be representative of different disease phenotypes and severity.

To our knowledge, the only questionnaire specific for ATTR-CA is Amylo-AFFECT-QoL [15]. This questionnaire is designed to assess QoL in AL-, ATTRwt- and ATTRv-CA, which have very different manifestations and prognosis. Furthermore, only 4 out of 33 questions investigate HF signs and symptoms, even if HF is the main factor affecting prognosis in amyloidosis, as shown also in the validation cohort of the same study [15]. Conversely, the ITALY questionnaires evaluate separately ATTRwt- and ATTRv-CA, and try to provide a comprehensive view of cardiac and systemic disease manifestations and their impact on QoL. The ITALY questionnaires were developed together with experts from 5 referral centres for ATTR-CA and groups of patients with ATTRwt- or ATTRv-CA ($n = 10$ each), and the questionnaires were tested in the same 5 centres. The questionnaires were then tested in a cohort of 140 patients, which is not small considering that ATTR-CA is still considered a rare disorder.

The baseline characteristics of the ITALY cohort suggested a mild to moderate disease severity: for example, 89% of patients were had NYHA class I or II symptoms. ATTRwt-CA patients were elderly and had worse cardiac involvement than those with ATTRv-CA, as suggested by higher NT-proBNP levels. During the 6-month follow-up, a slight disease progression was noted in both subgroups and particularly in ATTRwt-CA, where an increase in NYHA class, NT-proBNP, troponin T and RWT, and a decrease in 6-min walking distance (6MWD) was observed. The only

Table 3. Univariate predictors of baseline ITALY overall scores.

	ATTRwt-CA ($n = 118$)		ATTRv-CA ($n = 32$)	
Baseline variables	B-coefficient	*p*	B-coefficient	*p*
Male sex	–	.287	–	.586
Age	–	.712	–	.223
Hypertension	–	.664	–	.877
Diabetes	–	.324	–	.271
Peripheral neuropathy	–	.540	–	.358
NYHA class	−0.228	**.007**	–	.494
6MWD	0.319	**<.001**	–	.166
Laboratory parameters				
NT-proBNP	−0.222	**.011**	–	.418
hs-TnT	−0.230	**.041**	–	.882
eGFR	–	.208	–	.718
Hemoglobin	–	.155	–	.344
NAC score I, II, III	−0.442	**<.001**	–	.863
Transthoracic echocardiography				
LVEF	–	.158	–	.131
IVS	–	.059	–	.227
PWT	–	.134	–	.225
RWT	–	.094	–	.249
LVEDVi	–	.407	–	.595
LVESVi	–	.371	–	.599
LVMI	–	.146	–	.207
E/e'	–	.413	–	.916
LAVI	–	.182	–	.928
TAPSE	–	.073	–	.965
Systolic PAP	–	.731	–	.968
Disease-modifying therapy or clinical trial at baseline	–	.912	–	.928
KCCQ				
Physical limitation	0.685	**<.001**	0.425	**.023**
Symptom stability	0.315	**.001**	–	.680
Symptom frequency	0.700	**<.001**	0.525	**.007**
Symptom burden	0.642	**<.001**	–	.799
Self-efficacy	0.445	**<.001**	–	.407
Quality of life	0.694	**<.001**	0.560	**.004**
Social limitations	0.781	**<.001**	–	.091
Summary scores				
Total symptom score	0.719	**<.001**	0.539	**.005**
Symptom Summary score	0.759	**<.001**	0.575	**.003**
Clinical summary score	0.730	**<.001**	0.523	**.007**
Overall summary score	0.786	**<.001**	0.656	**<.001**
SF-36				
Physical functioning	0.661	**<.001**	0.556	**.007**
Role limitations due to physical health	0.514	**<.001**	0.603	**.002**
Role limitations due to emotional problems	0.449	**<.001**	0.569	**.006**
Energy/fatigue	0.705	**<.001**	0.669	**.001**
Emotional well-being	0.565	**<.001**	0.608	**.003**
Social functioning	0.593	**<.001**	0.531	**.011**
Bodily pain	0.542	**<.001**	–	.054
General health	0.638	**<.001**	0.573	**.005**
Overall score	0.644	**<.001**	–	.391

Results of univariate linear regression analysis are provided. Beta-coefficient values are shown only for significant predictors. Significant *p* values are reported in bold. 6MWD: 6-min walking distance; ATTR-CA: cardiac amyloid transthyretin amyloidosis (v, variant; wt, wild-type); hs-TnT: high-sensitivity troponin T; IVS: interventricular septum; KCCQ: Kansas City Cardiomyopathy Questionnaire; LAVI: left atrial volume index; LVEDVi: left ventricular end-diastolic volume index; LVESVi: left ventricular end-systolic volume index; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; NAC: National Amyloidosis Centre; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PWT: posterior wall thickness; RWT: relative wall thickness; TAPSE: tricuspid annular plane systolic excursion; SF-36: Short Form-36.

significant changes at 6 months in patients with ATTRv-CA were in NYHA class, 6MWD, interventricular septum thickness and LV mass index. In the whole cohort only 12 patients experienced major cardiovascular events (death or rehospitalization for cardiovascular causes), and the only clinical or instrumental significant difference compared with patients without events was a lower LVEF ($p = .033$).

The KCCQ is an excellent PROM for HF, but does not take in consideration signs and symptoms of peripheral neuropathy. SF-36, on the other hand, is an excellent PROM on health-related QoL, but does not explore specific aspects of ATTR-CA. Interestingly, KCCQ and SF-36 showed different changes in ATTRwt- and ATTRv-CA patients during the follow-up. In ATTRwt-CA changes were in line with disease progression, resulting in a worse QoL especially in domains exploring physical impairment (physical limitation, symptom summary score, clinical summary score at KCCQ, physical functioning and emotional well-being at SF-36). On the other hand, in ATTRv-CA QoL scores remained stable with the exception of overall summary score at KCCQ that showed a mild improvement. Although apparently in contradiction with a mild progressed cardiac disease shown by clinical and echocardiographic parameters, this result can be explained taking in

Table 4. Univariate predictors of ITALY overall scores at 6 months.

	ATTRwt-CA ($n = 89$)		ATTRv-CA ($n = 26$)	
6-month variables	β-coefficient	*p*	β-coefficient	*p*
NYHA class	−0.340	**.001**	–	.510
6MWD	0.406	**<.001**	–	.100
Laboratory parameters				
NT-proBNP	−0.258	**.022**	–	.305
hs-TnT	–	.967	–	.912
eGFR	–	.450	–	.278
Hemoglobin	–	.162	–	.215
NAC score I, II, III	−0.267	**.013**	–	.282
Transthoracic echocardiography				
LVEF	–	.758	0.417	**.038**
IVS	–	.383	–	.130
PWT	–	.150	–	.426
RWT	–	.841	–	.853
LVEDVi	–	.275	–	.128
LVESVi	–	.398	–	.777
LVMI	–	.418	–	.092
E/e'	–	.857	–	.266
LAVI	–	.293	–	.174
TAPSE	–	.382	–	.612
Systolic PAP	−0.276	**.015**	–	.911
Disease-modifying therapy or clinical trial at baseline	–	.912	–	.928
Disease-modifying therapy started or enrolment in clinical trial	–	.189	–	.907
KCCQ				
Physical limitation	0.708	**<.001**	0.615	**.001**
Symptom stability	0.432	**<.001**	–	.492
Symptom frequency	0.784	**<.001**	0.600	**.001**
Symptom burden	0.809	**<.001**	–	.429
Self-efficacy	0.549	**<.001**	–	.123
Quality of life	0.784	**<.001**	0.492	**.011**
Social limitations	0.308	**.030**	0.630	**.001**
Summary scores				
Total symptom score	0.797	**<.001**	0.562	**.003**
Symptom summary score	0.788	**<.001**	0.718	**<.001**
Clinical summary score	0.752	**<.001**	0.713	**<.001**
Overall summary score	0.820	**<.001**	0.737	**<.001**
SF-36				
Physical functioning	0.670	**<.001**	0.838	**<.001**
Role limitations due to physical health	0.484	**<.001**	0.535	**.015**
Role limitations due to emotional problems	0.472	**<.001**	0.619	**.003**
Energy/fatigue	0.780	**<.001**	0.755	**.001**
Emotional well-being	0.705	**<.001**	0.608	**<.001**
Social functioning	0.236	**.034**	0.637	**.002**
Bodily pain	0.631	**<.001**	0.723	**<.001**
General health	0.653	**<.001**	0.732	**<.001**
Overall score	0.823	**<.001**	0.855	**<.001**

Results of univariate linear regression analysis are provided. Beta-coefficient values are shown only for significant predictors. Significant *p* values are reported in bold. 6MWD: 6-min walking distance; ATTR-CA: cardiac amyloid transthyretin amyloidosis (v, variant; wt, wild-type); hs-TnT: high-sensitivity troponin T; IVS: interventricular septum; KCCQ: Kansas City Cardiomyopathy Questionnaire; LAVI: left atrial volume index; LVEDVi: left ventricular end-diastolic volume index; LVESVi: left ventricular end-systolic volume index; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; NAC: National Amyloidosis Centre; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PWT: posterior wall thickness; RWT: relative wall thickness; TAPSE: tricuspid annular plane systolic excursion; SF-36: Short Form-36.

consideration two aspects. First, peripheral neuropathy has a major impact on the QoL in ATTRv-CA [9], and changes in the severity of neuropathy could be much more relevant than a slight progression in cardiac disease. Second, disease-modifying therapies for ATTRv-CA were found to improve functional capacity and QoL. Most notably, patisiran therapy was associated with a mild improvement of mNIS + 7 both at 9 and 18 months [16]. In ITALY, 63% of ATTRv-CA patients were on patisiran both at baseline and at month 6, while no ATTRwt-CA patient was on patisiran and only one patient was enrolled in a trial on patisiran vs. placebo. None of the ATTRv-CA patients started patisiran during the follow-up, which means that all patients with patisiran at month 6 had already received the treatment for a period long enough to have positive effects on the QoL.

We aimed to generate PROMs specific for ATTR-CA that are easy to complete by patients and to calculate by clinicians. The questions were designed through an extensive literature revision identifying 5 domains to be explored with 6 questions for each domain, resulting in 30 items. This number is similar to the number of items in KCCQ and SF-36, and a 5-answers approach was chosen in agreement to PROMs with 0 points for answers indicating worst QoL and 4 points for the best QoL. A 'not evaluable' answer was added to questions assessing physical limitation when this limitation could be due to reasons other than amyloidosis. To simplify score calculation and comparison with other PROMs, ITALY scores were calculated as the sum of answers normalised to 100 with higher scores for better QoL. Indeed, this scale is already used by the majority of

PROMs. While many KCCQ scores exist, together with the overall summary score, we propose just 2 partial scores reflecting physical health and social or physiological health.

We also investigated how many patients needed help to fill out the questionnaires. This is an important aspect in PROMs, because the presence of another person, whether a physician or a relative, has a deep impact on the answers. On one hand, patients may have some hesitations about making uncomfortable responses when they are not alone. On the other hand, patients can be helped to understand questions and therefore give appropriate answers, although a well-designed questionnaire should not be difficult to understand for patients. ITALY questionnaires were filled by all patients at baseline and 6 months. However, some questionnaires remained incomplete with missing or not evaluable questions. In both ITALY questionnaires, items 1 and 2 investigate physical limitation on mobility and are the only items with a not evaluable answer, when patients are bedridden or with severely impaired mobility. This approach for physical limitations was already applied in KCCQ-36 for similar items and its aim is avoiding an overestimation of physical impairment when there are comorbidities with a great impact on mobility. Furthermore, ATTRv-CA patients filled the whole questionnaire more commonly than ATTRwt-CA patients and with less need for help, likely because of their younger age.

In ATTRwt-CA, the overall ITALY score displayed a close correlation with overall KCCQ and SF-36 scores, which all focused mostly on cardiac disease and its manifestations. The overall ITALY scores and the ITALY subscales did not change significantly over 6 months, while some partial KCCQ and SF-36 domains highlighted a mild impairment in QoL during the same period. The ATTRv-CA score displayed rather weak correlations with overall KCCQ and SF-36 scores at baseline and 6 months, likely because ATTRv-CA is a systemic disease whose clinical presentation is more variable than ATTRwt-CA, and the domains investigated in the ITALY score are different from those explored in KCCQ or SF36 scores. From a practical perspective, ITALY questionnaires are easy to complete, with an average filling time of about 10 min in the Pisa cohort (data not shown). The number of items is lower than the SF-36 ($n = 36$), but still higher than the KCCQ ($n = 23$). Nonetheless, multiple KCCQ summary scores are often considered, and their calculation may be time-consuming, while calculation of the ITALY score is simple and straightforward.

Several limitations must be acknowledged. The number of patients was relatively small (although still almost 3-fold greater than the cohort where the Italian version of the KCCQ was validated) [17], the follow-up rather short, and the number of patients not repeating the 6-month re-evaluation quite high. We did not examine the score responsiveness, i.e. the changes in score values after discharge from HF hospitalisation [18]. Furthermore, we are providing an English translation of the questionnaires in the Supplemental material, but we did not undergo the complex process of linguistic adaptation, which must cover all steps needed to ensure that the validity and reliability of the questionnaire is still intact when translating a questionnaire originally developed in another country and culture [19]. Finally, detailed information on the severity of peripheral neuropathy, the echocardiographic phenotype, and HF therapies was not collected, and we are then unable to assess their impact on patient QoL and score values.

In conclusion, the ITALY questionnaires are the first specific PROMs for ATTRwt- and ATTRv-CA. They have been created by experts in CA and patients and validated in a multicentre Italian cohort with 2 assessments over 6 months. Questionnaire completion seems feasible; the global scores and the scores exploring physical or social health can be easily calculated. ITALY score values display good correlations with non-ATTR-specific measures of QoL (KCCQ and SF-36).

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