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Health-related quality of life 1–3 years post-myocardial infarction: its impact on prognosis

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ABSTRACT

Objective To assess associations of health-related quality of life (HRQoL) with patient profile, resource use, cardiovascular (CV) events and mortality in stable patients post-myocardial infarction (MI).

Methods The global, prospective, observational TIGRIS Study enrolled 9126 patients 1–3 years post-MI. HRQoL was assessed at enrolment and 6-month intervals using the patient-reported EuroQol-5 dimension (EQ-5D) questionnaire, with scores anchored at 0 (worst possible) and 1 (perfect health). Resource use, CV events and mortality were recorded during 2-years' follow-up. Regression models estimated the associations of index score at enrolment with patient characteristics, resource use, CV events and mortality over 2-years' follow-up.

Results Among 8978 patients who completed the EQ-5D questionnaire, 52% reported 'some' or 'severe' problems on one or more health dimensions. Factors associated with a lower index score were: female sex, older age, obesity, smoking, higher heart rate, less formal education, presence of comorbidity (eg, angina, stroke), emergency room visit in the previous 6 months and non-ST-elevation MI as the index event. Compared with an index score of 1 at enrolment, a lower index score was associated with higher risk of all-cause death, with an adjusted rate ratio of 3.09 (95% CI 2.20 to 4.31), and of a CV event, with a rate ratio of 2.31 (95% CI 1.76 to 3.03). Patients with lower index score at enrolment had almost two times as many hospitalisations over 2-years' follow-up.

Conclusions Clinicians managing patients post-acute coronary syndrome should recognise that a poorer HRQoL is clearly linked to risk of hospitalisations, major CV events and death.

Trial registration number ClinicalTrials.gov Registry (NCT01866904) (https://clinicaltrials.gov).

Key questions

What is already known about this subject?
► Patients' self-reported health-related quality of life (HRQoL) can be assessed using the EuroQol-5 dimension (EQ-5D) for patients with stable coronary artery disease following myocardial infarction (MI).
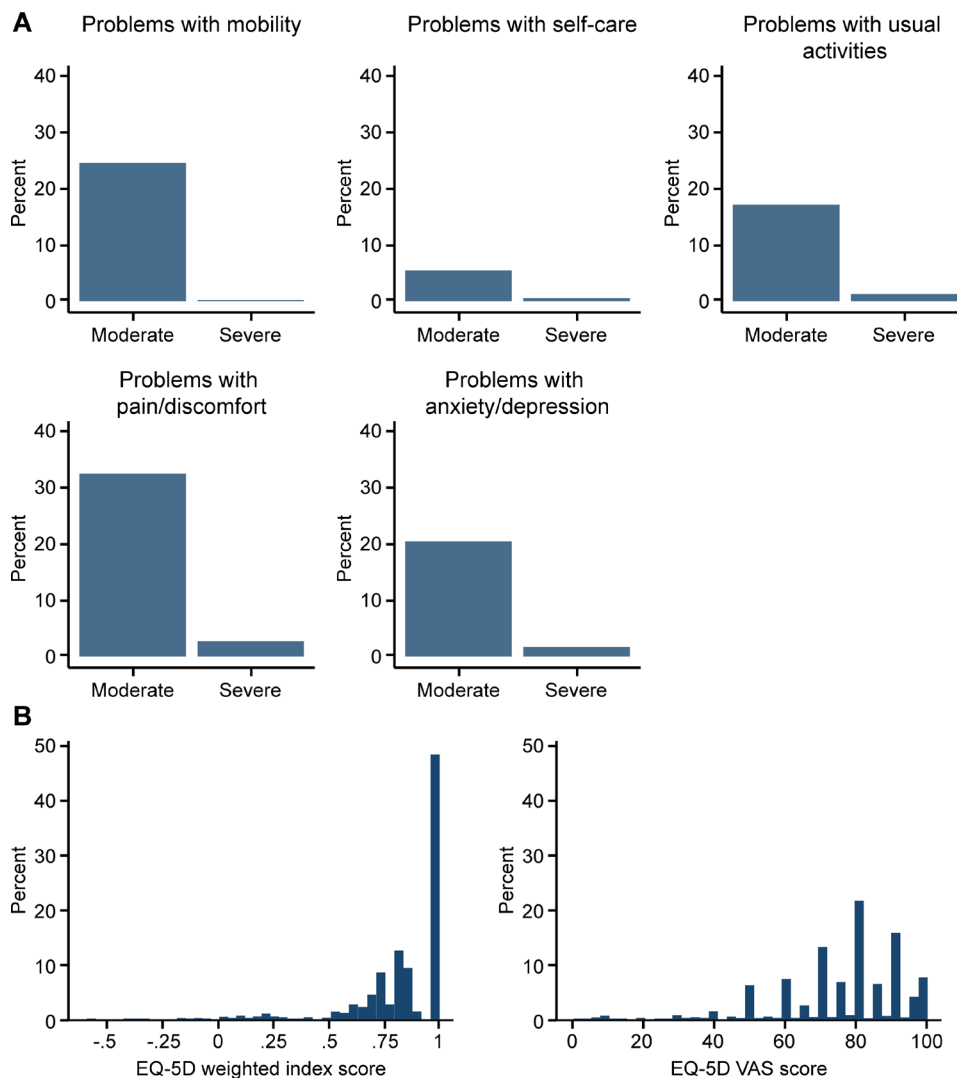
What does this study add?
► This study finds that a lower EQ-5D index score was associated with clinical and demographic factors assessed 1–3 years post-MI, and with subsequent hospitalisations, cardiovascular (CV) events and all-cause death.

How might this impact on clinical practice?
► Clinicians managing patients after acute coronary syndrome should recognise that patient's self-reported HRQoL is strongly associated with CV events and subsequent mortality.

clinical decisions for patients with stable coronary artery disease (CAD). Generic tools such as the EuroQol-5 dimension (EQ-5D)[2] can provide useful insights into a patient's well-being and prognosis, including after MI, beyond those offered by disease-specific tools, such as the Seattle Angina Questionnaire.[2 3]

A systematic review of HRQoL for patients with stable CAD, 1–3 years after MI,[4] found major issues with published studies, in that they did not report the approach to assessing HRQoL,[5–7] followed up patients for short time periods (up to 1 year post-MI)[5–10] and included small samples of patients (≤2000),[6 7 9 10] recruited from few countries.[7–11] Munyombwe *et al* identified some factors associated with lower HRQoL, including advancing age and presentation with non-ST-elevation myocardial infarction (NSTEMI).[5] Pocock *et al* found that EQ-5D index score at hospital discharge

INTRODUCTION

Improved survival following myocardial infarction (MI) has encouraged interest in identifying factors that are associated with subsequent cardiovascular (CV) events.[1] Clinicians require evidence about health-related quality of life (HRQoL) to inform

Figure 1 (A) Distributions of the EQ-5D items and (B) the consequent EQ-5D index score and VAS score in 8978 patients at enrolment. EQ-5D, EuroQol-5 dimension; VAS, Visual Analogue Scale.

following MI was an independent predictor of subsequent outcomes.[12 13] While these previous studies showed that the EQ-5D can report HRQoL in populations with stable CAD, little research has assessed whether HRQoL predicts subsequent clinical outcomes and resource use.

This article reports HRQoL for patients enrolled 1–3 years post-MI in a prospective, global registry. We aimed to: (1) assess the association of patient characteristics with HRQoL; (2) estimate the association of HRQoL with resource use, CV events and all-cause death; and (3) assess the effect of CV events on change in HRQoL between enrolment and 1-year's follow-up.

METHODS
Study design
TIGRIS (long-**T**erm r**I**sk clinical mana**G**ement and healthcare **R**esource utilization of stable coronary artery d**IS**ease in post-myocardial infarction patients) is a prospective, global registry of 9126 patients enrolled 1–3 years post-MI, during June 2013–November 2014,

from 369 centres across 25 countries in Europe, North America, Latin America, Asia and Australia, who were followed up for 2 years. Details of the TIGRIS Study have been reported.[14 15] In brief, patients included were aged ≥50 years with stable CAD, a documented history of MI occurring 1–3 years prior to enrolment and at least one of the following risk factors: age ≥65 years, diabetes mellitus requiring medication, history of a second prior MI, angiographic evidence of multivessel CAD and/or chronic non-end-stage kidney disease. Baseline data at enrolment included relevant medical history, demographics, details regarding the index MI before enrolment, and variables from routine physical examination and laboratory testing, where available.

Data collection and outcome measures
Patients were contacted every 6 months over the follow-up period, either by telephone or hospital visit. At each contact, patients were asked to complete the EQ-5D-3L survey instrument.[2 16] The EQ-5D-3L is a generic HRQoL

Table 1 Univariate associations of EQ-5D index score and EQ-5D VAS score by patient characteristics

	N	EQ-5D index score, mean (SD)	P value	EQ-5D VAS score, mean (SD)	P value
Age (years)					
50–60	2004	0.86 (0.21)	<0.001	76.50 (17.57)	<0.001
60–70	3442	0.86 (0.20)		77.22 (16.50)	
70–80	2885	0.83 (0.21)		75.09 (16.62)	
80+	647	0.77 (0.23)		72.42 (17.89)	
Sex					
Male	6827	0.87 (0.19)	<0.001	76.84 (16.42)	<0.001
Female	2151	0.77 (0.25)		73.45 (18.24)	
BMI (kg/m^2)					
<30	6882	0.86 (0.19)	<0.001	76.94 (16.38)	<0.001
30+	2096	0.78 (0.25)		73.06 (18.34)	
Heart rate (beats/min)					
<70	5151	0.85 (0.20)	<0.001	76.59 (16.83)	<0.001
70–79	2493	0.84 (0.21)		76.09 (16.35)	
80–89	1004	0.82 (0.23)		74.50 (17.75)	
90+	330	0.81 (0.22)		71.59 (19.28)	
Smoking status					
Never	3378	0.84 (0.21)	0.71	76.21 (17.01)	0.04
Former	4351	0.85 (0.21)		76.26 (16.79)	
Current	1247	0.84 (0.22)		74.73 (17.22)	
Years in education					
No formal education	355	0.79 (0.24)	<0.001	72.58 (19.48)	<0.001
1–9	2692	0.82 (0.22)		75.66 (16.74)	
10–12	2805	0.84 (0.22)		75.38 (17.27)	
13–15	1568	0.86 (0.19)		76.97 (16.12)	
16+	1453	0.89 (0.18)		77.87 (16.45)	
Type of index MI					
STEMI	4699	0.86 (0.20)	<0.001	76.83 (16.49)	<0.001
NSTEMI	3749	0.82 (0.22)		74.74 (17.59)	
Unknown	530	0.84 (0.21)		78.09 (15.43)	
Management of index MI					
PCI	7243	0.85 (0.21)	0.01	76.45 (16.66)	0.65
CABG	664	0.83 (0.22)		76.76 (16.01)	
Medical	1071	0.80 (0.22)		72.73 (18.90)	
Second prior MI					
No	8057	0.85 (0.21)	<0.001	76.46 (16.66)	<0.001
Yes	921	0.81 (0.23)		72.28 (18.74)	
Diabetes					
No diabetes	5978	0.86 (0.20)	<0.001	76.95 (16.36)	<0.001
Non-insulin-treated diabetes	2078	0.84 (0.21)		75.38 (17.34)	
Insulin-treated diabetes	863	0.77 (0.26)		71.50 (18.66)	
CKD					
No	8291	0.85 (0.21)	<0.001	76.46 (16.69)	<0.001
Yes	687	0.78 (0.25)		70.87 (18.92)	
History of major bleed					
No	8725	0.85 (0.21)	<0.001	76.08 (16.96)	0.11

Continued

Table 1 Continued

	N	EQ-5D index score, mean (SD)	P value	EQ-5D VAS score, mean (SD)	P value
Yes	253	0.78 (0.26)		74.35 (16.17)	
PAD					
No	8379	0.85 (0.20)	<0.001	76.48 (16.66)	<0.001
Yes	599	0.75 (0.25)		69.64 (19.31)	
Heart failure					
No	7947	0.85 (0.20)	<0.001	76.79 (16.44)	<0.001
Yes	1031	0.77 (0.26)		70.17 (19.40)	
Anaemia					
No	8721	0.85 (0.21)	<0.001	76.22 (16.81)	<0.001
Yes	257	0.73 (0.26)		69.55 (19.61)	
Angina					
No	8086	0.85 (0.20)	<0.001	76.70 (16.51)	<0.001
Yes	892	0.76 (0.24)		69.92 (19.32)	
Stroke					
No	8576	0.85 (0.21)	<0.001	76.25 (16.79)	<0.001
Yes	402	0.76 (0.25)		71.36 (19.24)	
Cardiovascular event (last 6 months)					
No	8544	0.85 (0.21)	<0.001	76.41 (16.63)	<0.001
Yes	434	0.79 (0.23)		68.53 (20.77)	
ER visit (last 6 months)					
No	8466	0.85 (0.21)	<0.001	76.42 (16.69)	<0.001
Yes	512	0.76 (0.24)		69.58 (19.51)	
COPD					
No	8335	0.85 (0.21)	<0.001	76.44 (16.77)	<0.001
Yes	643	0.77 (0.24)		70.66 (18.14)	
Prior peptic ulcer					
No	8684	0.85 (0.21)	<0.001	76.21 (16.83)	<0.001
Yes	294	0.78 (0.26)		70.58 (19.08)	
Diuretics					
No	6599	0.86 (0.20)	<0.001	77.28 (16.46)	<0.001
Yes	2258	0.79 (0.24)		72.29 (17.72)	
Region					
Asia and Australia	2799	0.89 (0.17)	<0.001	77.64 (14.95)	<0.001
Europe	4098	0.83 (0.22)		73.39 (18.01)	
North America	981	0.82 (0.23)		77.47 (17.38)	
Latin America	1100	0.81 (0.23)		80.49 (15.50)	

BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; EQ-5D, EuroQol-5 dimension; ER, emergency room; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; VAS, Visual Analogue Scale.

instrument with five dimensions of health (mobility, self-care, usual activities, pain and discomfort, anxiety and depression), for which there are three levels of response (no problems, some problems, severe problems). The EQ-5D-3L profiles reported by each patient were combined with health state preference values from the UK general population,[17] to give EQ-5D-3L health state index scores on a scale anchored at 0 (equivalent to death) and 1 (perfect health). Patients were also asked to report their own health status on the EQ-5D Visual Analogue Scale (VAS) from 0 (worst health you can imagine) to 100 (best health you can imagine). In CV disease, the EQ-5D-3L has been used widely internationally and found to have strong convergent validity with other HRQoL measures, and good discriminant ability in detecting differences in health status.[1] At each contact, patients were also asked to recall hospitalisations and

Table 2 Multivariable model for factors associated with EQ-5D index score as an ordinal measure with categories 1, 0.75–0.99, 0.60–0.74, <0.60, selected by a stepwise regression procedure using p<0.01 for inclusion

Variable	Common OR* (95% CI)	P value
Female	1.94 (1.76 to 2.14)	<0.001
Age (years)		
<70	Reference group	<0.001
70–80	1.25 (1.14 to 1.36)	
80+	2.01 (1.72 to 2.35)	
BMI ≥30 kg/m^2	1.57 (1.42 to 1.73)	<0.001
Heart rate (beats/min)		
<70	Reference group	<0.001
70–79	1.10 (1.00 to 1.21)	
80–89	1.26 (1.10 to 1.43)	
90+	1.42 (1.15 to 1.75)	
Smoking status		
Never	Reference group	<0.001
Former smoker	1.12 (1.02 to 1.23)	
Current smoker	1.30 (1.14 to 1.48)	
Years in education		
16+	Reference group	<0.001
13–15	1.20 (1.04 to 1.38)	
10–12	1.45 (1.28 to 1.65)	
1–9	1.52 (1.33 to 1.73)	
No formal education	1.82 (1.46 to 2.27)	
Angina	1.85 (1.62 to 2.10)	<0.001
Diabetes		
No diabetes	Reference group	<0.001
Non-insulin-treated diabetes	1.08 (0.98 to 1.19)	
Insulin-treated diabetes	1.52 (1.32 to 1.74)	
Stroke	1.69 (1.40 to 2.03)	<0.001
PAD	1.64 (1.40 to 1.91)	<0.001
ER visit (last 6 months)	1.62 (1.38 to 1.92)	<0.001
Prior peptic ulcer	1.40 (1.12 to 1.75)	0.003
COPD	1.44 (1.24 to 1.68)	<0.001
Heart failure	1.36 (1.19 to 1.55)	<0.001
Anaemia	1.49 (1.18 to 1.88)	0.001
Type of index MI		
STEMI	Reference group	<0.001
NSTEMI	1.21 (1.11 to 1.31)	
Unknown	1.32 (1.11 to 1.58)	
Diuretics	1.36 (1.23 to 1.50)	<0.001
Region		
Europe	Reference group	<0.001

Continued

Table 2 Continued

Variable	Common OR* (95% CI)	P value
Asia and Australia	0.60 (0.54 to 0.66)	
North America	0.93 (0.81 to 1.07)	
Latin America	1.14 (1.00 to 1.29)	

*Estimated using an ordinal logistic regression model. A common OR >1 means that category of patients has a poorer self-rated health compared with others (or compared with a reference group if the variable has >2 categories) after adjusting for the influence of other variables in the model. For instance, female patients have common OR=1.98, which means that they have almost double the odds of being below any cut-off value (<1, <0.75 or <0.6) for the EQ-5D index score compared with male patients.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; EQ-5D, EuroQol-5 dimension; ER, emergency room; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PAD, peripheral artery disease; STEMI, ST-elevation myocardial infarction.

visits to the emergency room (ER), general practitioner (GP), cardiologist or other specialists over the previous 6 months. These healthcare encounters were summed to report each patient's resource use over 2-years' follow-up. If a death occurred, efforts were made to identify the cause (CV or non-CV related). The primary endpoint of the TIGRIS Study was a composite comprising CV death, MI, stroke and unstable angina requiring urgent revascularisation. All outcome events and resource use measures were confirmed by the treating physician or hospital, including determination of final diagnosis, primary cause of hospitalisation, duration of hospital stay, procedures and interventions.

Statistical analysis

We summarised the responses to the EQ-5D-3L questionnaire at baseline enrolment according to the number (%) of patients reporting 'some' or 'severe' problems for each dimension, and by reporting histograms for the resulting index scores and VAS scores. The EQ-5D index score had a right-skewed distribution[18] and had several spikes in its distribution (figure 1). Hence, it has been grouped into four ordered categories: <0.60 (lowest HRQoL); 0.60–0.74 0.75–0.99; and 1 (highest HRQoL). Similarly, we grouped responses to the EQ-5D VAS score into five ordered categories: <60; 60–69; 70–79; 80–89; and ≥90 which represent 'lowest' to 'highest' self-rated health status.

We estimated the association of clinical factors with the index score category at enrolment using an ordinal logistic regression model. We reported the common OR of being in a 'lower' versus 'higher' index score category according to the presence versus absence of each
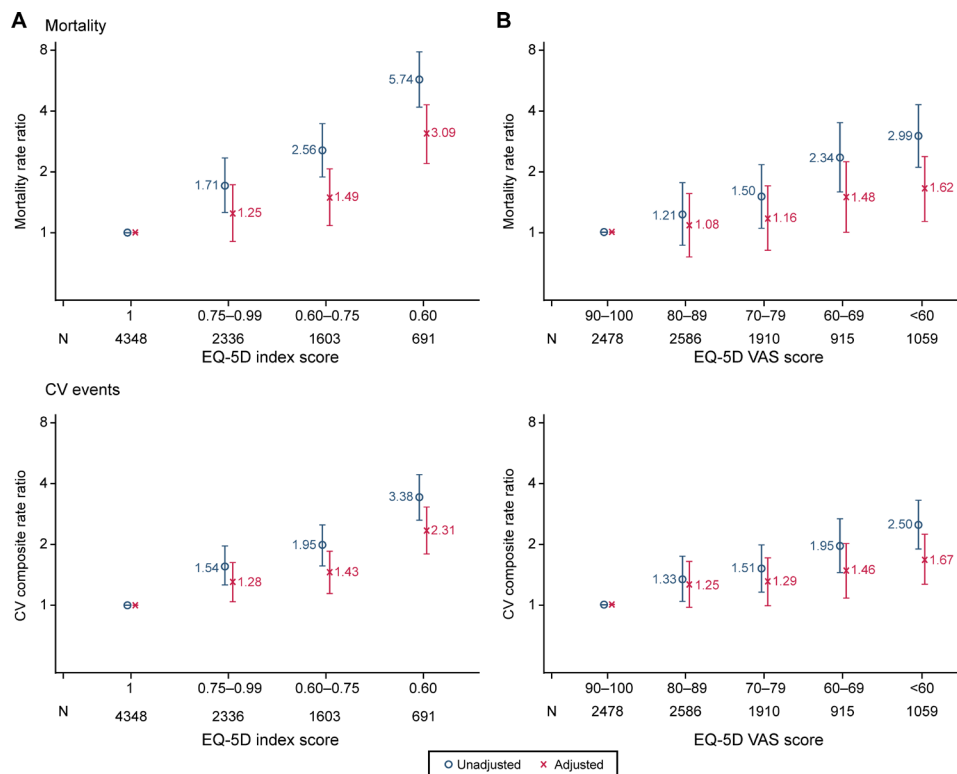
Figure 2 The associations of (A) baseline EQ-5D index score and (B) baseline VAS score with mortality and the composite outcome of CV death, MI, stroke and unstable angina requiring urgent revascularisation (using Poisson regression models with and without adjustment for other patient variables). Adjusted for variables in the TIGRIS index model: age ≥65 years; diabetes; second prior MI; chronic kidney disease; heart failure; peripheral artery disease; CV event in past 6 months; prior major bleed; medical management only of index MI; on diuretics at enrolment. CV, cardiovascular; EQ-5D, EuroQol-5 dimension; MI, myocardial infarction; VAS, Visual Analogue Scale.

risk factor, adjusting for other patient characteristics. We retained independent variables in the regression model according to a forward stepwise procedure with the criteria for an independent association of p<0.01.

We estimated the association of the index score category at enrolment with all-cause death, the composite CV outcome and each resource use measure. For all-cause death and the composite CV endpoint, Poisson regression models were used to recognise that rates were constant over time. We reported the incidence rate ratios and 95% CI for index scores at enrolment in each of the three lower categories, versus the category that represented perfect health. We also reported the association of the VAS score at enrolment with all-cause death and the CV outcome, and considered the association of the index score and VAS score simultaneously, adjusting for other factors.

We reported the association of the index score category and VAS score at enrolment with resource use up to 2 years for patients who survived up to 2 years and who had complete resource use data. Although each of these resource use measures had a right-skewed distribution, we used Ordinary Least Squares regression relying on the central limit theorem, to adjust for patient characteristics in reporting the mean resource use for each index score category as the requisite asymptotic assumptions were plausible, given the sample size.[19] For each model, we

adjusted for those patient characteristics previously identified in the TIGRIS Study as predictive of prognosis.[20] We took the same approach in reporting incidence rate ratios according to the independent association of each of the five EQ-5D health state dimensions at enrolment with both all-cause death and the composite CV outcome, adjusting for other factors.

Finally, we estimated the association of CV events (MI, stroke, unstable angina requiring urgent revascularisation, bleeding event requiring hospitalisation) that occurred between enrolment and 1-year's follow-up with the mean (95% CI) changes in the EQ-5D index score, and the EQ-5D VAS score over the same time period. We reported associations for those patients with complete data, which assume that HRQoL data were missing at random, conditional on the variables included in the regression model. All analyses were performed using STATA V.15.1.

RESULTS

Baseline patient characteristics

A total of 8978 (99.5%) patients completed EQ-5D questionnaires at enrolment. Table 1 presents key baseline characteristics with accompanying mean EQ-5D index and VAS scores (see also online supplemental table 1 for a fuller list of baseline variables). Before adjustment for

potential confounding factors, female sex, increasing age and presence of each comorbidity were each associated with lower mean index and VAS scores. For example, the mean HRQoL index score for men was 0.87 vs 0.77 for women.

Figure 1A shows the proportion of patients at study enrolment who reported 'moderate' or 'severe' problems according to each EQ-5D dimension. Pain and discomfort had the highest prevalence (33.1% 'moderate' and 2.7% 'severe' problems) followed by 'mobility' (24.4% and 0.2%, respectively). Over half (52%) of patients reported a 'moderate' or 'severe' problem on at least one of the EQ-5D dimensions. Figure 1B summarises EQ-5D index scores at enrolment and shows that 48% of patients had scores of 1 (perfect health), 26% between 0.75 and 0.99, 18% between 0.60 and 0.74%, and 8% less than 0.60.

Associations with index score at enrolment

Table 2 reports the independent association of each factor with the index score category at enrolment in a multi-variable model. Compared with men, women were more likely to have lower index scores, with an OR of 1.94 (95% CI 1.76 to 2.14). Other factors significantly associated with a lower index score were older age, obesity, current or ex-smoker, higher heart rate, less formal education, presence of each comorbidity (angina, insulin-treated diabetes mellitus, stroke, peripheral artery disease, prior peptic ulcer, chronic obstructive pulmonary disease, heart failure), ER visit in the previous 6 months and index MI unknown or NSTEMI (vs STEMI). When the VAS score rather than the index score was used as the summary measure of HRQoL, the results were similar (see online supplemental table 2). There were regional

differences in the index score (lowest in Latin America, highest in Asia/Australia), whereas the VAS score was lowest in Europe and highest in Latin America.

Impact of HRQoL on prognosis

Lower EQ-5D index scores were associated with higher risk of all-cause death and the composite outcome of CV death, MI, stroke and unstable angina requiring urgent revascularisation (figure 2A) over 2-years' follow-up. Patients with an index score of less than 0.60 and those with scores of 0.60–0.74 had rate ratios of all-cause death of 3.09 (95% CI 2.20 to 4.31) and 1.49 (95% CI 1.07 to 2.07), respectively, compared with those with an index score of 1, after adjustment for differences in other patient characteristics at enrolment. The corresponding rate ratios for the composite outcome were 2.31 (95% CI 1.76 to 3.03) and 1.43 (95% CI 1.12 to 1.82), respectively. The relationships between HRQoL at enrolment and both sets of subsequent outcomes were similar when the VAS score rather than the index score was used to predict subsequent outcomes (figure 2B). When the association of both HRQoL measures were considered simultaneously, the index score was independently associated with increased mortality risk (p<0.001), while the VAS score was not (p=0.84).

After adjustment for patient characteristics at enrolment, the EQ-5D dimensions that most strongly associated with all-cause death were problems with 'self-care' and 'mobility' (table 3), with estimated ORs of 1.70 (95% CI 1.'26 to 2.29) and 1.52 (1.14 to 2.03), respectively. The EQ-5D dimensions of 'pain/discomfort' and 'usual activities' were most strongly associated with the composite CV outcome. figure 3A reports the association of index scores

Table 3 The associations of the five specific problems in the EQ-5D on (A) all-cause death and (B) the composite outcome of CV death, MI, stroke and unstable angina requiring urgent revascularisation (using Poisson regression models with and without adjustment for other patient variables)

	Unadjusted rate ratio (95% CI)	P value	Adjusted* rate ratio (95% CI)	P value
A				
The specific problems				
Mobility	2.26 (1.69 to 3.02)	<0.001	1.52 (1.14 to 2.03)	0.004
Self-care	1.81 (1.35 to 2.43)	<0.001	1.70 (1.26 to 2.29)	0.001
Usual activities	1.48 (1.13 to 1.94)	0.005	1.18 (0.90 to 1.54)	0.24
Pain/discomfort	1.13 (0.90 to 1.41)	0.28	1.12 (0.90 to 1.39)	0.30
Anxiety/depression	0.79 (0.62 to 1.01)	0.06	0.91 (0.71 to 1.16)	0.44
B				
The specific problems				
Mobility	1.39 (1.10 to 1.74)	0.005	1.14 (0.90 to 1.43)	0.28
Self-care	1.13 (0.86 to 1.48)	0.39	1.11 (0.84 to 1.36)	0.47
Usual activities	1.54 (1.24 to 1.91)	<0.001	1.30 (1.05 to 1.62)	0.02
Pain/discomfort	1.41 (1.19 to 1.67)	<0.001	1.35 (1.14 to 1.60)	<0.001
Anxiety/depression	0.89 (0.74 to 1.08)	0.23	0.94 (0.78 to 1.14)	0.55

*Adjusted for variables in the TIGRIS risk index model: age ≥65 years, diabetes, second prior MI, chronic kidney disease, heart failure, peripheral artery disease, CV event in past 6 months, prior major bleed, medical management only of index MI, on diuretics at enrolment.
CV, cardiovascular; EQ-5D, EuroQol-5 dimension; MI, myocardial infarction.
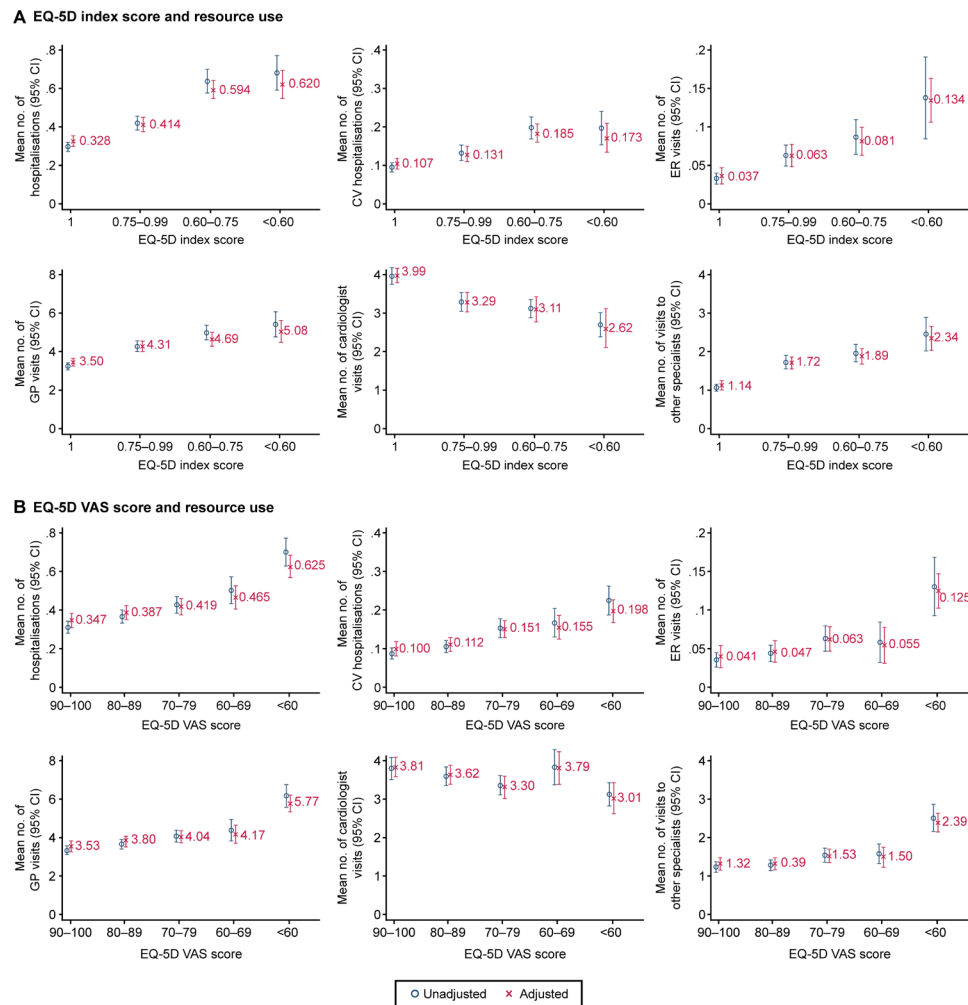
Figure 3 Health resource use over 2-years' follow-up by baseline self-rated health in 7846 patients with health resource data at every visit (using OLS regression models with and without adjustment for other patient variables). (A) EQ-5D index score and (B) EQ-5D VAS score adjusted for variables in the TIGRIS index model: age ≥65 years; diabetes; second prior MI; chronic kidney disease; heart failure; peripheral artery disease; CV event in past 6 months; prior major bleed; medical management only of index MI; on diuretics at enrolment. CV, cardiovascular; EQ-5D, EuroQol-5 dimension; ER, emergency room; GP, general practitioner; MI, myocardial infarction; OLS, Ordinary Least Squares; VAS, Visual Analogue Scale.

at enrolment with resource use over 2-years' follow-up for the 7846 patients who survived to that timepoint and provided complete information. A further 296 patients died, and 840 patients had missing resource use data. Lower index and VAS scores at enrolment were associated with higher subsequent use of healthcare resources, before and after adjustment for other patient characteristics at enrolment (figure 3B). For example, compared with patients who were in 'perfect health' at enrolment, the mean numbers of hospitalisations for any reason were 89% higher for patients with index score less than 0.60 and 81% higher for index score between 0.60 and 0.74. Similar patterns emerged for CV-specific hospitalisations, ER visits, visits to the GP and visits to other specialists, but in contrast, visits to cardiologists were less common for those with lower HRQoL.

Changes in index score over time
Among survivors, there is no evidence of an overall change in the index score over time. For the 5932 patients with

the EQ-5D recorded at every 6-monthly visit, the mean index score was 0.87 at all four follow-up visits vs 0.86 at baseline. For the 2754 patients who were alive at the end of the follow-up period, but missed at least one visit, the mean index score at baseline was 0.83.

The estimated effect of non-fatal CV and bleeding events on a patient's change in self-rated health over 1 year is shown in table 4. MI, unstable angina requiring revascularisation and a bleeding event requiring hospitalisation occurred in 103, 52 and 46 patients, respectively, and all events were associated with a deterioration in self-rated health. Stroke occurred in 28 patients but showed less impact on self-rated health. These effects were more marked for change in VAS score than for the change in index score, but the patterns were similar.

DISCUSSION
This prospective study of HRQoL 1–3 years post-MI included almost 9000 patients from 25 countries in four

Table 4 Influence of clinical events over 1 year on change in self-rated health at 1 year

	N	Mean change* (95% CI)	P value
A Change in EQ-5D index score			
Any event	223	−0.04 (−0.07 to −0.02)	<0.001
MI	103	−0.04 (−0.07 to −0.01)	0.02
Stroke	28	0.01 (−0.05 to 0.08)	0.68
Unstable angina requiring urgent revascularisation	52	−0.06 (−0.10 to −0.01)	0.02
Bleeding event requiring hospitalisation	46	−0.04 (−0.09 to 0.01)	0.15
B Change in EQ-5D VAS score			
Any event	221	−3.37 (−5.57 to −1.17)	0.003
MI	102	−4.02 (−6.63 to −1.41)	0.003
Stroke	27	−3.67 (−8.70 to 1.37)	0.15
Unstable angina requiring urgent revascularisation	52	−7.87 (−11.51 to −4.23)	<0.001
Bleeding event requiring hospitalisation	46	−5.57 (−9.44 to −1.71)	0.005

*Adjusted for other baseline predictors and estimated using an OLS regression model.
EQ-5D, EuroQol-5 dimension; MI, myocardial infarction; OLS, Ordinary Least Squares; VAS, Visual Analogue Scale.

continents. The TIGRIS Study was designed to assess the association of clinical factors with HRQoL at enrolment, the effect of HRQoL on subsequent outcomes and resource use, and the change in HRQoL associated with CV events. After adjustment for a full range of patient factors using a previously validated risk model,[20] the study found that HRQoL was associated with chronic comorbidities, being female, age >80 years, being obese, fewer years in education and having an NSTEMI index event. A lower index score category at enrolment was associated with a higher subsequent risk of all-cause death, of a major CV event and more hospitalisations over the 2-years' follow-up period. Patients who experienced any CV event had a reduction in the mean index score between enrolment and 1-year's follow-up.

We found that the EQ-5D index score at enrolment was on average 0.87 for men vs 0.77 for women, and women were more likely to have lower EQ-5D index scores after adjustment for other factors. In an age–sex matched general population, the corresponding index scores were 0.78 for men and 0.77 for women.[21] HRQoL post-MI may be lower for women than men because of a different profile of symptoms in the post-MI period[22] and lower access to cardiac rehabilitation services.[23] Previous studies reported that women have lower HRQoL than men post-MI but were focused on specific countries and did not consider HRQoL 1–3 years post-MI.[3 13 23 24]

Previous studies have also found that following MI, HRQoL is lower in older patients, following NSTEMI and for patients with comorbidities.[5 25] Lower HRQoL in NSTEMI has been attributed to more symptomatic disease, a history of angina and multimorbidity.[5 23] Previous research has found that for chronic disease, more generally, obesity, lower socioeconomic status and presence of comorbidities are associated with lower HRQoL.[26–28] Our study is unique in finding that these risk factors were independently associated with HRQoL in the context of a large multinational study. We also found that the mean index score was lower for patients attending centres in Latin America and higher for those in Asia, but it is unclear whether this reflects differences in patient management, severity of their initial MI or other regional features.

Our study shows the importance of HRQoL measured 1–3 years after MI in predicting future events and resource use. We found that poorer HRQoL (ie, a lower EQ-5D index score) predicted a higher risk of all-cause death and a composite of major CV events. While VAS score categories also predicted these outcomes, the associations were weaker, and when both scores were considered simultaneously, the VAS score was not independently associated with these outcomes. Methodological guidelines also support the use of the index score in preference to the VAS score.[2] Consistent with a previous systematic review of the use of EQ-5D in CVD,[3] we found that the presence of problems on the 'self-care' and 'mobility' dimensions of the EQ-5D index were most strongly associated with all-cause mortality, whereas problems on the 'pain/discomfort' and 'usual activities' dimensions were most strongly associated with CV events.

This study estimated the effect of CV events on changes in EQ-5D index scores between enrolment and 1-year's follow-up. Our finding that 'any CV event', MI, unstable angina and bleeding event requiring hospitalisation were each associated with a mean reduction in the index score is consistent with previous studies.[5–11 22] The PEGASUS-TIMI 54 trial reported decrements of similar magnitude.[29] Our study also added to the limited literature that has reported that lower index scores are associated with increased mean number of hospitalisations and ER visits.[8] Future studies could use these estimates in cost-effectiveness models that evaluate new treatments for stable patients following MI.

The main strengths of the study are the large sample size, wide spread of centres, prospective design and use of a validated risk adjustment model when examining the

association of HRQoL score with subsequent outcomes. A limitation is that CV events during the follow-up period were identified at each centre but were not confirmed by an independent event validation committee. Also, the finding that HRQoL was not significantly lower following stroke may reflect that only few (n=32) patients had this event over 1-year's follow-up. Also, as assessment of HRQoL at enrolment was at least 1-year post-MI, those who died within a year or did not consent to participate, were excluded. Further research is required to consider the association of HRQoL following MI with subsequent outcomes over longer time periods.

CONCLUSIONS

In a large global population of patients enrolled 1–3 years post-MI, self-reported health status provided valuable insights. First, HRQoL is associated with both objective evidence of disease and sociodemographic characteristics. Second, poorer HRQoL is strongly associated with increased hospitalisations. Third, poorer HRQoL 1–3 years after MI is an independent predictor of CV events and all-cause death. We recommend that clinical management post-MI should pay greater attention to patients' perceptions of their own health status.

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REFERENCES

1 Doll JA. Quality of life after myocardial infarction: more PROgress needed. *Heart* 2020;106:8–9.
2 EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
3 Dyer MTD, Goldsmith KA, Sharples LS, *et al*. A review of health utilities using the EQ-5D in studies of cardiovascular disease. *Health Qual Life Outcomes* 2010;8:13.
4 National Institute for Health and Care Excellence (NICE). Ticagrelor for preventing atherothrombotic events after myocardial infarction. NICE technology appraisal guidance 420. London: NICE, 2016. Available: https://www.nice.org.uk/guidance/ta420 [Accessed 20 Jul 2020].
5 Munyombwe T, Hall M, Dondo TB, *et al*. Quality of life trajectories in survivors of acute myocardial infarction: a national longitudinal study. *Heart* 2020;106:33–9.
6 Goss F, Haerer W, Brachmann J, *et al*. Low mortality and rate of cardiac events in patients after acute coronary syndrome systematically managed by office-based cardiologists in Germany: 1-year outcomes of the ProAcor study. *Circulation* 2015;132:A19221.
7 Henriksson C, Larsson M, Herlitz J, *et al*. Influence of health-related quality of life on time from symptom onset to hospital arrival and the risk of readmission in patients with myocardial infarction. *Open Heart* 2014;1:e000051.

8 Nam J, Briggs A, Layland J, *et al*. Fractional flow reserve (FFR) versus angiography in guiding management to optimise outcomes in non-ST segment elevation myocardial infarction (FAMOUS-NSTEMI) developmental trial: cost-effectiveness using a mixed trial- and model-based methods. *Cost Eff Resour Alloc* 2015;13:19.

9 Seidl H, Hunger M, Leidl R, *et al*. Cost-effectiveness of nurse-based case management versus usual care for elderly patients with myocardial infarction: results from the KORINNA study. *Eur J Health Econ* 2015;16:671–81.

10 Varnfield M, Karunanithi M, Lee C-K, *et al*. Smartphone-based home care model improved use of cardiac rehabilitation in postmyocardial infarction patients: results from a randomised controlled trial. *Heart* 2014;100:1770–9.

11 Stafford M, Soljak M, Pledge V, *et al*. Socio-economic differences in the health-related quality of life impact of cardiovascular conditions. *Eur J Public Health* 2012;22:301–5.

12 Pocock S, Bueno H, Licour M, *et al*. Predictors of one-year mortality at hospital discharge after acute coronary syndromes: a new risk score from the EPICOR (long-tErm follow uP of antithrombotic management patterns In acute CORonary syndrome patients) study. *Eur Heart J Acute Cardiovasc Care* 2015;4:509–17.

13 Pocock SJ, Huo Y, Van de Werf F, *et al*. Predicting two-year mortality from discharge after acute coronary syndrome: an internationally-based risk score. *Eur Heart J Acute Cardiovasc Care* 2019;8:727–37.

14 Westermann D, Goodman SG, Nicolau JC, *et al*. Rationale and design of the long-Term rIsk, clinical manaGement, and healthcare Resource utilization of stable coronary artery dISease in post-myocardial infarction patients (TIGRIS) study. *Clin Cardiol* 2017;40:1197–204.

15 Brieger D, Pocock SJ, Blankenberg S, *et al*. Two-year outcomes among stable high-risk patients following acute MI. Insights from a global registry in 25 countries. *Int J Cardiol* 2020;311:7–14.

16 Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37:53–72.

17 Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;35:1095–108.

18 Basu A, Manca A. Regression estimators for generic health-related quality of life and quality-adjusted life years. *Med Decis Making* 2012;32:56–69.

19 Nixon RM, Wonderling D, Grieve RD. Non-parametric methods for cost-effectiveness analysis: the central limit theorem and the bootstrap compared. *Health Econ* 2010;19:316–33.

20 Pocock SJ, Brieger D, Gregson J, *et al*. Predicting risk of cardiovascular events 1 to 3 years post-myocardial infarction using a global registry. *Clin Cardiol* 2020;43:24–32.

21 Kind P, Dolan P, Gudex C, *et al*. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998;316:736–41.

22 Tu JV, Austin PC, Walld R, *et al*. Development and validation of the Ontario acute myocardial infarction mortality prediction rules. *J Am Coll Cardiol* 2001;37:992–7.

23 Bahall M, Khan K. Quality of life of patients with first-time AMI: a descriptive study. *Health Qual Life Outcomes* 2018;16:32.

24 Kang K, Gholizadeh L, Inglis SC, *et al*. Interventions that improve health-related quality of life in patients with myocardial infarction. *Qual Life Res* 2016;25:2725–37.

25 Lacey EA, Walters SJ. Continuing inequality: gender and social class influences on self perceived health after a heart attack. *J Epidemiol Community Health* 2003;57:622–7.

26 Maheswaran H, Petrou S, Rees K, *et al*. Estimating EQ-5D utility values for major health behavioural risk factors in England. *J Epidemiol Community Health* 2013;67:172–80.

27 Grandy S, Fox KM. EQ-5D visual analog scale and utility index values in individuals with diabetes and at risk for diabetes: findings from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). *Health Qual Life Outcomes* 2008;6:18.

28 Lubetkin EI, Jia H, Franks P, *et al*. Relationship among sociodemographic factors, clinical conditions, and health-related quality of life: examining the EQ-5D in the U.S. general population. *Qual Life Res* 2005;14:2187–96.

29 Magnuson EA, Li H, Wang K, *et al*. Cost-effectiveness of long-term ticagrelor in patients with prior myocardial infarction: results from the PEGASUS-TIMI 54 trial. *J Am Coll Cardiol* 2017;70:527–38.