ORIGINAL ARTICLE

Trajectories of Health-Related Quality of Life in Coronary Artery Disease

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BACKGROUND: Health-related quality of life (HRQOL) assessment is an important health outcome for measuring the efficacy of treatments and interventions for coronary artery disease (CAD). HRQOL is known to improve over the first year after interventions for CAD, but there is limited knowledge of the changes in HRQOL beyond 1 year. We investigated heterogeneity in long-term trajectories of HRQOL in patients with CAD.

METHODS AND RESULTS: Data were obtained from 6226 patients identified from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease with at least 1-vessel CAD who underwent their first catheterization between 2006 and 2009. HRQOL was assessed using the Seattle Angina Questionnaire, a 19-item disease-specific measure of HRQOL for patients with CAD. Group-based trajectory analysis was used to identify various subgroups of Seattle Angina Questionnaire trajectories over time while adjusting for missing data through a longitudinal multiple imputation model. Multinomial logistic regression was used to identify the predictors of differences among the identified subgroups. Our analysis revealed significant improvements in HRQOL across all the 5 domains of Seattle Angina Questionnaire overtime for the whole data. Multitrajectory analyses revealed 4 HRQOL trajectory subgroups including high (25.1%), largely increased (32.3%), largely decreased (25.0%), and low (17.6%) trajectories. Age, sex, body mass index, diabetes mellitus, previous history of myocardial infarction, smoking, depression, anxiety, type of treatment received, and perceived social support were significant predictors of differences among these trajectory subgroups.

CONCLUSIONS: This study highlights variations in longitudinal trajectories of HRQOL in patients with CAD. Despite overall improvements in HRQOL, about a quarter of our cohort experienced a significant decline in their HRQOL over the 5-year period. Understanding these HRQOL trajectories may help personalize prognostic information, identify patients and HRQOL domains on which clinical interventions are most beneficial, and support treatment decisions for patients with CAD.

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WHAT IS KNOWN

- Coronary artery disease is known to impact the health-related quality of life (HRQOL) of patients living with the disease.
- Treatment of coronary artery disease is known to result in improved HRQOL within the first year of treatment, but there is limited knowledge of the HRQOL trajectory beyond 1 year.

WHAT THE STUDY ADDS

- This study characterized heterogeneity in longitudinal trajectories of HRQOL in patients with coronary artery disease and identify 4 distinct subgroups of patients with different longitudinal HRQOL trajectories.
- Despite overall improvements in HRQOL, about a quarter of the patients experienced a significant decline in their HRQOL over a 5-year period.
- The knowledge of these HRQOL trajectories may help personalize prognostic information and support treatment decisions for patients with coronary artery disease.

Health-related quality of life (HRQOL) measurements are important patient-centered health outcomes that are useful for assessing both the impact of disease burden and effectiveness of treatment interventions. Previous research has shown that patients with coronary artery disease (CAD) have poorer HRQOL than healthy controls, whereas treated CAD patients reported better HRQOL than untreated patients.[1–3] Several demographic, clinical, and psychosocial risk factors have been reported to influence HRQOL in patients with CAD.[4–7] For example, coronary artery bypass graft (CABG) surgery is associated with significantly larger improvements in HRQOL than percutaneous coronary intervention (PCI) or medication within the first year of treatment.[3] Gender differences in HRQOL have also been reported in several studies, with women more likely to report poorer HRQOL status than men.[4–11] These differences in patients' characteristics introduce heterogeneity in patient-reported HRQOL overtime.

In recent years, there has been increased interest in identifying patients with CAD who are less likely to have favorable health outcomes based on longitudinal trajectories of HRQOL. Conventional statistical models such as mixed-effects regression and generalized estimating equations generally estimate mean longitudinal changes in HRQOL but are limited in identifying individual trajectories of HRQOL over time. Understanding these subgroups of patients can help identify groups for which additional or alternative disease management options can be pursued.

In addition, previous research has documented that several clinical, psychosocial, and family environmental factors influence HRQL in children with epilepsy.

The objectives of this study were to identify subgroups of longitudinal HRQOL trajectories in patients with CAD over a 5-year period and determine the patients' characteristics that discriminate among these trajectory subgroups. We hypothesized that longitudinal trajectories of patient-reported HRQOL in CAD may be heterogeneous and that this heterogeneity could be explained by patient-specific demographic, clinical, and psychosocial characteristics.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Data Source

The cohort was formed from a comprehensive, prospective, longitudinal inception cohort of all adult residents in the province of Alberta, Canada, undergoing cardiac catheterization for CAD, captured through the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) registry.[12–14] The APPROACH registry contains detailed demographic and clinical information and is merged quarterly with mortality data from the Vital Statistics registry. Individuals in the APPROACH registry are followed longitudinally after catheterization for assessment of subsequent procedures (ie, PCI or CABG surgery), and QOL in patients who consent to follow-up. For this analysis, we included all Alberta residents over the age of 18 years who underwent first cardiac catheterization between January 1, 2006, and December 31, 2009, and had at least 1-vessel CAD (Duke Coronary Index between 3 and 13). All eligible patients were approached consecutively for consent at the time of catheterization. Data collected at catheterization included demographic characteristics (sex, age, and address), clinical comorbidities, measures of disease severity, coronary angiography results, and self-reported HRQOL measures, including the Seattle Angina Questionnaire (SAQ). The SAQ measure was mailed within 1 week of the first catheterization (baseline) and 1, 3, and 5 years post afterward. Although there were 14 345 eligible subjects with at least 1-vessel CAD (Duke Coronary Index between 3 and 13) that underwent a cardiac catheterization during the study period, only the 6226 who had at least 1 response to the QOL surveys were included in this analysis.

Measures

Seattle Angina Questionnaire

The SAQ is a 19-item self-administered questionnaire that measures 5 dimensions of HRQOL over the past 4 weeks: physical limitation, angina stability, angina frequency, QOL, and treatment satisfaction.[15] The items are scored on 5- or

6-point Likert scales. The sum of item scores each domain is then transformed to scores ranging from 0 (no functioning) to 100 (highest level of functioning). The SAQ has been shown to be a valid, responsive, and reliable instrument in several studies. A 10-unit change in an SAQ domain is considered to be clinically important.[16,17] The SAQ has been used as primary and secondary end points in clinical trials and used to predict health outcomes such as mortality.

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a self-completed instrument consisting of 7-item anxiety (HADS-A) and depression (HADS-D) subscales each of which are comprised of items rated on 4-point Likert scales.[18] The total HADS score ranges between 0 and 42 with 0 to 14 being considered as low, 15 to 28 considered as moderate, and 29 to 42 being considered as high. For each subscale (anxiety and depression subscales), the scores ranged between 0 and 21, where 0 to 7 was considered low, 8 to 14 being moderate, whereas 15 to 21 was considered high. HADS has undergone extensive reliability and validity testing in different chronic conditions and has been widely validated in cardiac patients and shown to have good psychometric properties.[19] Only baseline information on HADS was included in this analysis (ie, questionnaires were mailed within 1 week of the first catheterization).

Medical Outcomes Study Social Support Scale

The MOS-SS (Medical Outcomes Study Social Support) Survey is a 19-item, self-reported measure of perceived social support.[20] The MOS-SS comprises 4 domains and an overall score, called overall social support index. The domains include emotional/informational support, tangible (or instrumental) support, positive social interaction, and affection. Emotional/informational support includes 8 items, tangible support contains 4 items, affectionate support 3 items, and the positive social interaction contains 4 items. Each item is designed to be answered on a 5-point scale ranging from none of the time to all of the time, with higher values indicating more support. Although the score on each domain range between 2 and 20, the overall support index ranges between 0 and 100. The MOS-SS has excellent psychometric properties and has been validated in several populations including CAD population.[21,22] Although MOS-SS was administered at each visit, only total MOS-SS data were included in this analysis (ie, questionnaires were mailed within 1 week of the first catheterization).

Statistical Analysis

Descriptive analysis of the obtained data was conducted using means, SD, and frequency distributions. Given that longitudinal studies are prone to missing data, we characterized the missing data on the SAQ domains over time. Multinomial logistic regression analysis was used to identify possible patient characteristics that may explain the missing data patterns observed in the longitudinal data. To minimize the potential bias because of missing data, we implemented a longitudinal multiple imputation model based on Markov chain Monte Carlo methods for the SAQ outcomes, whereas adjusting for important explanatory variables including age, gender, body mass index, depression, anxiety, treatment decisions, smoking status, hypertension, hyperlipidemia, diabetes mellitus, prior myocardial infarction (MI), prior revascularization procedure, calendar year of catheterization, hospitals of catheterization, coronary anatomy, left ventricular ejection fraction, and vital status.[23,24] Consistent with previous research that suggests that between 3 and 10 copies of the original data are sufficient to get coherent estimates, our longitudinal multiple imputation model was used to create 5 imputed datasets.

Group-based multitrajectory analysis was used to characterize differing patterns of HRQOL trajectories over time.[25–28] This method is a multivariate extension of group-based trajectory analysis that can jointly model trajectories of multiple outcomes over time.[28] Using a maximum likelihood estimation method that assumed a multivariate censored normal distribution, the multitrajectory analysis was used to capture heterogeneity in multivariate longitudinal HRQOL trajectories by identifying latent subgroups of individuals with similar change patterns across the 5 dimensions of SAQ. The output of a multitrajectory model includes estimated probabilities of group membership for each individual and each group and an estimated trajectory curve over time for each group. Fit statistics, such as Akaike information criterion and Bayesian information criterion, and average posterior group membership probabilities (no <70%) were used for model selection. Consistent with previous recommendations about the implementation of group-based trajectory analysis in longitudinal studies with missing data,[29] the multitrajectory analysis conducted here was implemented on the 5 imputed data sets obtained from the multiple imputation model. The estimated subject-specific probabilities of group membership and overall group memberships were derived by combining the imputation-specific estimates of these probabilities using Rubin rule.[24]

For each trajectory subgroup, minimum clinically important change was used to quantify the proportion of patients who achieved meaningful changes (ie, improvement or worsening) in their HRQOL during the first year. Consistent with previous research,[16,17] a 10-point change on each SAQ domain was used to estimate the proportion of patients in each trajectory group that achieved a minimum clinically important change on each domain. Descriptive statistics, including means, SD, percentages, were used to summarize subjects' demographic, clinical, and psychosocial characteristics across the identified trajectory subgroups. Fisher exact test and ANOVA were used to assess univariate associations between categorical and continuous patients' characteristics and trajectory subgroup membership, respectively. Patients' characteristics that are significantly associated with trajectory group membership are then entered as predictors into the multinomial logistic regression. The adjusted associations are reported using odds ratio and 95% confidence interval. Results were considered statistically significant with a 2-sided P value of <0.05. All analyses were conducted in SAS v9.4.[30] Ethics approval was obtained from the University of Calgary Conjoint Health Research Ethics Board (REB14-1320). The corresponding author had full access to all the data in this study and took responsibility for its integrity and the data analysis.

Table 1. Baseline Characteristics of Study Participants

Patients' Characteristics	
Sample size	6226
Age, y, mean (SD)	65.4 (10.9)
Sex (male), n (%)	1208 (19.4)
Treatment type, n (%)	
PCI	3580 (58.5)
CABG	1579 (25.4)
MED	1067 (17.1)
Left ventricular ejection fraction, n (%)	
>50%	3508 (62.2)
35%–50%	1215 (21.5)
20%–34%	223 (4.0)
<20%	63 (1.1)
Not done	634 (11.2)
HADS-depression, mean (SD)	4.1 (3.3)
HADS-anxiety, mean (SD)	5.6 (3.9)
Diabetes mellitus, n (%)	1491 (24.0)
Hypertension, n (%)	4458 (71.6)
Hyperlipidemia, n (%)	4812 (77.3)
Prior MI, n (%)	879 (14.1)
Prior thrombolytic therapy, n (%)	234 (3.8)
Total social support score, mean (SD)	74.6 (23.3)
Indication for cardiac catheterization, n (%)	
Stable angina	2906 (46.7)
MI	741 (11.9)
Unstable angina	1979 (31.8)
Other	600 (9.6)
BMI, mean (SD)	28.8 (5.0)
Smoking, n (%)	1410 (22.7)
Five-year mortality rate, n (%)	782 (12.6)
SAQ domains, mean (SD)	
Angina frequency	85.1 (20.7)
Angina stability	72.5 (28.3)
Quality of life	66.4 (24.6)
Physical limitation	73.3 (23.7)
Treatment satisfaction	87.7 (15.9)

BMI indicates body mass index; CABG, coronary artery bypass graft; HADS, Hospital Anxiety and Depression Scale; MED, medical treatment; MI, myocardial infarction; PCI, percutaneous coronary intervention; SAQ, Seattle Angina Questionnaire; and SD, standard deviation.

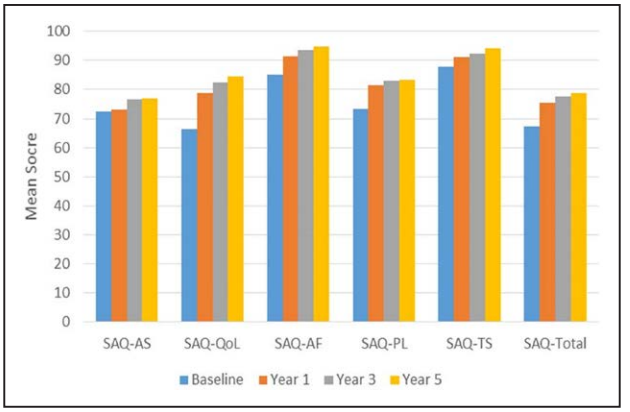

Figure 1. Longitudinal means of SAQ domain scores. AF indicates angina frequency; AS, angina stability; PL, physical limitation; QoL, quality of life; SAQ, 19-item Seattle Angina Questionnaire; and TS, treatment satisfaction.

RESULTS

Table 1 describes the demographic, clinical, and psychosocial characteristics of subjects at baseline. Of the 6226 subjects in this study, 80.6% were men, with an age range between 24 and 94 years (mean 65.38±10.93 years), with most being overweight or obese (78%). More than half of the subjects (57.5%) received PCI, whereas 25.4% had CABG. The majority of patients (62.2%) had a left ventricular ejection fraction >50%. The prevalence of diabetes mellitus, hypertension, and hyperlipidemia was 24.0%, 71.6%, and 77.3%, respectively (Table 1).

Of the 6226 patients included in this analysis, 42.3% and 31% patients completed 2 and 3 measurements on each SAQ domain, respectively. Only 3.9% of our cohort had complete data on all the domains and at all 4 measurement occasions, whereas 12.6% died during the first 5 years after their first catheterization. Table I in the Data Supplement describes the characteristics of participants with at least 1, 2, 3, and complete assessments. A comparison of baseline characteristics between patients with complete data (on all domains and at all measurement occasions) and patients with at least 1, 2, and 3 assessments suggest that there are significant differences among these groups of patients with respect to sex, comorbid diabetes mellitus, comorbid depression, prior MI, left ventricular ejection fraction, smoking status, social support, and indications for catheterization. We therefore assumed that the nonresponses were missing at random.

Preliminary analyses of overall mean changes in SAQ domains over time revealed significant improvements in HRQOL across the 5 domains of SAQ between baseline and 5-year follow-up (Figure 1). But multitrajectory analysis revealed the presence of 4 subgroups of HRQOL trajectories after cardiac catheterization based on the 5 SAQ domains (Figure 2). The multiple imputation model developed for the multitrajectory analyses showed consistent results across the copies of the imputed data sets as shown by the small variability around the mean group membership probabilities and mean posterior probability of each trajectory group that exceeds 0.89, showing excellent model adequacy (Table II in the Data Supplement). Specifically, 25.1% of the patients had consistently high HRQOL subgroup trajectory with increasing HRQOL scores across SAQ

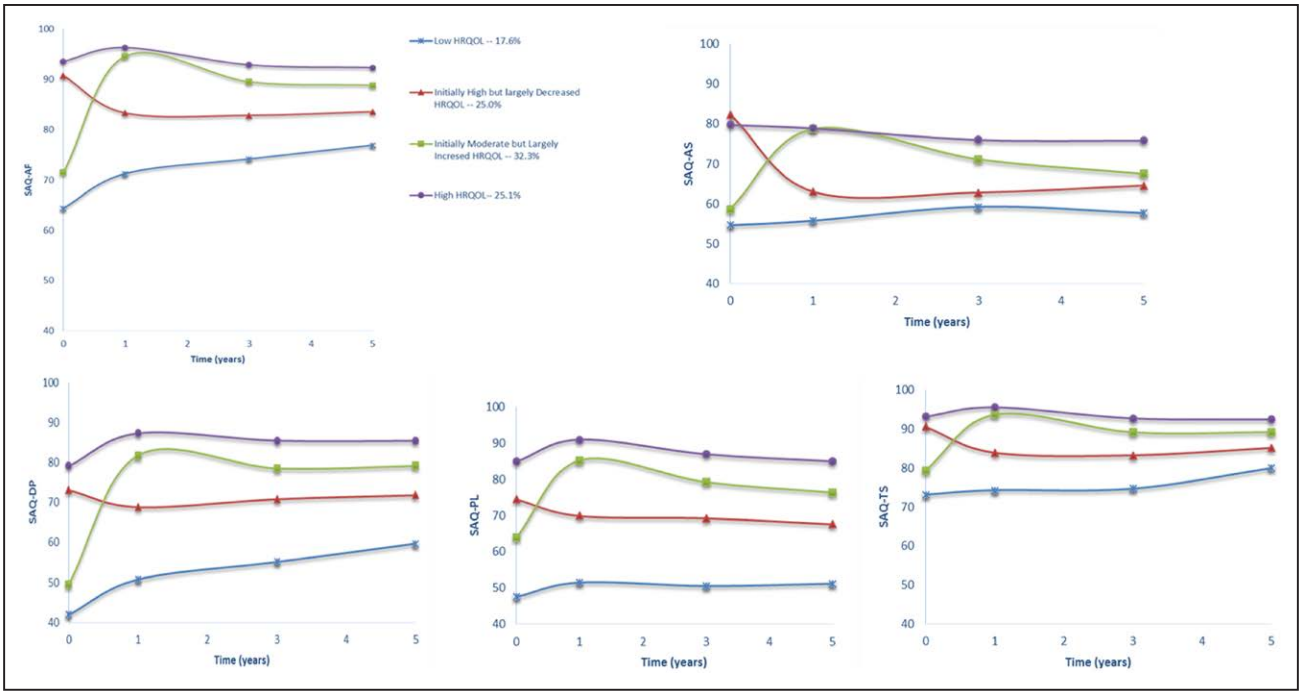

Figure 2. Longitudinal health-related quality of life (HRQOL) trajectory subgroups by Seattle Angina Questionnaire (SAQ) domains.

Group 1: low HRQOL; group 2: initially high but largely decreased HRQOL; group 3: initially moderate but largely increased HRQOL; group 4: high HRQOL. AF indicates angina frequency; AS, angina stability; DP, disease perception; PL, physical limitation; QoL, quality of life; and TS, treatment satisfaction.

angina frequency, QOL, physical limitation, and treatment satisfaction domains in the first year and then slight decrease for subsequent years; but a consistently moderate decline on the angina stability domain over time. The initially high but largely decreased trajectory group comprised of 25.0% of the subjects; who initially had high HRQOL at baseline but had substantial decrease in SAQ angina stability domain and a moderate decrease in other domains during their first year after cardiac catheterization which then remained constant over time. The initially moderate but largely increased HRQOL trajectory subgroup, which consists of 32.3% of the patients, who initially had low HRQOL at baseline but a significantly large increase in HRQOL across the 5 SAQ domains within the first year followed by a moderate decrease in subsequent years. The low HRQOL trajectory subgroup consists of 17.6% of the sample who initially had very poor HRQOL but then had moderately increase in angina frequency and QOL domains over time. This group had no significant improvement in angina stability and physical limitation domains overtime but exhibited some improvements in treatment satisfaction domain during 3 to 5 years after their first cardiac catheterization.

Figure 3 describes the distribution of the proportion of patients that achieved clinically meaningful change in HRQOL on each SAQ domain and across trajectory groups within the first postcatheterization. The proportion of subjects that had clinically meaningful improvements (10-unit change) in HRQOL varied across trajectory subgroups and SAQ domains. Specifically, the majority of patients in the initially moderate but largely increased trajectory group had clinical meaningful improvements within a year after catheterization across SAQ domains. On the other hand, patients in the initially high but largely decreased group often experience clinically meaningful decline across SAQ domains.

Table 2 describes the demographic, clinical, and psychosocial characteristics of patients in each trajectory subgroup. Univariate analyses revealed significant differences among the trajectory subgroups with respect to age, sex, treatment received, depression, anxiety, left ventricular ejection fraction, smoking status, body mass index, baseline SAQ domain scores, indications for catheterization, as well as the prevalence of depression, anxiety, hypertension, diabetes mellitus, prior MI, and postbaseline 5-year mortality rate. Table 3 describes the adjusted effects of patients' demographic, clinical, and psychosocial characteristics on the identified trajectory subgroup membership. First, patients in the low group were more likely to be older, obese patients with diabetes mellitus and prior MI, who smoke and endorse more depression and anxiety symptoms. On the other hand, subjects in this group were less likely to be males, or patients with PCI or CABG, and are likely to report

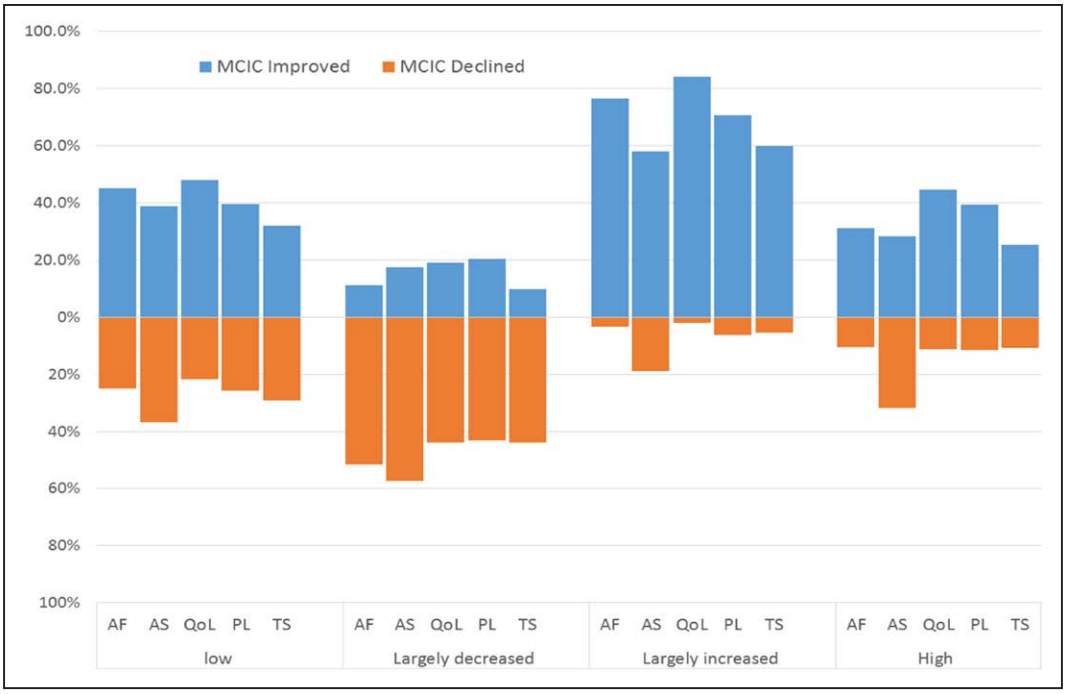

Figure 3. Distribution of patients achieving minimum clinically important change (MCIC) across Seattle Angina Questionnaire (SAQ) domains and trajectory subgroups.
AF indicates angina frequency; AS, angina stability; PL, physical limitation; QoL, quality of life; and TS, treatment satisfaction.

better perceived social support. Second, patients in the initially high but largely decreased group were more likely to be current smokers but less likely to receive CABG treatment. This group of patients was also less likely to have diabetes mellitus or endorse more depression and anxiety symptoms. Finally, patients in the high group were more likely to be male patients who receive PCI treatment than patients in the moderate but largely increased group but were less likely to be treated for unstable angina or endorse more depression or anxiety symptoms.

Additional sensitivity analyses conducted on data obtained from patients with at least 2 repeated assessments, and those with at least 3 assessments consistently identified 4 trajectory subgroups of patients in these data sources (Figures I and II in the Data Supplement). However, the patterns of longitudinal trajectories and proportion of patients in the trajectory subgroups varied across the types of analysis conducted. For example, although 26.4% of the patients who had at least 1 repeated assessments had largely decreased HRQOL over time, 28.7% and 32.3% of the patients who had at least 2 and at least 3 repeated assessments were most likely to report largely decreased HRQOL, respectively, over time. Similarly, the 5-year survival distribution by trajectory subgroups revealed significant differences in the mortality rate across the subgroups, with higher mortality obtained in almost all the groups except for patients in the high group (Figure III in the Data Supplement).

DISCUSSION

This study investigated heterogeneity in long-term HRQOL trajectories, as measured by SAQ, of patients with CAD after catheterization, and identified 4 subgroups of HRQOL longitudinal trajectories. Our analyses revealed that although a majority of patients reported an overall improvement in HRQOL 1 year after catheterization, ≈25% had decreased HRQOL during this first year and no significant improvement afterward. These findings highlight the impact of heterogeneity (including between-patient and within-patient variations) in patient-reported HRQOL trajectories on the evaluation of longitudinal changes in HRQOL and the need for modern multivariate methods that can capture this heterogeneity in CAD studies. Information about these trajectory subgroups and trends across multiple domains of SAQ can be used to identify aspects of patients' HRQOL for which targeted interventions can be designed.

Another interesting finding of this study is the large prevalence of subjects (≈42.6%) with low or largely decreased HRQOL in this population-based cohort. Previous research reports that 20% of individuals undergoing PCI and much <20% of patients undergoing CABG report residual angina 1-year post-treatment.[31–33] This contradiction might be explained in 2 ways. First, our study includes medically managed patients, unlike previously published studies that focused on individuals undergoing PCI or CABG only.[33] The subgroup of

Table 2. Characteristics of Study Participants by Trajectory Subgroups of SAQ Domains

Patients' Characteristics	Low (n_1=1094)	Initially High but Largely Decreased (n_2=1556)	Initially Moderate but Largely Increased (n_3=2009)	High (n_4=1567)	*P* Value
Age, y, mean (SD)	66.9 (11.9)	65.4 (11.4)	65.2 (10.7)	64.6 (9.9)	<0.01
Sex (male), n (%)	754 (68.9)	1238 (79.6)	1634 (81.3)	1392 (88.8)	<0.01
Treatment types					<0.01
PCI	556 (50.8)	989 (63.6)	988 (49.2)	1047 (66.8)	
CABG	234 (21.4)	249 (16.0)	762 (37.9)	334 (21.3)	
MED	304 (27.8)	318 (20.4)	259 (12.9)	186 (11.9)	
Left ventricular ejection fraction, n (%)					
>50%	556 (55.8)	849 (61.2)	1137 (62.0)	966 (67.7)	<0.01
35–50%	237 (23.8)	295 (21.3)	404 (22.0)	279 (19.6)	
20–34%	39 (3.9)	63 (4.5)	77 (4.2)	44 (3.1)	
<20%	23 (2.3)	12 (1.0)	20 (1.1)	8 (0.6)	
Not done	141 (14.2)	168 (12.1)	195 (10.6)	130 (9.1)	
HADS-depression, mean (SD)	6.7 (3.6)	3.7 (3.0)	5.1 (3.2)	2.6 (2.5)	<0.01
HADS-anxiety, mean (SD)	8.3 (4.0)	5.2 (3.5)	6.6 (3.7)	3.9 (3.2)	<0.01
Diabetes mellitus, n (%)	349 (31.9)	408 (26.2)	442 (22.0)	292 (18.6)	<0.01
Hypertension, n (%)	823 (75.2)	1143 (73.5)	1412 (70.3)	1080 (68.9)	<0.01
Hyperlipidemia, n (%)	850 (77.7)	1188 (76.4)	1556 (77.5)	1218 (77.7)	0.78
Prior MI, n (%)	216 (19.7)	208 (13.4)	300 (14.9)	155 (9.9)	<0.01
Prior lytic, n (%)	42 (3.8)	62 (4.0)	58 (2.9)	72 (4.6)	0.06
Social support score, mean (SD)	65.4 (25.2)	73.8 (23.4)	75.1 (21.1)	80.4 (21.4)	<0.01
Indication for cardiac catheterization, n (%)					
Stable angina	457 (41.8)	757 (48.7)	878 (43.7)	814 (52.0)	0.12
MI	132 (12.1)	189 (12.2)	249 (12.4)	171 (10.9)	
Unstable angina	371 (33.9)	471 (30.3)	682 (34.0)	455 (29.0)	
Other	134 (12.3)	139 (8.9)	200 (10.0)	127 (8.1)	
BMI, mean (SD)	29.5 (6.0)	28.8 (4.9)	28.7 (4.8)	28.6 (4.6)	<0.01
Smoking, n (%)	332 (30.4)	388 (24.9)	427 (21.3)	263 (16.8)	<0.01
SAQ domains, mean (SD)					
Angina frequency	63.1 (24.6)	93.7 (10.8)	68.6 (21.6)	95.5 (9.5)	<0.01
Angina stability	53.0 (29.0)	80.9 (24.0)	57.8 (27.7)	81.1 (24.3)	<0.01
Quality of life	41.5 (20.7)	76.6 (17.1)	44.2 (19.2)	80.2 (16.9)	<0.01
Physical limitation	48.0 (20.4)	78.6 (20.1)	61.9 (21.0)	86.8 (16.4)	<0.01
Treatment satisfaction	73.0 (20.1)	92.6 (10.5)	78.9 (16.9)	94.8 (8.9)	<0.01
Baseline total SAQ, mean (SD)	45.0 (16.0)	75.2 (10.5)	51.4 (14.0)	78.8 (9.4)	<0.01

SAQ scores range from 0 to 100, with a higher score indicating better dimensional scores. HADS scores range from 0 to 30, with a higher score indicating more symptoms indicative of significant levels of anxiety and depression. BMI indicates body mass index; CABG, coronary artery bypass graft; HADS, Hospital Anxiety and Depression Scale; MED, medical treatment; MI, myocardial infarction; PCI, percutaneous coronary intervention; SAQ, Seattle Angina Questionnaire; and SD, standard deviation.

patients who were medically managed likely included individuals with less severe disease as well as those with diffuse and complex disease not suitable for invasive treatment. Hence, the heterogeneity in this group might explain the high proportion of individuals with poor or declining HRQOL in the entire cohort. Another possible explanation is the difference in the longitudinal measurement of the primary outcome of interest. The majority of existing studies investigate changes in HRQOL during the first year of follow-up after undergoing PCI or CABG, a period during which maximum improvement in HRQOL is often observed. As our study shows, this improvement is usually not sustainable after the first year of follow-up. Hence, a larger portion of patients might report declining HRQOL outcomes in the longer term.

Our analyses also identified several baseline risk factors including age, sex, type of treatment received,

Table 3. Association (Odds Ratio, 95% Confidence Interval) Between Patients' Characteristics and SAQ Trajectory Subgroup Membership

Patients' Characteristics	Low vs Initially Moderate but Largely Increased	Initially High but Largely Decreased vs Initially Moderate but Largely Increased	High vs Initially Moderate but Largely Increased
Age	1.02 (1.01–1.03)*	1.00 (0.99–1.02)	0.99 (0.98–1.01)
Sex (male)	0.60 (0.49–0.72)*	1.07 (0.79–1.46)	1.90 (1.53–2.36)*
Treatment type			
PCI vs MED	0.60 (0.43–0.84)*	0.85 (0.64–1.13)	1.42 (1.06–1.91)*
CABG vs MED	0.30 (0.23–0.39)*	0.29 (0.22–0.38)*	0.69 (0.47–1.01)
Left ventricular ejection fraction			
>50% vs not done	0.70 (0.48–1.01)	0.85 (0.65–1.11)	1.12 (0.85–1.48)
35–50% vs not done	0.86 (0.54–1.38)	0.93 (0.67–1.29)	0.94 (0.69–1.28)
<35 vs not done	0.81 (0.51–1.29)	0.98 (0.62–1.55)	0.88 (0.55–1.43)
HADS-depression	1.08 (1.01–1.15)*	0.87 (0.82–0.92)*	0.82 (0.77–0.87)*
HADS-anxiety	1.06 (1.02–1.09)*	0.94 (0.90–0.98)*	0.89 (0.84–0.93)*
Diabetes mellitus	1.38 (1.12–1.71)*	1.26 (1.05–1.52)*	1.00 (0.83–1.20)
Hypertension	1.13 (0.92–1.39)	1.21 (0.99–1.47)	1.00 (0.86–1.28)
Prior MI	1.30 (1.02–1.67)*	0.95 (0.69–1.31)	0.82 (0.56–1.19)
Prior lytic	1.35 (0.79–2.29)	1.12 (0.69–1.80)	1.30 (0.88–1.93)
Total social support score	0.99 (0.99–1.00)*	1.00 (0.99–1.00)	1.01 (1.00–1.01)
Indication for cardiac catheterization			
Stable angina	1.0	1.0	1.0
MI	1.06 (0.79–1.43)	0.94 (0.73–1.21)	0.77 (0.58–1.02)
Unstable angina	1.14 (0.92–1.41)	0.91 (0.75–1.09)	0.77 (0.64–0.92)*
Other	1.13 (0.85–1.51)	0.97 (0.71–1.33)	0.94 (0.70–1.27)
BMI	1.03 (1.01–1.05)*	1.01 (1.00–1.03)	1.00 (0.98–1.02)

BMI indicates body mass index; CABG, coronary artery bypass graft; HADS, Hospital Anxiety and Depression Scale; MED, medical treatment; MI, myocardial infarction; PCI, percutaneous coronary intervention; and SAQ, Seattle Angina Questionnaire.
*$P<0.05$.

diabetes mellitus diagnosis, prior MI, body mass index, depression, anxiety, social support, and smoking, which were predictive of the differences among the trajectory subgroups.[6–10,34–40] In fact, individuals in the low or initially high but largely decreased trajectory subgroups are more likely to be older obese women with diabetes mellitus and MI, who smoke, endorse more depression and anxiety symptoms, and to have received medical management alone for CAD. These findings are consistent with the previously reported body of evidence confirming the impact of these factors on HRQOL of patients with CAD. For example, previous research suggested sex disparity in HRQOL of patients with CAD.[6,7] Other studies have reported age, obesity, and diabetes mellitus are important determinants of worse overall HRQOL in patients with CAD.[34–40] Similarly, previous research studies have identified the impact of psychosocial characteristics such as depression, anxiety, and perceived social support on HRQOL of patients with CAD.[8–10] Moreover, smoking was identified as a strong predictor of subjects' reporting low or declining HRQOL in this study. This is consistent with previous research that has shown that smokers are likely to report worse HRQOL than nonsmokers or those that are quite smoking after revascularization procedures.[40] Finally, our analyses revealed that subjects who had PCI or CABG are more likely to be in high or largely HRQOL trajectory subgroups than medically managed subjects, which is in line with previously reported findings that better health outcomes (including HRQOL) are often reported after revascularization procedures.[3,4,33]

Our study findings are, to a greater extent, dependent on the assumptions made about missing data. These findings are consistent with previous research studies that have shown that missing data can influence the estimation of the number of groups, group sizes, and group-specific HRQOL trajectory patterns. In addition to adopting a multiple imputation method to deal with missing data in our analyses, we conducted a sensitivity analyses to assess the robustness of our

study findings for individuals with at least 2 and often 3 repeated assessments and the tenability of multiple imputation method for our study. We found 4 trajectory subgroups to be optimal in these data sets along with similar patterns of longitudinal trajectories. Although our sensitivity analysis supports our study conclusions, there are some variations in the proportion of patients in each group across these data sets. In particular, the sensitivity analysis with 3 repeated assessments showed trajectory patterns that were considerably different from the trajectory patterns obtained with at least 2 measurement occasions. This suggests that the individuals with a smaller number of observations may have different HRQOL scores than the ones with more observations. Consequently, the use of multiple imputation is appropriate in this study and overcomes the problem of selection bias. We recommend that researchers conduct sensitivity analyses to assess the robustness of their study conclusions to different assumptions or characterizations of missing data in their study cohort.

The group-based multitrajectory analysis method used in this study has several advantages for analyzing longitudinal HRQOL data. Unlike conventional statistical models for longitudinal data that estimate marginal changes in HRQOL trajectories over time, such as generalized estimating equations, and mixed-effects regression models, the group-based trajectory methodology is more flexible in characterizing heterogeneity in patients' longitudinal trajectories while describing risk factors that discriminate among these patient subgroups. Second, another advantage of this methodology is its flexibility in simultaneously modeling longitudinal trajectories across multiple HRQOL dimensions thereby accounting for correlation among multiple domains. Third, this methodology also provides a parsimonious framework for modeling longitudinal changes across multiple domains of HRQOL dimensions instead of conducting multiple sets of analyses.

The findings of this study have several clinical implications. The longitudinal HRQOL are potentially useful for providing patients and clinicians with information about changes in their HRQOL, which may be a better trigger for action, rather than a certain absolute threshold for determining patients in need of an intervention. In this era of precision medicine, the group-based trajectory analysis approach and the identified trajectories can also be used to develop patient-centered clinical risk prediction tools, which estimate the patient-specific risk of poor health outcomes. These tools can aid clinical decision-making about optimal treatment strategies for patients with CAD, especially for patients with significantly decreased HRQOL in the first year after catheterization. They can be used in clinical trials to identifying clinically important trajectories that predict greater treatment benefits.

One key strength of this study is the application of multitrajectory analysis to identify subgroups of individuals with similar longitudinal HRQOL trajectories across multiple dimensions of the SAQ. Unlike the conventional statistical analyses that model mean changes in HRQOL on each domain over time, this methodology identifies clusters of patients with similar longitudinal trajectories thus predicting patient-specific probabilities of group membership. Ours is a novel application of this methodology in characterizing trajectories of HRQOL in patients with CAD. Further research is needed to validate the findings in other prospective longitudinal studies of patients with CAD.

This study is not without its limitations. One limitation of the multitrajectory analysis methodology is that it assumes that a patient's most probable group assignment does not vary across domains. It is indeed possible that patients who are in one trajectory type on one domain may be in a different one for another. An alternative analytic approach to address this is independent modeling of the longitudinal trajectories on each SAQ domain. We did not pursue this approach because these domains are thought to comprise a system of variables that reflect HRQOL, and so they are empirically and conceptually highly related. Second, of the 14 345 eligible patients, only 6226 patients provided at least 1 HRQOL report. Complete data were obtained in only 4% of our study cohort with 58% of patients missing at least 2 assessments. We adopted multiple imputation with the Markov Chain Monte Carlo method to deal with missing data thus adjusting for a wide range of risk factors that might explain patterns of missing data in our study. Future research will investigate other methods for adjusting for missing data including pattern mixture models and selection models when multitrajectory analysis used to model incomplete longitudinal data. Third, although the type of treatment received at baseline was identified as a significant predictor of longitudinal HRQOL trajectories across multiple subgroups of our cohort, it is possible that changes in medical therapy and further revascularization procedures during follow-up not captured in our data influenced these trajectories. This might limit the generalizability of our study findings. Future research will aim to validate our study findings in other longitudinal studies of patients with CAD where this information is collected.

In conclusion, this study investigates heterogeneity in long-term HRQOL trajectories of patients with CAD across multiple domains of SAQ. Our analyses revealed 4 trajectory subgroups in our data cohort: 25% of the patients experienced a decrease in their HRQOL, whereas the remaining patients experienced different levels of improvement over the 5-year period. The understanding of these subgroups and the risk factors that explain the differences among the groups may help personalize prognostic information, identify patients who are likely

to improve or deteriorate with interventions, and support treatment decisions for patients with CAD.

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FOOTNOTES

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