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ORIGINAL ARTICLE

Age-dependency of EHRA improvement based on quality of life at diagnosis of atrial fibrillation

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Abstract

Background: In this study, the relationship between AF-related quality of life (AFEQT) at baseline in AF-patients and the improvement on perceived symptoms and general state of health (EHRA, European Heart Rhythm Association score) at 12 months was assessed across predefined age categories.

Methods: Between November 2014 and October 2019 patients diagnosed with AF de novo in four hospitals embedded within the Netherlands Heart Network were prospectively followed for 12 months. These AF-patients were categorized into quartiles based on their AFEQT score at diagnosis and EHRA score was measured at diagnosis and 12 months of follow-up. Stratified analyses were performed using age categories (<65 vs. ≥65 years; <75 vs. ≥75 years).

Results: In total, 203/483 (42.0%) AF-patients improved in EHRA score after 12 months of follow-up. AF-patients in the lowest AFEQT quartile were more likely to improve, compared to patients in the highest AFEQT quartile (OR [95%CI]:4.73 [2.63–8.50]). Furthermore, patients ≥65 years and patients <75 years at diagnosis with lower AFEQT scores at baseline were most likely to improve in EHRA score after 12 months, compared to similarly aged patients with higher AFEQT scores at baseline.

Conclusion: The present study indicates that AF-patients with a lower quality of life at diagnosis were most likely to improve their EHRA score after 12 months. This effect was most prominent in patients ≥65 years of age and patients <75 years of age, compared to patients >65 and ≥75 years, respectively. Future research should focus on further defining characteristics of these age groups to enable the implementation of age-tailored treatment.

KEYWORDS
atrial fibrillation, quality of life, risk factors, risk stratification, symptom improvement

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia with a profound effect on the quality of life (QoL) of patients.[1–3] AF presents itself in various forms and with various adverse outcomes, which can impact the patients' general state of health both in the short- and the long-terms. Therefore, AF management requires strategies to manage the patients' physical symptoms, but also the psychological well-being.[3,4] There is great variability within the AF-patient population in the change in symptoms and response to therapy, making improvement hard to predict.[5] Therefore, assessing indicators for symptom improvement may provide valuable information for selecting appropriate treatment options in the clinic.[5]

The prevalence of AF increases sharply between 60 and 65 years, after which it steadily increases until the age of 80–85 years.[6,7] Furthermore, age strongly influences the occurrence of AF-related symptoms and declines in functional capacity as younger patients report more dizziness and palpitations, while older patients tend to feature a greater degree of dyspnea and fatigue.[8] Underlying comorbidities have been reported as one of the most important drivers for the limiting effects of AF on physical capacity.[9] Elderly patients tend to experience more comorbidities. Moreover, age is prominently featured in various clinical risk stratification schemes routinely employed in AF management.[10,11] For instance, the CHA_2DS_2-VASc stroke risk stratification score uses age categories (<65, ≥65–74, and ≥75 years) to help guide clinicians in predicting high-risk patients.[10] Therefore, it is crucial to account for the patients' age at the diagnosis of AF to obtain an accurate estimate of the predicted progression of their perceived general state of health, and subsequently, tailor treatment according to the patients' predicted disease trajectory.

A widespread and simple to use method to assess and quantify symptoms related to AF is the European Heart Rhythm Association (EHRA) score. The EHRA score helps classify patients based on the limitations they experience during normal daily activity. Previous studies have indicated that this score is associated with Health Related Quality of Life (HRQoL).[12,13] The evaluation of HRQoL by health professionals is emerging as an important factor in the assessment and follow-up of patients with AF to aid in providing patient-centered care.[14] A commonly used and validated way to determine the AF-related quality of life is the Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaire.[15] Based on the relationship between the score of the AFEQT questionnaire and AF-related symptoms, HRQoL at diagnosis could potentially be used to predict future improvement in AF-symptoms.[12,16] As age is a prominent factor in both the experienced symptoms at the onset of AF and the disease course, we hypothesize that the relationship between HRQoL and perceived AF-symptoms differs across age-groups.[5,8,9] By establishing the relationship between age, HRQoL and AF-symptoms, patient subgroups can be identified with suboptimal health benefits during the AF disease course. In particular, insights on vulnerable patient subgroups may help tailor AF management policies to maximize clinical outcomes based on patient characteristics and patient-reported outcome measures.

Therefore, we assessed the relationship between HRQoL (AFEQT) at baseline and the improvement on perceived symptoms and general state of health (EHRA score) at 12 months in AF-patients. Furthermore, we assessed potential differences between predefined age categories in this relationship to identify patient subgroups with the greatest potential for improvement in AF-symptoms.

2 | METHODS

2.1 | Study population

In this prospective cohort, patients newly diagnosed with AF in the outpatient clinics in any of the four hospitals embedded within the Netherlands Heart Network (NHN) in the time period between November 2014 and October 2019 were included. In short, the NHN is a joint effort of healthcare providers in primary, secondary, and tertiary cares in 800 000 head population in a rural and urban region in the southeast of the Netherlands, with the aim to improve the quality of care for cardiac patients by optimizing the complete healthcare chain.[17]

Patients were included in this study when they were ≥18 years, newly or recently diagnosed with non-valvular AF, were competent to read and agree on the informed consent, and had provided written informed consent.

2.2 | Procedure

In the hospitals embedded within the NHN a regional care standard has been implemented for AF-patients who visit the outpatient AF clinic to standardize the procedures and quality of care within the region. During 45–60 min patient consultation sessions within these outpatient AF clinics, AF-nurses provide education to the AF-patients and complete the required registrations to improve guideline adherence of cardiologists through better documentation of patient information. The education strategy contains information on available treatment options and the importance of treatment compliance, enabling patients to make well-informed decisions on their treatment. Furthermore, the AF-nurse makes an inventory of the general health status and AF-related complaints of the patient to inform the medical specialists with more detailed patient information to support the shared decision-making process. The AF-nurses collect data on the patients' demographics, anthropometry, patient vitals, various AF-related risk stratification scores, onset of symptoms, and results from the AFEQT questionnaire on HRQoL. For this study, the AF-nurse assessed eligibility, provided information on the study and obtained written informed consent. AF-patients included in the study were followed-up after 12 months (T1) to evaluate the initiated treatment and to record patient characteristics and outcomes.

In total, 561 AF-patients had an available EHRA score at both baseline and after 12 months of follow-up. AF-patients with a missing AFEQT score ($n = 76$) or missing information on selected confounders (CHA_2DS_2VASc: $n = 1$; OSAS: $n = 1$) were excluded from analyses. In total, 483 (86.1%) AF-patients with complete information were eligible for analyses.

2.3 | Outcome measure

The extent of AF-related symptoms and patients' perception of their general state of health was measured using the EHRA at diagnosis (T0) and after 12 months of follow-up (T1). The EHRA score is a 4 level scale ranging from EHRA class I (no symptoms) to EHRA class IV (disabling symptoms; normal daily activity discontinued).[18] Improvement on the perceived symptoms of AF was determined by comparing EHRA scores at 12 months of follow-up (T1) with the EHRA score at time of diagnosis (T0). Any point improvement of EHRA score was perceived as clinically relevant. Therefore, the unmodified EHRA score was used during this study. Patients with a lower EHRA score at T1, compared to T0, were categorized as EHRA improver (1), while patients with an equal or higher EHRA score at T1 compared to T0 were categorized as EHRA non-improver (0).

2.4 | Exposure assessment and background variables

Patients completed the AFEQT questionnaire at baseline to assess their perceived HRQoL. In contrast to more generic QoL questionnaires, which often include non-health-related features of life, the AFEQT questionnaire focuses on AF-related HRQoL, in which the impact of AF and treatment on an individual's QoL are determined. To this end, the AFEQT is a validated and reliable questionnaire featuring 20-items targeted at AF-patients to quantify HRQoL across 4 subdomains, including symptoms, daily activities, treatment concerns and treatment satisfaction using a 7-point Likert response scale.[15] The overall AFEQT score is calculated based on the answers from the first three subdomains (18 questions) and ranges from 0 (severe impairment/low QoL) to 100 (no limitation/high QoL). Patients were categorized into quartiles ranging from low to high based on the AFEQT scores observed in this study, with the highest quartile as reference (AFEQT score; Q1: <54.63; Q2: ≥54.63-<75.00; Q3: ≥75.00–89.05; Q4: ≥89.05.

Additional background variables from patients as recorded by AF-nurses were age (0: ≥65; 1: <65 years), gender (0: man; 1: woman), CHA_2DS_2VASc score at T0 (0: 0–1; 1: ≥2), HAS-BLED score at T0 (0: 0–1; 1: ≥2), body mass index (BMI; 0: <25; 1: ≥25 kg/m^2), diabetes mellitus (0: yes; 1: no), hypertension (0: no; 1: yes), obstructive sleep apnea syndrome (OSAS; 0: no; 1: yes), and location of AF-diagnosis (0: GP; 1: Hospital). The recorded background variables were selected based on their inclusion as cardiovascular risk factors in guidelines from the European Society of Cardiology.[19]

2.5 | Statistical analyses

Patient characteristics at baseline were described using general descriptive analyses on outcome measures and background variables.

In addition, multivariable-adjusted logistic regression analyses were performed to estimate Odds ratios (ORs) and 95% confidence intervals (CIs) to assess the association between AFEQT score at baseline (T0) and the improvement of EHRA score between baseline (T0) and 12 months of follow-up (T1). Categorized age, gender, CHA_2DS_2VASc score, HAS-BLED score were included in all models as *a priori* confounders. Potential confounders (i.e. BMI, DM, hypertension, OSAS, and location of AF-diagnosis) were added to the unstratified multivariable-adjusted model using backward elimination ($p < .10$). Based on this procedure DM and OSAS were included in all statistical models.

In separate analyses, patients were stratified into age groups (<65/≥65 years, and <75/≥75 years) based on cut-offs included in the CHA_2DS_2VASc score, a routinely employed risk prediction rule for estimating the risk of stroke in patients with non-valvular AF. Confounder subsets in stratified analyses were identical to overall analyses to maintain the comparability of models.

Furthermore, tests for multicollinearity between the CHA_2DS_2VASc and HAS-BLED scores were performed. No indications of multicollinearity were observed. In addition, sensitivity analyses were performed with the independent adjustment of models by CHA_2DS_2VASc and HAS-BLED scores which showed similar results to main analyses (data not shown). Moreover, sensitivity analyses on EHRA improvement were performed excluding patients with a score of EHRA I. Results attenuated strongly and became non-statistically significant (data not shown). Lastly, sensitivity analyses were performed to assess whether analyses could be performed to assess the relationship between the AFEQT score and decrease in EHRA score. Unfortunately, the number of patients who reported a decrease in EHRA score was too low ($n = 43$) to obtain robust results upon further stratifying patients.

All analyses were performed using IBM SPSS (IBM SPSS Statistics for Windows, version 26.0, IBM Corp.). p-values <.05 were considered statistically significant.

3 | RESULTS

Baseline characteristics of AF-patients, categorized into quartiles based on the AFEQT score ranging from low HRQoL (Q1) to high HRQoL (Q4), are presented in Table 1. Patients with a lower AFEQT score were more often female (Q1: 55.0%; Q4: 26.4%), had a higher mean age (Q1: 70.6 ± 10.6; Q4: 9.4 ± 9.4) and a higher CHA_2DS_2VASc score (2+; Q1: 80.0%; Q4: 71.1%) compared to patients with a higher AFEQT score. Patients in the fourth AFEQT score quartile (Q4)

TABLE 1 Baseline characteristics of AF-patients categorized into quartiles based on the AFEQT score at baseline

	AFEQT score at baseline, *n* (%)			
	First quartile (Q1) (4.63 to <54.63)	**Second quartile (Q2) (≥54.63 to <75.00)**	**Third quartile (Q3) (≥75.00 to <89.05)**	**Fourth quartile (Q4) (≥89.05 to 100)**
Total	120 (100)	120 (100)	122 (100)	121 (100)
Gender				
Men	54 (45.0)	61 (50.8)	69 (56.6)	89 (73.6)
Women	66 (55.0)	59 (49.2)	53 (43.4)	32 (26.4)
Age				
Mean (SD)	70.6 (10.6)	69.9 (9.6)	67.9 (9.3)	67.9 (9.4)
CHA_2DS_2VASc score (T0)				
0–1	24 (20.0)	24 (20.0)	30 (24.6)	35 (28.9)
2+	96 (80.0)	96 (80.0)	92 (75.4)	86 (71.1)
HAS-BLED (T0)				
0–1	58 (48.3)	74 (61.7)	77 (63.1)	64 (52.9)
2+	62 (41.6)	46 (38.3)	45 (36.9)	57 (47.2)
OSAS[b]				
No	115 (95.8)	117 (97.5)	115 (94.3)	119 (98.3)
Yes	5 (4.2)	3 (2.5)	7 (5.7)	2 (1.7)
Diabetes mellitus				
No	100 (83.3)	99 (82.5)	102 (83.6)	104 (86.0)
Yes	20 (16.7)	21 (17.5)	20 (16.4)	17 (14.0)
BMI				
<25	36 (33.3)	35 (34.0)	36 (36.4)	27 (28.4)
≥25	72 (66.7)	68 (66.0)	63 (63.6)	68 (71.6)
Hypertension				
No	48 (40.0)	48 (40.0)	53 (43.4)	60 (49.6)
Yes	72 (60.0)	72 (60.0)	69 (56.6)	61 (50.4)
Location of diagnosis				
GP	46 (39.0)	27 (22.7)	42 (35.0)	42 (34.7)
Hospital	72 (61.0)	92 (77.3)	78 (65.0)	79 (65.3)
Atrial fibrillation at completion of AFEQT questionnaire				
No	71 (62.8)	91 (80.5)	95 (78.5)	94 (81.7)
Yes	42 (37.2)	22 (19.5)	26 (21.5)	21 (18.3)

more often had a higher HAS-BLED score at baseline (2+; Q1: 41.6; Q4: 47.2%), were more often overweight or obese (Q1: 66.7%; Q4: 71.6%) and less often had a diagnosis of hypertension (Q1: 60.0; Q4: 50.4%), compared to patients in lower AFEQT quartiles. Finally, patients in lower AFEQT quartiles more often experienced AF at the time of completion, when compared to patients in higher AFEQT quartiles (Q1: 37.2%; Q4: 18.3%).

3.1 | Improvement in EHRA score

In total, 203 (42.0%) AF-patients improved in EHRA score. In patients who improved in EHRA score a mean (SD) improvement of −1.31 (0.55) was observed. Results from multivariable-adjusted analyses on the association between AFEQT score and the improvement in EHRA score after 12 months of follow-up are presented in Table 2. Patients with a lower AFEQT score at baseline, indicating a lower HRQoL, more often improved in EHRA score, compared to patients in the highest AFEQT quartile at baseline (Q4; Table 2). This association was statistically significant across the Q1–Q3 quartiles and became stronger across quartiles with lower AFEQT scores. Furthermore, the mean observed EHRA improvement was larger across decreasing AFEQT quartiles, although standard deviations were relatively wide (mean [SD]: Q1: −1.39 [0.55]; Q2: −1.31 [0.57]; Q3: −1.20 [0.50]; Q4: −1.27 [0.60]).

3.2 | Results stratified by age (<65; ≥65)

In total, 68/134 (50.7%) of the patients diagnosed with AF <65 years of age and 135/349 (38.7%) of the patients diagnosed with AF

≥65 years of age improved in EHRA score by at least one point. On average, those who improved in symptoms improved by −1.24 (0.49) and −1.34 (0.58) (mean [SD]), for age at diagnosis of <65 and ≥65 years, respectively. Results from multivariable-adjusted analyses testing the association between AFEQT and the improvement of EHRA score after 12 months of follow-up stratified into age categories of <65 and ≥65 years are presented in Table 3. Results for patients aged ≥65 years at AF-diagnosis were similar to unstratified analyses. However, multivariable-adjusted ORs were stronger compared to overall analyses for the first and second quartile of AFEQT score, when compared to the fourth quartile (OR [95%CI]: 6.07 [2.89–12.74] and 4.75 [2.29–9.84], respectively). In patients with an AF-diagnosis before 65 years solely the first AFEQT score quartile was statistically significantly associated with an increased EHRA score, compared to the fourth AFEQT quartile (OR [95%CI]: 2.77 [1.00–7.67]). Similar to overall analyses, a positive association was observed for diabetes mellitus in patients with an AF-diagnosis before 65 years of age. However, this association was not statistically significant (OR [95%CI]: 3.06 [0.76–12.31]).

TABLE 2 Overall associations with improvement of EHRA score after 12 months (T1)

AFEQT score (T0)	Total study population, *n* (%)	Improvement of EHRA score (T1)	
		n (%)	Adj. OR (95% CI)[a]
First quartile (4.63 to <54.63)	120 (24.8)	70 (58.3)	**4.73 (2.63–8.50)**
Second quartile (≥54.63 to <75.00)	120 (24.8)	58 (48.3)	**3.42 (1.91–6.15)**
Third quartile (≥75.00 to <89.05)	122 (25.3)	49 (40.2)	**2.33 (1.30–4.18)**
Fourth quartile (≥89.05 to 100)	121 (25.1)	26 (21.5)	1 (Ref.)

[a] Multivariable-adjusted models were corrected for age (<65; ≥65), gender (men; women), HAS_BLED (0–1; ≥2), CHA^2DS^2-VASc (0–1; ≥2), Diabetes mellitus (no; yes) and OSAS (no; yes).

Bold indicates statistically significant *p*-values.

3.3 | Results stratified by age (<75; ≥75)

In total, 138/330 (41.8%) of the AF-patients diagnosed <75 years of age and 65/153 (42.4%) of the AF-patients diagnosed ≥75 years of age improved in EHRA score by −1.31 (0.56) and −1.29 (0.52) (mean [SD]), respectively. Results from multivariable-adjusted analyses testing the association between AFEQT and the improvement of EHRA score after 12 months of follow-up stratified into age categories of <75 and ≥75 years are presented in Table 4. Both age groups showed similar associations to overall analyses presented in Table 2. The association between improved EHRA score was the strongest in the first AFEQT score quartile, compared to the fourth AFEQT quartile in patients in the category <75 years (OR [95% CI]: 5.46 [2.67–11.15]). Similar to other analyses, the strength of the association increased across decreasing AFEQT score quartiles in stratified analyses on <75 years. This increase was less prominently visible in analyses stratified on ≥75 years at AF-diagnosis. In analyses on this stratum, the strongest association with EHRA improvement was observed in the second AFEQT quartile, when compared to the fourth. In addition, the association with EHRA improvement comparing the third and the fourth AFEQT quartile was non-significant in this stratum.

TABLE 3 Associations stratified by age categories (<65; ≥65 years) with improvement of EHRA score after 12 months (T1)

	Age <65			Age ≥65		
	Total study population, *n* (%)	Improvement of EHRA score (T1)		Total study population, *n* (%)	Improvement of EHRA score (T1)	
		n (%)	Adj. OR (95%CI)		*n* (%)	Adj. OR (95%CI)
AFEQT score (T0)[a]						
First quartile (4.63 to <54.63)	33 (24.6)	20 (60.6)	**2.77 (1.00–7.67)**	87 (24.9)	50 (57.5)	**6.07 (2.89–12.74)**
Second quartile (≥54.63 to <75.00)	31 (23.1)	15 (48.4)	1.54 (0.55–4.37)	89 (25.5)	43 (48.3)	**4.75 (2.29–9.84)**
Third quartile (≥75.00 to <89.05)	37 (27.6)	21 (56.8)	2.30 (0.85–6.23)	85 (24.4)	28 (32.9)	**2.40 (1.13–5.10)**
Fourth quartile (≥89.05 to 100)	33 (24.6)	12 (36.4)	1 (Ref.)	88 (25.2)	14 (15.9)	1 (Ref.)

[a] Multivariable-adjusted models were corrected gender (men; women), HAS_BLED (0–1; ≥2), CHA^2DS^2-VASc (0–1; ≥2), Diabetes mellitus (no; yes) and OSAS (no; yes).

Bold indicates statistically significant *p*-values.

TABLE 4 Associations stratified by age categories (<75; ≥75 years) with improvement of EHRA score after 12 months (T1)

	Age <75			Age ≥75		
	Total study population	Improvement of EHRA score (T1)		Total study population	Improvement of EHRA score (T1)	
	n (%)	*n* (%)	Adj. OR (95%CI)	*n* (%)	*n* (%)	Adj. OR (95%CI)
AFEQT score (T0)[a]						
First quartile (4.63 to <54.63)	71 (21.5)	44 (62.0)	**5.46 (2.67–11.15)**	49 (32.0)	26 (53.1)	**3.75 (1.31–10.71)**
Second quartile (≥54.63 to <75.00)	77 (23.3)	35 (45.5)	**2.80 (1.40–5.62)**	43 (28.1)	23 (53.5)	**4.93 (1.68–14.45)**
Third quartile (≥75.00 to <89.05)	96 (29.1)	40 (41.7)	**2.43 (1.25–4.73)**	26 (17.0)	9 (34.6)	2.11 (0.62–7.19)
Fourth quartile (≥89.05 to 100)	86 (26.1)	19 (22.1)	1 (Ref.)	35 (22.9)	7 (20.0)	1 (Ref.)

[a] Multivariable-adjusted models were corrected for gender (men; women), HAS_BLED (0–1; ≥2), CHA^2DS^2-VASc (0–1; ≥2), Diabetes mellitus (no; yes) and OSAS (no; yes).

Bold indicates statistically significant *p*-values.

4 | DISCUSSION

In the present study, we aimed to assess the relationship between AFEQT score at baseline in AF-patients and the improvement in EHRA score at 12 months of follow-up. In addition, we aimed to identify patient subgroups that most commonly experienced EHRA score improvement during this time period. In summary, AF-patients with a lower AFEQT score at diagnosis were more likely to improve their EHRA score during follow-up, when compared to patients with a higher AFEQT score at diagnosis. In analyses stratified by age categories, patients above the age of 65 and below the age of 75 with lower AFEQT scores at baseline were most likely to improve their EHRA score between baseline and 12 months of follow-up.

The findings of this study highlight the importance of accounting for both the patients' perception of their general state of health and patient characteristics, such as age, at the moment of diagnosis to predict symptom improvement in the year post-diagnosis. While the clinical value of the interrelatedness of the AFEQT questionnaire and EHRA score has been described in previous studies, little is known on the predictive value of these factors over time.[12,13,16,20] Krisai et al.[16] state that patient-reported QoL might be a more robust and comprehensive patient-reported metric, when compared to symptom status, because of the stability over time independent from AF-treatment and the better prediction of future adverse cardiac events. Previous studies have indicated that low QoL is associated with the prevalence of specified AF-related symptoms, such as dyspnea at rest, exercise intolerance and chest discomfort or tightness.[12,16] In light of these findings, the results from the present study indicate that patients with a low QoL may gain the most from specialized and intensive treatment regimens (e.g. multidisciplinary cardiac rehabilitation), as these patients likely experience a higher disease-burden at the onset of AF.[16] At present, most AF-treatment protocols, aside from stroke prevention through anticoagulation medication use, are based on evaluating and resolving the symptomatic burden of patients.[9] Inclusion of patient-reported outcome measures into regular care, such as QoL, can provide insight on the symptomatic burden, aiding clinicians in shared-decision making prior to treatment. In addition, the availability of the HRQoL at diagnosis may help guide clinicians in setting realistic expectations of anticipated symptom improvements during patient consultations.[5] However, it remains paramount to consider the patient's unique characteristics and risk factors when assessing patient-reported outcomes in the clinic to obtain an accurate estimation of patient disease progression.

Cardiovascular risk factors, such as age, are routinely employed to estimate the stroke risk of AF-patients within the CHA_2DS_2-VASc score.[10,21,22] As such, cardiovascular risk factors can be seen as important predictors for the disease course of AF. Because of the general importance of age as a predictor of stroke risk within the CHA_2DS_2-VASc score with an increase in stroke risk across increasing age cut-offs (<65, ≥65–74 and ≥75 years, respectively), similar age cut-offs were employed in this study.[10] Our results indicate that patients with a low HRQoL above 65 and below 75 years old have the greatest potential to show improvement in symptoms, when compared to patients under 65 and above 75 years of age, respectively. These observations need further validation in future large-scale studies. Validation of these results will enable future research to further define patient subgroups for which symptom improvements or other cardiovascular outcomes can be predicted using patient-reported outcome measures. Using this information, treatment recommendations can be made based on the risk stratification of patient groups by evidence-based cut-offs (e.g. by combining information on HRQoL and age) because of additional insight into the predicted disease course. This would enable clinicians to tailor treatment strategies to the expected patient-specific disease course based on both clinical and patient-reported characteristics, likely increasing the effectiveness of treatment regimens and averted negative clinical outcomes.

Besides identifying patient subgroups who are most likely to benefit from intensive treatment regimens, future studies should also focus on linking the disease course of cardiovascular patients

with patient-reported predictors at diagnosis, such as HRQoL. One such cardiovascular outcome has been described in previous research by Freeman et al. in which EHRA score was associated with a higher risk of hospitalizations.[12] In the same study, the EHRA score was inversely correlated with AFEQT score.[12] Based on these findings we speculate that the AFEQT-derived HRQoL at diagnosis can also be used as a predictor to predict disease course of AF-patients, aside from symptoms. Future research is needed to specify association between QoL at diagnosis and outcomes such as resource utilization and costs (e.g. hospitalization and treatment) and the occurrence of adverse cardiac events (e.g. MACE). Robust information on the interrelatedness of the patients' perception of their general state of health, patient-relevant outcomes and healthcare resource utilization could, in turn, provide valuable avenues for the implementation into value-based healthcare.[23,24] Based on the findings from this study, patients with a low HRQoL and an age between 65 and 75 years might prove to be valuable targets for which greater health benefits can be attained through the implementation of patient-tailored treatment policies. However, further information is needed on why symptom improvements were less frequently observed in patients below 65 years and above 75 years of age. In addition, more information is needed on which treatment strategies and lifestyle recommendations are especially beneficial for these specific patient groups to provide the most optimal healthcare.

This study was subject to some limitations. Firstly, no information was available on the use of rate or rhythm control in our patient population. Because of this caveat, we were unable to discern whether there was a difference in patients within the AFEQT quartiles with regard to these treatment types. Previous studies have indicated that the presence of symptoms is associated with the selection of rate or rhythm control in AF-patients.[25,26] Furthermore, patients with an age above 75 years more often are prescribed rate control medication.[25,26] In general, patients with more prominent AF-symptoms are more likely to be managed with rhythm control, which likely also leads to improved symptom control.[27–29] Not controlling for these differences in treatment may have confounded our results, because it makes it difficult to discern whether EHRA improvement has occurred either as an effect of elapsing time or treatment. Second, we scored patients according to the original EHRA score, instead of the modified EHRA score (mEHRA).[13,18] Because of this, we were unable to distinguish whether patients who were not affected in their normal daily activity were either not troubled by symptoms (mEHRA class 2a) or troubled by symptoms (mEHRA class 2b).[13] As we were mainly interested in full point improvements on the EHRA score, we do not believe that the use of the unmodified EHRA score affected our results. Furthermore, we restricted our stratified analyses to selected age categories for this study. It is likely that other patient characteristics, such as gender and BMI, may also be used to define patient subgroups that show varying associations between AFEQT and EHRA. Analyses on these subgroups was beyond the scope of this study. Moreover, statistical floor effects may have influenced the results within this study as patients with EHRA class I at baseline were unable to further improve on their symptoms. In addition, we observed that patients in lower AFEQT quartiles more often experienced AF at the time of completing the AFEQT questionnaire. Therefore, this group of patients might also have experienced more symptoms at baseline, and such, may have had more opportunity to improve. Furthermore, in stratified analyses, the number of patients diagnosed <65 years of age was limited, which may have affected the robustness of results in these particular analyses. Finally, because of the limited number of patients who decreased in EHRA score between baseline and follow-up we were unable to assess the worsening of symptoms in this study.

In conclusion, the present study indicates that AF-patients with a lower QoL at baseline were most likely to improve their EHRA score after 12 months. This effect was most prominent in patients ≥65 years of age and patients <75 years of age, compared to patients <65 and ≥75 years, respectively. Future research should focus on verifying these results and on further defining characteristics of patients within these age groups to enable the implementation of age-tailored treatment. In addition, future research should elaborate on whether patient-reported outcome measures, such as QoL, can be used to predict the cardiovascular disease course.

COMPLIANCE WITH ETHICAL STANDARDS

All participants provided written informed consent at the onset of the study. The protocol of the AF-NET study was submitted for approval to the Medical Research Ethics Committee United (MEC-U) in the Netherlands (reference number: 14.083). The MEC-U confirmed that the Medical Research Involving Human Subjects Act does not apply to the AF-NET study and, therefore, official approval of this study by the MEC-U is not required.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest. The sponsors of the Netherlands Heart Network were not in any way involved in the design, conduct, analysis, or writing of this manuscript.

AUTHOR CONTRIBUTIONS

L.T. and H.C. conceived the study. L.T., H.C., and J.P. carried out the statistical analyses and drafted the manuscript. All authors contributed to the interpretation of the data. H.V., P.V., P.P., S.J., G.S., J.D., H.K., and L.D. critically revised the manuscript. All authors approved the final manuscript as submitted.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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