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Poor Health-Related Quality of Life Is a Predictor of Early, But Not Late, Cardiac Events After Percutaneous Coronary Intervention

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Poor health-related quality of life (HRQL) is associated with mortality in cardiac patients. Patients (N = 667) with poor HRQL after percutaneous coronary intervention had a higher incidence of early (≤6 months) major adverse cardiac events (MACE) than did patients with good HRQL, whereas there was no difference for late (>6 months) MACE over a 2-year follow-up period. Poor HRQL remained an independent predictor of early, but not late MACE, adjusting for other risk factors. The same pattern was found for early and late death/non-fatal myocardial infarction. However, further research is warranted before recommending the use of HRQL measures as screening tools in clinical practice. (Psychosomatics 2007; 48:331–337)

Health-related quality of life (HRQL), defined as the impact of disease on the patient's functioning as perceived and reported by the patient, is gaining increasing recognition as an important endpoint. A recent report from the National Heart, Lung, and Blood Institute Working Group on Outcomes Research in Cardiovascular Disease emphasized the importance of focusing on patient-centered outcomes such as HRQL in order to bridge the gap between research and clinical practice.[1] The various self-report measures used to assess HRQL are designed to evaluate how daily activities and physical, emotional, and social functioning are affected by the cardiac condition and its treatment. HRQL assessment may also serve as a valuable factor in risk-stratification in research and clinical practice and may help guide clinical decision-management, given the discrepancies found between physician-rated and patient-rated functional status.[2] However, despite studies showing that impaired HRQL comprises a risk factor for mortality and hospitalization in patients with established coronary artery disease (CAD)[3,4] and heart failure,[5–8] independent of traditional biomedical risk factors, it is not yet standard procedure to assess HRQL in research and clinical practice.[9] Also, the effect of HRQL on adverse clinical outcome has not yet been evaluated in a pure sample of patients treated with percutaneous coronary intervention (PCI).

Post-PCI patients often experience new coronary events within the first 6 months after PCI.[10] These early events are mainly caused by factors related to the procedure itself, such as recoil of the vessel wall and neointimal hyperplasia. Late events, that is, events occurring after 6 months, are usually related to new lesions elsewhere in the coronary system. Hence, new coronary events after PCI can be divided into early and late events.[11]

Because identifying high-risk patients is a cornerstone of current cardiovascular care, one potential use of formal HRQL assessment could be the identification of patients at risk for adverse clinical outcomes.[3] By describing the association between measures that quantify HRQL with

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prognosis, it is possible to create a better appreciation of how to interpret scores on these measures and support their broader use in clinical practice.[6]

In the current study, we examined the impact of HRQL on clinical outcome in exhausted patients after PCI. Specifically, we investigated whether poor HRQL at the time of the index PCI was associated with major adverse cardiac events (MACE) and a composite of death and nonfatal myocardial infarction (MI) at follow-up, adjusting for demographic and clinical risk factors. Since early (≤6 months) and late (>6 months) events post-PCI may have a different pathological basis, we explored the effect of HRQL on early and late events separately.

METHOD

Patient Population and Study Design

Consecutive post-PCI patients (N = 667) age 35–68 from the university hospitals of Maastricht, Rotterdam, Nijmegen, and the Catharina Hospital in Eindhoven, The Netherlands, who were included in the randomized EXhaustion Intervention Trial (EXIT), participated in the current study. Details of the study design have been published elsewhere.[10] In brief, EXIT was designed to evaluate the effect of a behavioral intervention targeting symptoms of exhaustion on new cardiac events occurring during a mean follow-up period of 2 years post-PCI. Hence, patients who were included in the EXIT trial all reported exhaustion at baseline.

Exhaustion is defined as unusual fatigue, increased irritability, and demoralization, and is associated with a 2- to 3-fold increased risk of adverse clinical outcome in patients with established heart disease, independent of disease severity.[12,13] Evidence from studies examining the physiological correlates of exhaustion indicates that exhaustion, as defined in the current study, cannot be thought of as a somatoform or similar disorder, as listed in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV-TR). Exhaustion has been related to increased inflammation,[14,15] impaired fibrinolysis,[16] and low vagal tone,[17] all of which have been associated with the pathogenesis of CAD. Also, a recent study showed that exhaustion, but not depression, in women with CAD was related to increased inflammation.[18]

In the EXIT trial, exhaustion caseness was determined on the basis of a two-step procedure. In the first step, at 2 weeks post-PCI, patients were asked to complete the Maastricht Questionnaire (MQ), which is a self-report measure to determine those who are vitally exhausted; it uses a standardized cutoff score of ≥14 (i.e., 7 or more complaints).[19] In the second step, patients who scored as exhausted on the basis of the MQ were subjected to the Maastricht Interview for Vital Exhaustion (MIVE), using a cutoff score of ≥7 to determine exhaustion caseness.[10] MIVE comprises 23 questions and has been shown to be a more powerful predictor of adverse clinical events than the MQ.[20]

Of 1,254 patients interviewed, 527 patients were excluded before the intervention, and 17 patients were excluded post-intervention (for example, because of missing informed-consent documentation, not fulfilling the inclusion criteria, etc.).[10] Of the 710 patients included in the EXIT study, 667 patients (94%) completed a questionnaire to assess HRQL at baseline. Nonresponders were more likely to be women, smokers, and to have diabetes, but less likely to be prescribed beta-blockers and nitrates (all $p<0.05$). No other statistically significant differences were found between responders and nonresponders on baseline characteristics.

The EXIT study was approved by the medical ethics committees of the participating hospitals, and the study was conducted in accordance with the Helsinki Declaration. All patients provided written informed consent.

Demographic variables included sex and age. Clinical variables (indication for PCI, previous MI, previous PCI, previous coronary artery bypass graft [CABG], heart failure, multi-vessel disease, diabetes, smoking, cardiac and antidepressant medication) were obtained from the patients' medical records. Comorbidity was assessed by asking the patients whether they had seen a medical specialist in the year before the PCI.

Health-Related Quality of Life (HRQL)

HRQL was measured with the Dutch version of the MacNew Heart Disease Health-Related Quality of Life questionnaire.[21,22] Items are answered on a 7-point Likert scale, with 1: poor HRQL, and 7: good HRQL. The internal consistency of the Dutch version of the scale is good, with Cronbach α ranging from 0.79 to 0.91 for the subscales Emotional, Physical, and Social Functioning, and 0.92 for the total scale.[21] For the purpose of the current study, we only used the total score. The scale was administered at baseline.

Clinical Endpoints

The primary endpoint was MACE (a composite of death, nonfatal MI, CABG, and PCI), and the secondary

endpoint was a composite of death or nonfatal MI. Endpoints were separated into early (≤6 months) versus late events (>6 months). The median follow-up was 2 years, and follow-up data were complete for all patients (100%).

Statistical Analysis

Before we performed statistical analyses, scores on the MacNew questionnaire were categorized, with the lowest tertile indicating poor HRQL. Others have also advocated the use of categorization in order to enhance clinical interpretability.[9] Discrete variables were compared by means of the chi-square test (with Fisher's exact test when appropriate), and continuous variables were examined with Student's *t*-tests for independent samples. Univariable and multivariable Cox proportional-hazards regression analyses were performed to investigate the impact of poor HRQL on the occurrence of new cardiac events during follow-up. In multivariable analyses, we entered HRQL, sex, age, comorbidity, CAD history (defined as MI, PCI, or CABG before the index event), multi-vessel disease, smoking, participation in a behavioral intervention, and the use of antidepressant medication. We chose to enter the covariates sex,[23,24] age,[25] comorbidity,[24] previous cardiac history,[25] and smoking[26] in the multivariable analyses, because they have all been associated with impaired HRQL after revascularization or in patients with heart failure. The variable Multi-Vessel Disease was added to control for disease severity, and the variables participation in a behavioral intervention and the use of antidepressants were added because there were significant differences on these variables between the two HRQL groups at baseline. All statistical tests were two-tailed; $p<0.05$ was used for all tests to indicate statistical significance. Hazard ratios (HR) with 95% confidence intervals (CI) are reported. All statistical analyses were performed with SPPS Version 12.0.1 software.

RESULTS

Baseline Characteristics

Patient baseline characteristics stratified by HRQL are presented in Table 1. Patients with poor HRQL were more likely to have participated in a behavioral intervention (60% versus 49%; $p=0.01$), to have a previous cardiac history (48% versus 39%; $p=0.02$), and to be treated with antidepressants (10% versus 4%; $p=0.01$) than patients with good HRQL. There were no other statistically significant differences between groups on baseline characteristics.

Predictors of Major Adverse Cardiac Events (MACE)

There were 66 early (≤6 months) MACE, with 20 events (33%) listed as death or non-fatal MI. Late (>6 months) MACE comprised 83 events, with death and non-fatal MI accounting for 33 of the events (40%).

The incidence of early MACE was higher in patients with poor HRQL than in patients with good HRQL (32/221 [15%] versus 34/446 [8%]; $p=0.008$). By contrast, there was no difference in the incidence of late MACE for patients with poor versus good HRQL (26/221 [12%] versus 57/446 [13%]; $p=0.80$).

In multivariable analyses, poor HRQL remained an independent predictor of early MACE and was associated with a twofold increased risk (HR: 2.20; 95% CI: 1.34–3.61), adjusting for sex, age, comorbidity, CAD history, multi-vessel disease, smoking, participation in a behavioral intervention, and the use of antidepressant medication (Table 2). By contrast, poor HRQL was not a predictor of late MACE (HR: 0.81; 95% CI: 0.50–1.32; Table 2). Multivessel disease was also an independent predictor of early MACE, whereas comorbidity and cardiac history were associated with late MACE (Table 2).

Predictors of Death and Non-Fatal Myocardial Infarction (MI)

The majority of MACE in the current study comprised revascularization procedures, which are largely symptom-driven. Since patients' symptoms (e.g., the patient's perception of HRQL) may influence the rate of reinterventions, we performed secondary analyses to investigate whether poor HRQL was related to "hard" events, defined as a composite of death and non-fatal MI. In multivariable analyses, poor HRQL (HR: 2.65; 95%CI: 1.08–6.52) was also a predictor of early death/non-fatal MI, adjusting for sex, age, comorbidity, CAD history, multi-vessel disease, smoking, participation in a behavioral intervention, and the use of antidepressant medication (Table 3). As with late MACE, poor HRQL (HR: 0.65; 95% CI: 0.30–1.44) was not a predictor of late death/non-fatal MI (Table 3). Age, cardiac history, and multi-vessel disease were also independent predictors of early death/MI, whereas comorbidity and cardiac history were associated with late death/MI (Table 3).

DISCUSSION

To our knowledge, this is the first study to examine the impact of poor HRQL on early versus late cardiac events

in a pure sample of post-PCI patients. Patients with poor HRQL at the time of the index PCI were at a twofold increased risk of early MACE, adjusting for demographic and clinical risk factors. However, poor HRQL did not predict events occurring beyond 6 months after revascularization. Since it is widely recognized that the decision to perform a reintervention is, to a large part, influenced by symptom reporting, we conducted secondary analyses, using "hard" events, that is, a composite of death and non-fatal MI, as an endpoint. We found a similar pattern, with poor HRQL predicting early, but not late, deaths/non-fatal MIs. This finding suggests that the impact of poor HRQL on MACE was not purely driven by revascularization procedures.

TABLE 1. Baseline Characteristics Stratified by Health-Related Quality of Life (HRQL)

	Good HRQL (N = 446)	Poor HRQL (N = 221)	p
Demographics			
Female sex	91 (20)	54 (24)	0.24
Age, years, mean (SD)	53 (7)	53 (7)	0.63
Intervention			
Behavioral intervention	218 (49)	132 (60)	0.01
Clinical risk factors			
Comorbidity	42 (9)	30 (14)	0.10
Indication for percutaneous coronary intervention (PCI)			
Stable angina	63 (14)	20 (9)	
Unstable angina	248 (56)	134 (61)	
Myocardial infarction (MI)	88 (20)	34 (15)	
Post-MI angina	39 (9)	29 (13)	
Other	8 (2)	4 (2)	0.09
Cardiac history[a]	173 (39)	106 (48)	0.02
Heart failure	9 (2)	2 (1)	0.29
Multi-vessel disease	87 (20)	37 (17)	0.39
Diabetes mellitus	50 (11)	29 (13)	0.47
Smoking	81 (18)	53 (24)	0.08
Medication			
Beta-blockers	337 (76)	155 (70)	0.13
Calcium antagonists	159 (36)	94 (43)	0.09
ACE-inhibitors	93 (21)	54 (24)	0.29
Nitrates	246 (55)	133 (60)	0.22
Diuretics	51 (11)	30 (14)	0.43
Lipid-lowering	335 (75)	165 (75)	0.90
Antidepressants	18 (4)	21 (10)	0.01

All values are N (%), unless otherwise indicated. SD: standard deviation.
[a]MI, PCI, or CABG (coronary artery bypass graft) before the index PCI.

TABLE 2. Predictors of Early (≤6 months) and Late (>6 months) Major Adverse Cardiac Events (MACE; adjusted analyses)

	Early MACE		Late MACE	
Predictor variables	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Poor HRQL	2.20 (1.34–3.61)	0.002	0.81 (0.50–1.32)	0.40
Female sex	0.93 (0.51–1.70)	0.82	1.13 (0.66–1.93)	0.66
Age	1.00 (0.97–1.04)	0.95	1.02 (0.98–1.05)	0.35
Behavioral intervention	1.55 (0.94–2.58)	0.09	0.82 (0.53–1.27)	0.37
Comorbidity	0.47 (0.17–1.31)	0.15	3.33 (1.95–5.70)	<0.001
Cardiac history[a]	0.69 (0.41–1.17)	0.16	2.12 (1.33–3.36)	0.002
Multi-vessel disease	2.08 (1.19–3.64)	0.01	1.11 (0.64–1.92)	0.72
Smoking	0.53 (0.25–1.12)	0.10	1.50 (0.91–2.47)	0.12
Antidepressants	0.72 (0.22–2.32)	0.58	1.29 (0.59–2.84)	0.52

HR: hazard ratio; CI: confidence interval; HRQL: health-related quality of life.
[a]Myocardial infarction, percutaneous coronary intervention (PCI), or coronary artery bypass graft before the index PCI.

The results of the current study showed that poor HRQL, as assessed by the disease-specific MacNew Heart Disease Health-Related Quality of Life questionnaire, was a short- but not long-term predictor of adverse clinical outcome in PCI patients. This is in contrast to several other studies of patients with acute coronary syndrome or heart failure that found poor HRQL to be a predictor of poor prognosis and hospitalization,[3–8] although it should be noted that Rumsfeld and colleagues[4] found that the Physical Component Summary but not the Mental Component Summary of the Short-Form Health Survey–36 was associated with increased risk of mortality. The follow-up in these studies ranged from 6 months[4,8] to 36 months,[7] but all studies evaluated the respective endpoints at one time-point and not at two time-points, as in the current study. However, in PCI patients, it may be important to separate events into early versus late events, given that the new cardiac events often experienced by PCI patients within the first 6 months are usually related to the procedure, itself.[10,11] Hence, given the current findings, assessment of HRQL at the time of PCI may not be a good predictor of later clinical outcome because it may comprise a proxy for disease severity and impending complications.

An alternative explanation for the different results in the current study, as compared with previous studies, may be attributed to PCI patients' generally being more healthy than MI, CABG, and heart-failure patients. Also, the patients in the current study were relatively younger, especially compared with those in studies focusing on heart failure, which included patients up to age 80.[5–7] In the studies by Soto and colleagues[6] and Heidenreich and colleagues,[5] age was related to mortality and rehospitalization, although, in the latter study, age was not associated with impaired HRQL.[5] It should also be noted that the PCI patients included in the current study all had exhaustion symptoms. Given that there is a conceptual overlap between exhaustion and HRQL, it may be that there is little additional room for HRQL to predict poor clinical outcome; exhaustion has been shown to predict morbidity and mortality post-PCI.[13]

The results of the current study have some bearing on research and clinical practice. HRQL is an important patient-centered outcome, with heart failure patients preferring improved HRQL over prolonged survival.[27] Also, the study of HRQL and its determinants have been advocated as a means by which to bridge the gap between research and clinical practice.[1] Nevertheless, we still know little about the mechanisms responsible for the relationship between impaired HRQL and prognosis. For poor HRQL to be conceptualized as a risk factor on a par with established, traditional, biomedical risk factors, there must be one or more plausible mechanisms (e.g., physiological or behavioral) that may be responsible for the link between poor HRQL and adverse prognosis. Also, studies need to demonstrate that HRQL is modifiable and that its modification will lead to improved clinical outcome. Although a substudy of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) clinical trial showed that treatment with sertraline had a beneficial effect on HRQL scores, both in the total group and in patients with recurrent depression,[28] to our knowledge, no studies have investigated whether improvement in HRQL leads to a concomitant increase in survival. Research is also warranted to investigate the short- and long-term prognostic value of the multitude of HRQL measures available, with a focus on both disease-specific and generic instruments. These measures need to be not only valid and reliable, but also brief, and the results must be directly applicable to clinical prac-

TABLE 3. Predictors of Early (≤6 Months) and Late (>6 Months) Death or Non-Fatal Myocardial Infarction (MI; adjusted analyses)

	Early Death/MI		Late Death/MI	
Predictor Variables	**Hazard Ratio (95% CI)**	**p**	**Hazard Ratio (95% CI)**	**p**
Poor HRQL	2.65 (1.08–6.52)	0.03	0.65 (0.30–1.44)	0.29
Female sex	0.68 (0.25–1.81)	0.44	1.01 (0.43–2.35)	0.98
Age	1.07 (1.00–1.15)	0.04	1.00 (0.93–1.03)	0.41
Behavioral intervention	1.56 (0.61–3.96)	0.35	1.51 (0.74–3.09)	0.26
Comorbidity	0.36 (0.05–2.76)	0.33	3.86 (1.61–9.25)	0.002
Cardiac history[a]	0.28 (0.09–0.83)	0.02	2.49 (1.19–5.21)	0.02
Multi-vessel disease	3.55 (1.33–9.48)	0.01	1.27 (0.53–3.03)	0.60
Smoking	0.87 (0.25–3.04)	0.83	1.87 (0.88–3.97)	0.10
Antidepressants	0.00 (0.00–0.00)	0.98	1.47 (0.44–4.93)	0.53

CI: confidence interval; HRQL: health-related quality of life.

[a]MI, PCI (percutaneous coronary intervention); or CABG (coronary artery bypass graft) before the index PCI.

tice.[9] Finally, results on HRQL and prognosis should be replicable in multiple settings and across cardiovascular-disease patient groups.[29]

The current study has several limitations. First, the results may not be generalizable to the total sample, given that responders and nonresponders on the HRQL measure differed on some baseline characteristics. Second, given the relatively small number of "hard" events, we had to adopt MACE as a primary endpoint. However, MACE is a relevant outcome measure to both patients and clinicians, and the same results were found for early MACE and early death/non-fatal MI versus late MACE and late death/non-fatal MI. Third, there may also be a potential selection bias, both in relation to the patient selection for the original EXIT trial and for the current study, since 43 patients (6%) had to be excluded because HRQL data were missing. The latter patients may have had a poorer HRQL than responders, although this would lead to an underestimation of the impact of HRQL on clinical events, rather than an overestimation. Also, in multivariable analyses, we did not adjust for measures of distress, such as anxiety and depression. It is possible that poor HRQL may be confounded by emotional distress. Finally, the results may not be applicable to all post-PCI patients, because the current study only focused on those who had exhaustion.

The current study also has several strengths. HRQL was assessed with a disease-specific instrument, which may be more sensitive to capturing the symptoms of cardiac patients than a generic measure. Also, the response rate on the HRQL questionnaire at baseline was high, at 94%.

In conclusion, this study demonstrated that poor HRQL was an independent predictor of cardiac events occurring from 0 to 6 months post-PCI, but not of events occurring beyond 6 months. These findings support the use of the MacNew questionnaire to identify patients in research and clinical practice who are at risk for early events post-PCI in order to optimize risk-stratification in this subgroup of patients. However, before a sound recommendation for the use of HRQL measures as screening tools in clinical practice can be offered, further research across cardiovascular disease patient groups is warranted to identify mechanisms responsible for the relationship between poor HRQL and prognosis, whether improvement in HRQL leads to increased survival, to compare the short- and long-term prognostic value of the multitude of HRQL measures available, and to adopt multiple assessments of HRQL in order to be able to evaluate the impact of changes in HRQL on prognosis. Multiple assessments of HRQL may also be a better risk indicator for adverse clinical outcome than a single, "snapshot" assessment.[9]

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