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Impact of Cardiovascular Events on Change in Quality of Life and Utilities in Patients After Myocardial Infarction

A VALIANT Study (Valsartan In Acute Myocardial Infarction)

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Objectives The objective of this study was to determine the impact of nonfatal cardiovascular (CV) events on changes in health-related quality of life (HRQL).

Background There is limited understanding of the impact of nonfatal CV events on long-term changes in HRQL in survivors of myocardial infarction (MI).

Methods The VALIANT (Valsartan In Acute Myocardial Infarction) trial enrolled 14,703 patients post-MI complicated by Killip class II or higher (scale measuring heart failure severity post-MI ranging from class I to IV) and/or reduced ejection fraction. The HRQL substudy included 2,556 (17.4%) patients who completed the EQ-5D with 5 questions, with responses mapped to utility weight on a scale of 0 to 1 and a visual analog scale (VAS) ranging from 0 (worst) to 100 (best) imaginable health state. EQ-5D was administered at baseline and 6, 12, 20, and 24 months. The trajectory of EQ-5D scores was developed by using linear mixed effects regression models with calculation of deviation from this trajectory after nonfatal CV events. Patients who died before the next EQ-5D assessment were excluded.

Results Over a 2-year period, 597 patients experienced a nonfatal CV event and survived to have another EQ-5D assessment. Their baseline EQ-5D scores were lower than patients without a subsequent nonfatal CV event (VAS 61.0 $\pm$ 19 vs 68.2 $\pm$ 18 [$p < 0.001$] and US-based utility score 0.76 $\pm$ 0.22 vs 0.83 $\pm$ 0.17 [$p < 0.001$]). These patients with CV events experienced a trajectory-adjusted 6.6 point decrease ($p < 0.001$) in VAS scores and a 0.07 decrease ($p < 0.001$) in utility score after the nonfatal CV event.

Conclusions MI survivors suffering a CV event experienced significantly worse HRQL than their previous trajectory, suggesting that generic instruments can be responsive to nonfatal events. Reduction in nonfatal CV events may affect longitudinal changes in HRQL. (J Am Coll Cardiol HF 2014;2:159–65) © 2014 by the American College of Cardiology Foundation

Advances in therapies for acute myocardial infarction (MI) have increased the numbers of survivors living with chronic coronary artery disease (CAD) and impaired left ventricular function (1). These patients are at heightened risk for subsequent nonfatal and fatal events (2–4). From a medical perspective, providers are often focused on secondary preventive efforts and attenuation of the risk of consequences of the infarct such as heart failure, recurrent MI, and sudden

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Abbreviations and Acronyms

CAD = coronary artery disease

CI = confidence Interval

CV = cardiovascular

HRQL = health-related quality of life

LVEF = left ventricular ejection fraction

MI = myocardial infarction

VAS = visual analog scale

death. Although these efforts are of utmost importance, health-related quality of life (HRQL) has emerged as an additional target of therapy and outcome measure for large clinical trials in post-MI patients (5). Given the expanding therapies for patients with CAD, often without clear survival benefit, understanding patient-reported outcomes in this population is becoming even more important.

Health status and HRQL are independent predictors of adverse events in a variety of study groups, including those with CAD (6) and heart failure (7). Characterization of HRQL commonly has focused on the clinical and psychosocial determinants of these perceptions immediately after the MI (8–10). Patients with a history of CAD have significantly impaired HRQL compared with the general U.S. population (11). However, there are gaps in our understanding of the long-term change in HRQL, especially beyond the first few months. Researchers have identified several baseline predictors of worsening HRQL post-MI, including persistence and severity of angina (10), depression, inadequate social support, adverse effects of therapies, and anxiety about the uncertainty of their prognosis (8,12). Much of the variance in HRQL response is unexplained by baseline clinical factors (13). One potential explanation of decreased HRQL could be the occurrence of recurrent MI, heart failure, and stroke. However, little is known about the quantitative impact of subsequent nonfatal cardiovascular (CV) events on changes in HRQL. Identification of the impact of these nonfatal CV events on change in HRQL will provide a potential explanation for some of the unexplained variance in HRQL responses in clinical practice and clinical trials, and possibly aid researchers in the design of future trials assessing patient-reported outcomes. Thus, the aim of the present study was to determine the impact of nonfatal CV events on change in the trajectory of visual analog scale (VAS) and utility scores in a cohort of patients who had experienced an acute MI.

Methods

The details of the enrollment and exclusion criteria, follow-up, and results of the VALIANT (Valsartan In Acute Myocardial Infarction) trial have been reported elsewhere (14,15). Briefly, the study included 14,703 patients age ≥18 years of age with an acute MI occurring between 12 hours and 10 days before randomization with clinical evidence of acute heart failure, radiological evidence of heart failure, or left ventricular ejection fraction (LVEF) ≤35% as assessed by echocardiogram or left ventriculogram or LVEF <40% as assessed by radionuclide scan. The patients were randomly assigned to receive captopril (up to 50 mg 3 times daily), valsartan (up to 160 mg twice daily), or the combination of these 2 drugs (up to captopril 50 mg 3 times daily and valsartan 80 mg twice daily).

Health status measurement. Of the 24 countries participating in VALIANT, patients from sites in 10 countries (Argentina, Australia, Canada, Denmark, France, Germany, Italy, Sweden, the United Kingdom, and the United States) were eligible to participate in the HRQL substudy. Health status was measured by using the EQ-5D, a self-administered instrument comprising 2 components: a descriptive profile and a single-index VAS (16). The instrument has excellent psychometric properties in patients with a previous MI (17). The descriptive profile assesses health status on 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents were asked to indicate whether they have: 1) no problems; 2) some/moderate problems; or 3) extreme problems with each of the 5 dimensions. Their responses were then mapped to previously derived utility weights for each of the 243 possible combinations (18). These utility weights are intended to represent society's ratings of the desirability of a given health state. Utility weights have been derived from populations in numerous countries, including the United Kingdom and the United States (19,20). The VAS records the patient's personal perspective of their current health status on a vertical rating scale with scores ranging from 0 to 100, with 0 representing the worst imaginable health status and 100 representing the best imaginable health state (18). The VAS has been considered a representation of patients' overall HRQL.

The EQ-5D was administered at baseline, which was either at the time of discharge from the hospital after the acute MI or at 15 days' post-randomization, whichever came first. It was then repeated at 6, 12, 20, and 24 months for the first 2 years of follow-up and annually thereafter throughout the trial follow-up period.

CV events. The trial case report form documented the following CV events: 1) hospitalization for heart failure, defined as the unplanned treatment of new or worsening heart failure requiring the use of intravenous diuretic agents, inotropes, or vasodilators during any hospital admission or overnight stay in a health care facility; 2) recurrent MI, defined as an increase in cardiac enzyme levels and either typical clinical presentation or typical electrocardiograph changes (evolving ST-segment or T-wave changes, new left bundle branch block, or new Q/QS waves in contiguous leads); 3) stroke, defined as a focal neurological deficit lasting >24 hours; and 4) sudden death/cardiac arrest, defined as the occurrence of sudden death or cardiac arrest with or without premonitory heart failure or MI. In addition, each event was adjudicated by a central clinical endpoints committee to ensure consistent adjudication of the first nonfatal CV event. The primary analysis focused all unadjudicated nonfatal CV events as reported by the site investigator. A secondary analysis focused on only the nonfatal CV events that were adjudicated by the clinical endpoints committee.

Statistical analysis. To assess representativeness of the HRQL substudy sample, we compared baseline demographic and clinical characteristics between patients who completed the baseline EQ-5D and those who did not. Among those with EQ-5D data, patients were stratified according to the occurrence of a CV event during the 24-month period after randomization. We then compared baseline characteristics and EQ-5D scores between those who experienced a CV event and those who did not. For descriptive purposes, the overall VAS change scores were calculated between baseline and 2 years in patients with and without a nonfatal CV event who did not die during follow-up. Change scores were compared by using Wilcoxon rank sum tests.

The primary analysis was limited to patients who experienced a nonfatal CV event during the first 24 months of follow-up. All EQ-5D assessments from baseline through the first assessment after a CV event were retained. Data from patients who died before the next EQ-5D assessment were excluded from the primary analysis. We modeled linear trajectories of EQ-5D scores across time by using mixed linear regression models (21). The models were specified with random intercepts and slopes such that a linear trajectory representing EQ-5D scores before the event was modeled for each patient. To evaluate the impact of a nonfatal CV event, we estimated the mean of the deviations between observed scores after the CV event (heart failure hospital stay, acute MI, stroke, and resuscitated sudden death/cardiac arrest) and expected scores on the basis of the patients' pre-event trajectories. We then analyzed the effect of each type of CV event separately. For patients who had >1 CV event before the next EQ-5D assessment, events were categorized on the basis of the type of event that occurred first. If multiple events occurred on the same date, we categorized the events on the basis of the event hierarchy of MI > congestive heart failure > stroke > resuscitated sudden death. Analyses were performed by using the VAS scores and the utility weights from the United Kingdom and United States separately.

Four sensitivity analyses were performed. First, we excluded patients who experienced >1 CV event before the next EQ-5D assessment. Second, we used only the CV events that were adjudicated positively by the clinical endpoints committee for the trajectory-adjusted change scores. Third, we stratified patients with interim events into 2 groups (those who completed the VAS within 100 days of the non-fatal CV event and those who completed the VAS ≥100 days after the event) to determine whether the time interval between the event and the HRQL assessment had an effect on the magnitude of the primary outcome. Finally, we performed an analysis in which we included data from patients who died before the next HRQL assessment. We assigned a 0 for the VAS scores to determine the impact of including patients with fatal CV events on the primary outcome. All analyses were conducted by using SAS version 9.1.3 (SAS Institute, Inc., Cary, North Carolina).

Results

The VALIANT patients who completed the baseline EQ-5D tended to be healthier than the patients who did not complete the instrument. The HRQL cohort had a better Killip class (scale measuring severity of heart failure signs post-MI ranging from I to IV) at the time of index MI (Killip III or IV: 19.2% vs. 24.6%; $p < 0.001$), lower proportion with history of hypertension (48.5% vs. 56.7%; $p < 0.001$) or heart failure (11.5% vs. 15.5%; $p < 0.001$), lower systolic blood pressure (120.9 ± 16 mm Hg vs. 123.0 ± 17 mm Hg; $p < 0.001$), fewer female subjects (26.8% vs. 32.0%; $p < 0.001$), and more percutaneous revascularization for the index MI (20.0% vs. 13.7%; $p < 0.001$). Of the 2,556 patients with baseline EQ-5D data, 342 patients (13.4%) died and 36 patients (1.4%) were lost to follow-up. Among the remaining 2,178 patients, all but 19 patients had a follow-up period >365 days. Patients with a history of MI, heart failure, stroke, and other co-morbid illnesses had more impaired VAS scores at baseline than patients without these illnesses.

Of the 2,556 patients, 1,785 (69.8%) did not experience a nonfatal CV event, and 771 (30.2%) had at least 1 event within 2 years of randomization. Among the 771 patients, 174 (22.6%) died before the next EQ-5D assessment, resulting in 597 patients in the final analysis. Of these, 93 (15.6%) experienced ≥2 events before the next EQ-5D assessment. The mean duration between the nonfatal CV event and the repeat EQ-5D assessment was 88 ± 70 days. The most common event was heart failure hospitalization ($n = 309$), followed by recurrent MI ($n = 214$), stroke ($n = 57$), and resuscitated sudden death ($n = 17$). Patients with an event were older, more likely female, had a higher systolic blood pressure and heart rate, lower LVEF, worse Killip class, and more co-morbid illnesses at baseline (Table 1).

Outcomes. The distribution of baseline VAS scores was skewed toward a better HRQL (Fig. 1) with a mean of 65.6 ± 18. Patients with a CV event during follow-up who lived until the next EQ-5D assessment had a worse overall HRQL at baseline than patients without an event (VAS score 61.0 ± 19 vs. 68.2 ± 18; $p < 0.001$). The utilities are concentrated toward the upper end of the range, with majority of patients expressing a utility score of >0.8 (Fig. 2). Utility weights were also significantly lower among patients with a CV event compared with those patients who did not have a CV event (Table 1). Patients without a CV event experienced an improvement in their overall VAS scores (9.6 ± 20 points) during the 2-year follow-up compared with a decrement in overall VAS scores (−8.3 ± 34 points) during the same follow-up period among patients who experienced nonfatal CV events.

Patients with a nonfatal CV event experienced a trajectory-adjusted mean change of −6.6 (95% confidence interval [CI]: −8.9 to −4.3; $p < 0.001$) in VAS scores after the event, suggesting a significant deterioration in their

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Table 1 Baseline Characteristics for Patients With and Without a Subsequent CV Event Over 2-Year Follow-Up

	Patients With CV Event and Subsequent EQ-5D (n = 597)	Patients Without an Event (n = 1,785)	p Value
Age, yrs	68.6 ± 11	63.1 ± 12	<0.001
Race			
White	539 (90.3)	1,688 (94.6)	
Black	30 (5.0)	37 (2.1)	
Other	28 (4.7)	60 (3.4)	0.003
Female	188 (31.5)	429 (24.0)	<0.001
Blood pressure, mm Hg			
Systolic	121.9 ± 16	120.2 ± 16	0.008
Diastolic	69.7 ± 10	70.8 ± 11	0.103
Heart rate, beats/min	76.2 ± 14	74.6 ± 13	0.035
LVEF, %	33.7 ± 12	35.6 ± 13	<0.001
Killip class			
I	155 (26.1)	660 (37.0)	
II	292 (49.2)	839 (47.1)	
III	98 (16.5)	203 (11.4)	
IV	49 (8.3)	80 (4.5)	<0.001
Serum creatinine, mg/dl	1.1 ± 0.3	1.1 ± 0.3	<0.001
Medical history			
MI	200 (33.5)	333 (18.7)	<0.001
Hypertension	337 (56.5)	799 (44.8)	<0.001
Diabetes mellitus	185 (31.0)	354 (19.8)	<0.001
HF	109 (18.3)	133 (7.5)	<0.001
Stroke	50 (8.4)	58 (3.3)	<0.001
Smoking	147 (24.7)	640 (35.9)	<0.001
CABG	81 (13.6)	118 (6.6)	<0.001
PCI	73 (12.2)	151 (8.5)	0.022
Index MI characteristics			
Median days from MI to randomization	4.2	4.2	0.959
Thrombolytic therapy	219 (36.9)	713 (39.9)	<0.001
Primary PCI	88 (14.7)	411 (23.0)	<0.001
Medications			
ACE inhibitors	250 (41.9)	736 (41.2)	0.472
ARBs	14 (2.4)	21 (1.2)	0.070
Beta-blockers	430 (72.0)	1,378 (77.2)	<0.001
Aspirin	536 (89.8)	1,670 (93.6)	<0.001
Statins	275 (46.1)	930 (52.10)	<0.001
Quality of life scores			
Baseline VAS	61.0 ± 19	68.2 ± 18	<0.001
Baseline utility (UK based)	0.70 ± 0.29	0.80 ± 0.23	<0.001
Baseline utility (US based)	0.76 ± 0.22	0.83 ± 0.17	<0.001

Values are mean ± SD or n (%). p values were used to compare patients with cardiovascular (CV) events during follow-up with patients without a CV event during follow-up after excluding the 174 patients who died before a follow-up EQ-5D assessment could occur.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; VAS = visual analog scale.

HRQL. The trajectory-adjusted decrements in VAS scores were consistent across each CV event (Table 2), with the largest decline (−35.6) noted after a resuscitated sudden death on the basis of parameter estimates. The trajectory-adjusted mean change in the EQ-5D utility scores also significantly worsened with the use of US-based utility

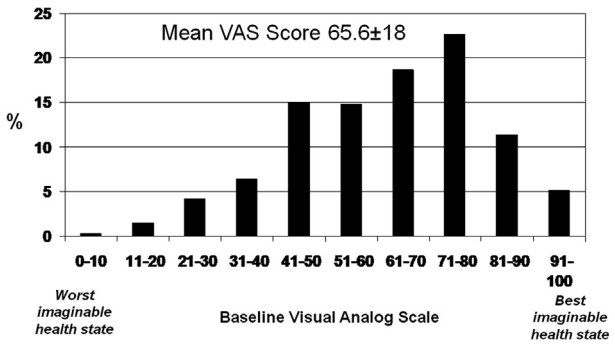

Figure 1 Distribution of Baseline Visual Analog Scale Responses

Distribution of visual analog scale (VAS) scores from the EQ-5D at baseline, which was 15 days post-randomization or at discharge from the index hospitalization (whichever came first). The scores were stratified by 10-point increments, with a lower score representing more impaired health-related quality of life, and the proportion of patients in each stratum is represented.

weights (−0.07 [95% CI: −0.10 to −0.05]; p < 0.001) or UK-based utility weights (−0.08 [95% CI: −0.11 to −0.04]; p < 0.001). When evaluating EQ-5D utility scores, significant trajectory-adjusted decrements occurred among patients who experienced MI, stroke, or heart failure hospitalization (Table 3). Resuscitated sudden death was no longer significantly associated with decrements in utility weights.

Sensitivity analyses excluding patients who had >1 event but did not die before the next HRQL assessment provided results consistent with the primary analysis. Patients who completed the VAS assessment within 100 days of the nonfatal CV event had a larger trajectory-adjusted mean change in VAS score (−8.4 [95% CI: −11.4 to −5.4]; p < 0.001) than those patients who completed repeat assessment beyond 100 days after a nonfatal CV event

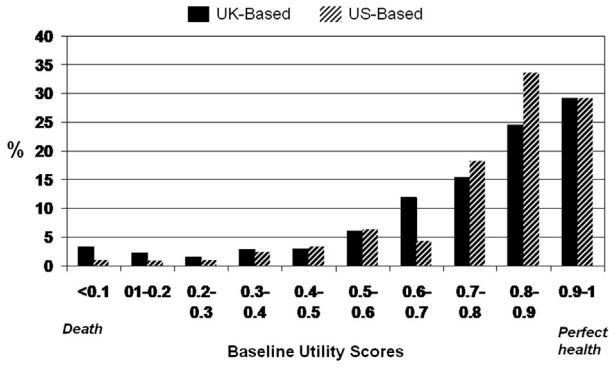

Figure 2 Distribution of Baseline Utility Scores

Distribution of baseline EQ-5D scores on the basis of the UK utility weights and U.S. utility weights. The scores are stratified in increments of 0.1, ranging from –0.6 to 1, with 1 representing a perfect utility. A total of 51 patients (UK based) and 11 patients (U.S. based) had a utility that was <0 and were grouped in the <0.1 group.

Table 2 Mean Adjusted Trajectory VAS Changes After a Nonfatal CV Event Within 2 Years Post-MI, Excluding Patients Who Died

		VAS		EQ-5D Utility Weights (U.S.)		EQ-5D Utility Weights (UK)	
	n	Trajectory-Adjusted Mean Change (95% CI)	p Value	Trajectory-Adjusted Mean Change (95% CI)	p Value	Trajectory-Adjusted Mean Change (95% CI)	p Value
Any CV event	597	−6.6 (−8.9 to −4.3)	<0.001	−0.07 (−0.10 to −0.05)	<0.001	−0.08 (−0.11 to −0.04)	<0.001
MI	214	−5.6 (−9.5 to −1.7)	0.005	−0.06 (−0.10 to −0.02)	0.003	−0.06 (−0.11 to −0.01)	0.014
Hospital stay for HF	309	−5.0 (−8.2 to −1.8)	0.003	−0.05 (−0.08 to −0.01)	0.007	−0.05 (−0.10 to −0.01)	0.028
Stroke	57	−11.7 (−19.7 to −3.6)	0.006	−0.15 (−0.22 to −0.07)	<0.001	−0.18 (−0.28 to −0.08)	0.001
Resuscitated sudden death	17	−35.6 (−46.7 to −24.6)	0.005	−0.25 (−0.64 to 0.13)	0.105	−0.22 (−0.64 to 0.20)	0.155

CI = confidence interval; other abbreviations as in Table 1.

(−0.92 [95% CI: −4.0 to 2.2]; p = 0.565). When using only centrally adjudicated nonfatal CV events, the trajectory-adjusted mean change in the VAS score significantly decreased by −6.8 (95% CI: −9.4 to −4.1; p < 0.001) after an interim nonfatal CV event. Finally, when 0 was assigned to the next VAS score among patients who died after the interim CV event, the magnitude of the trajectory-adjusted mean change score was larger, as expected, with an adjusted VAS change score of −12.0 (95% CI: −14.4 to −9.5; p < 0.001) and an adjusted utility weight change of −0.13 (95% CI: −0.15 to −0.10; p < 0.001) (Table 4).

Discussion

In this study, we found that MI survivors who experienced a recurrent nonfatal CV event had a significant decrease in health status (both VAS and health utilities) beyond what was expected on the basis of their trajectories preceding the event. The most common nonfatal event was heart failure hospitalization followed by recurrent MI, both of which significantly reduced patients' perceptions of their HRQL. Sensitivity analyses consistently showed a decrement in patient perceptions after a CV event. To the best of our knowledge, this is one of the first studies to systematically address the impact of nonfatal CV events on longitudinal change in HRQL in post-MI patients, and it may explain some of the variation in HRQL changes in this patient group.

The patients enrolled in VALIANT had a markedly impaired baseline VAS score of 65.6, which is similar to mean scores reported in patients with chronic obstructive lung disease (VAS score 65) (22), heart failure (VAS score 63) (23), chronic kidney disease (VAS score 60) (24), and a variety of cancers (VAS scores ranging from 43 to 84) (25). Patients who did not experience a subsequent nonfatal event had significant improvements in their VAS scores over 2 years despite the baseline score being better than the baseline score of patients who subsequently experienced a CV event during the 2-year follow-up. Previous studies have shown variable changes in HRQL in the first few months post-MI, with some patients experiencing decreased physical functioning (9,26), some having no significant changes (12), and others noting improved physical health (8,10,27,28). In addition to the well-established factors that influence changes in HRQL post-MI, such as persistence of angina or dyspnea (26), depression (5,8,12), revascularization (11), and optimism regarding prognosis with adjustment to their disease (13), the occurrence of these nonfatal events may be another important factor affecting change scores.

There are a few key implications of our findings. First, therapies that reduce the occurrence of nonfatal events (with neutral effects on mortality due to competing risks) may translate into eventual meaningful differences in HRQL. Second, between-treatment differences in HRQL may be difficult to demonstrate over longer follow-up periods with the agglomeration of nonfatal events in the trial population. Thus, interventions that directly improve specific HRQL domains may be mitigated by the occurrence of nonfatal events. Finally, the significant changes in patient utilities after nonfatal CV events may influence cost-effectiveness analysis that assumes static utilities during follow-up.

Study limitations. The clinical severity of nonadjudicated events cannot be classified. However, use of only adjudicated CV events did not meaningfully change the direction or

Table 3 Mean Adjusted Trajectory Utilities Changes After a Nonfatal CV Event Within 2 Years Post-MI, Including Patients Who Died

		VAS		EQ-5D Utility Weights (U.S.)		EQ-5D Utility Weights (UK)	
	n	Trajectory-Adjusted Mean Change (95% CI)	p Value	Trajectory-Adjusted Mean Change (95% CI)	p Value	Trajectory-Adjusted Mean Change (95% CI)	p Value
Any CV event	771	−12.0 (−14.4 to −9.5)	<0.001	−0.13 (−0.15 to −0.10)	<0.001	−0.13 (−0.16 to −0.10)	<0.001
MI	271	−12.1 (−16.6 to −7.7)	<0.001	−0.12 (−0.16 to −0.07)	<0.001	−0.12 (−0.18 to −0.07)	<0.001
Hospital stay for HF	356	−9.0 (−12.3 to −5.6)	<0.001	−0.10 (−0.14 to −0.06)	<0.001	−0.11 (−0.15 to −0.06)	<0.001
Stroke	66	−17.7 (−26.0 to −9.4)	<0.001	−0.20 (−0.28 to −0.12)	<0.001	−0.21 (−0.31 to −0.12)	<0.001
Resuscitated sudden death	78	−31.3 (−38.5 to −24.0)	<0.001	−0.32 (−0.41 to −0.24)	<0.001	−0.29 (−0.38 to −0.19)	<0.001

Abbreviations as in Table 1.

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Table 4 Mean VAS Score at Baseline Stratified According to Comorbid Illness

Medical Problem at Baseline		Baseline VAS score
History of MI	Yes	61.5
	No	66.4
History of HF	Yes	58.4
	No	66.1
History of stroke	Yes	55.4
	No	65.8
History of COPD	Yes	59.2
	No	65.9
History of chronic renal insufficiency	Yes	54.8
	No	65.4

Unadjusted VAS scores are given; patients may have >1 co-morbid illness.
COPD = chronic obstructive pulmonary disease; other abbreviations as in Table 1.

magnitude of the estimated change in HRQL. Data from patients who died within 1 year after CV events were not included in the analysis, and these patients may represent a sicker population than survivors. We did not adjust for other factors that may affect change in HRQL, including revascularization and anginal burden. The EQ-5D assesses global health status and may not be as responsive as a disease-specific instrument. However, because the EQ-5D is a generic measure, it allows for comparisons of HRQL decrements across a range of clinical conditions, and the large changes suggest that even this generic instrument may be responsive to major nonfatal events and could serve as a "benchmark" for differences in change scores between randomized therapies. Patients who completed EQ-5D within 100 days of a subsequent CV event seemed to have a more dramatic decrement in their HRQL compared with those patients who completed the EQ-5D beyond 100 days, suggesting that HRQL may gradually recover somewhat over time. We do not have details of the heart failure hospitalization, including duration of stay, multiple re-admissions, or New York Heart Association class during the hospitalization. A significant strength of this study is the large sample size of patients with complex MI complicated by signs of heart failure, low LVEF, or both, with a large number of patients who developed interim recurrent CV events that enabled characterization of the impact of these events on subsequent HRQL.

Conclusions

Post-MI patients who experience a subsequent nonfatal CV event had a significant worsening of their HRQL in addition to a worse overall baseline HRQL compared with post-MI patients who did not experience another CV event over 2 years. These events may explain some of the variance in HRQL changes after an acute MI. The responsiveness of a generic instrument to nonfatal events calibrates effect size and suggests utility of this measure in clinical trials. Future studies should evaluate the temporal changes in HRQL after CV events, along with measures of health status, to evaluate the persistence of patients' perceptions and their ability to adjust to their current health state. Longitudinal analysis of HRQL should consider the incorporation of nonfatal CV events as time-varying covariates in multivariable models to determine the relative role of baseline factors and recurrent events on patient perceptions. Finally, the results have practical implications for the design of future trials to assess patient-reported outcomes.

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