Original research paper

Prospective utility study of patients with multiple cardiovascular events

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Abstract

Objectives: The effects of acute coronary syndrome (ACS) events on health-related quality of life (HRQoL) and the time dependency of these effects are unknown. This study aimed to characterise health utilities in ACS patients to aid development of future economic models estimating the cost per quality-adjusted life-year impact of ACS events and potential treatments.

Methods: Multicentre, non-interventional, longitudinal evaluation of health utility in patients experiencing ACS or stroke events. EuroQol-5 dimension 3 level (EQ-5D-3L) surveys were sent to patients (≥18 years) from three UK centres 1 month after hospital discharge for myocardial infarction (MI), unstable angina (UA), or stroke. Patient demographics, lifestyle, and baseline utility score were collected in the first survey. Follow-up surveys were sent at 6, 12, 18, and 24 months to prospectively capture utility and subsequent health events. Two methods of patient identification were adopted – prospective, where the patient's qualifying event occurred after the study index date, and retrospective, where the patient's qualifying event occurred prior to the study index date. General healthy population utility values were assumed for pre-event HRQoL.

Results: Between January 2011 and March 2014, 2,103 prospectively (n=1,350)/retrospectively (n=753) identified patients (mean age 68.3 years; 67.9% male) responded: MI 55.9% (*n*=1,176), UA 42.7% (*n*=898), stroke 1.4% (*n*=29); 24% had type 2 diabetes. Post-event utility values were lower than general healthy population values, although significant differences in utility between subsequent 6 (n=1,031 change= -0.002), 12 (n=1,096 change= -0.008), 18 (n=1,246 change= -0.007) and 24 (n=1,277 change= -0.004) month timepoints were not detected. Through multivariate regressions analyses, wheelchair use, current smoking, secondary mental and joint health events were associated with the greatest statistically significant utility decrements.

Conclusions: This study indicates that health utility decreases following a CV event and,although some improvement occurs over the subsequent 24 months, general healthy population utility is not necessarily attained.

KEYWORDS

Acute coronary syndrome; Cardiovascular disease; Health utilities; Health-related quality of life

SHORT TITLE

PROSPECTIVE UTILITY STUDY OF MULTIPLE CV EVENTS

Introduction

Cardiovascular (CV) disease causes substantial morbidity and mortality worldwide, being the primary cause of non-communicable disease-related death in the USA and Europe [1–3]. Acute coronary syndrome (ACS) is an umbrella term for clinical conditions characterised by signs and symptoms of myocardial ischemia. ACS includes unstable angina (UA), ST segment elevation myocardial infarction (MI), and non-ST elevation MI, differentiated by ECG and biomarker (troponin) changes. Following an initial ACS event, the likelihood of a subsequent event, with its associated morbidity and mortality, increases [4,5]. Furthermore, such events are associated with more chronic conditions such as heart failure and strokes (REACH registry), long-term disability, and resulting costs to individual patients and society as a whole [6,7].

Patient-reported health status measures are often used as endpoints in clinical trials, although they are rarely used in the real-world setting [8]. As such, the published data often reflects a healthier clinical trial eligible patient cohort and does not reflect the real-world cohort fully. Furthermore, most published utilities represent post-event health states without distinguishing between the acute impact of the CV event and the chronic post-event effects [9]. Consequently, the effects of initial and subsequent ACS events on health-related quality of life (HRQoL) and the variables that may contribute to the magnitude of these effects are not well characterised or referenced. For health technology appraisal bodies in the UK, characterisation of health utilities in patients with ACS helps when estimating the economic impact of both ACS events and potential treatments to mitigate these events.

The objectives of this study were to quantify: (1) The utility associated with a CV event; and (2) The change (decrement or increment) in utility associated with a CV event over a time frame of 24 months.

Materials and methods

Study design

The study was a multicentre, non-interventional, longitudinal evaluation of health utility in patients who had experienced an ACS or stroke event. Patients were surveyed for a maximum of 2 years from their discharge date following their qualifying ACS or stroke event. The main study endpoint was health utility index value determined from the EuroQoL 5-Dimensions 3 level Questionnaire (EQ-5D-3L).

Setting

Three National Health Service (NHS) trust hospitals (Barnet Hospital, Royal Free London NHS Foundation Trust; University Hospital of Wales, Cardiff and Vale University Health Board; and Peterborough City Hospital, Peterborough and Stamford Hospitals NHS Foundation Trust) with well-characterised CV patient populations participated in the study. In the national MINAP dataset of management of ACS patients, these centres were all normal or above normal in performance with evidence-based therapies.

Patients

Patients experiencing an ACS event or a stroke following an ACS event, were eligible for inclusion. Potential study participants were identified from participating site health records and, 1 month post discharge following a qualifying CV event (MI, UA, or stroke), were mailed an informed consent form and an initial study survey.

Patients had to meet each of the following criteria to be considered eligible for inclusion in the study: age ≥18 years; experiencing a qualifying event of ACS (MI or UA) or stroke

(defined as: stroke with a prior history of CV disease and with their most recent previous event prior to their qualifying stroke being an ACS event). Stroke and ACS patients were sought to understand the impact of stroke deliberately, particularly as ACS patients often do not survive a subsequent stroke event and therefore are unavailable usually to contribute.

Patients were excluded if they met any of the following criteria: stroke but no history of CV disease; stroke and prior history of CV disease, but their most recent CV event was not an ACS event (i.e. stroke, stable angina, myocarditis etc…); prior diagnosis of type 1 diabetes mellitus; prior elective or emergency coronary revascularisation or coronary artery bypass graft surgery in the 6 weeks before their subsequent CV event. Patients who had undergone revascularisation more than 6 weeks before their CV event were assumed to have stabilised and were considered eligible for the study.

Patients were identified by two methods; (1) prospectively, when the patient's qualifying event occurred after the start of the study; or (2) retrospectively (Cardiff only) when the patient's qualifying event had occurred before the start of the study. The inclusion of both prospectively and retrospectively identified patients enabled the collection of both early-term and late-term time-dependent utility data from the start of the study. Inclusion of the retrospectively identified cohort also ensured adequate sampling of later timepoints, when patients in the prospectively identified group may have been lost to follow-up.

Evaluations

HRQoL was measured using the EuroQol five dimension – three level (EQ-5D-3L) outcome measure [10], a standardised measure of health status that has been validated in a wide range of health conditions and as a general population health measure in the UK and many

other countries [11], and utilising the United Kingdom value set[12]. The visual analogue scale (VAS) part of the EQ-5D was not utilised as the study was designed to generate utility scores to inform economic models; as VAS scores are not used in this process they were deemed an unnecessary burden to the patients.

The initial study survey included a demographic questionnaire; health status, as measured by the EQ-5D (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and a question regarding current wheelchair use. Patients who provided signed informed consent and completed the initial survey were considered study responders. Study responders were mailed up to five surveys (one initial survey and four follow-up surveys at 6, 12, 18, and 24 months after their qualifying event). The follow-up surveys consisted of the EQ-5D, the current wheelchair-use query, and two additional questions regarding the occurrence and type of any injury or illness that may have affected their health since they had completed the preceding study survey.

The retrospectively identified patients were sent informed consent forms and surveys (initial and follow-up) consistent with the process established for the prospectively identified patients, except that that they could only receive a maximum of four surveys (at 6-, 12-, 18-, and 24-month follow-ups) depending on the time elapsed since their qualifying CV event had occurred.

Accrual period and sample size

The study accrual period (identification of potential study subjects, informed consent form, and initial survey mailings) began in January 2011, following activation of the first study site on January 5, 2011, and continued until May 2012. Data collection continued until March 2014 when the last follow-up patient questionnaire was returned.

Data sources and measurement

The majority of study variables were assessed by patient-completed questionnaires. The data captured included baseline characteristics, HRQoL, and the occurrence and type of secondary illness or injury affecting health between surveys. Patient questionnaires were anonymised: all included a unique identifier on each page that linked the questionnaire to each patient's unique participant code. Type of qualifying event (MI, UA, or stroke) and subsequent in-hospital death during the study period were recorded by the site investigator based on institutional health records (it was not possible to capture deaths in the community, prior to study entry).

At the Barnet and Peterborough study sites, questionnaire data and investigator-reported variables were entered into a Microsoft® Excel spreadsheet by investigator staff. To allow for interim data reviews and provide data back-ups, copies of the spreadsheets were regularly transferred from the study sites during the study period. Spreadsheet data were uploaded into a site-specific Microsoft Access database; surveys were mailed via commercial courier.

Completed questionnaires from patients enrolled at the Cardiff study site were scanned into the site-specific Access database using optical character recognition software. Qualifying CV event type and death during the study period were recorded by investigator staff in a text file provided for uploading into the site-specific Access database linked to the scanned survey data. A separate study database was maintained for each study site; data from all sites were amalgamated only for study analyses. Routine quality assurance checking was undertaken by two members of the analysis team.

Sample size and statistical considerations

It was determined that a population of 669 patients would be needed to attain a power of 80% at a 5% α level to detect a difference in EQ-5D score of 0.03. A difference of 0.03 in EQ-5D score is consistent with previously reported minimum clinically meaningful differences in health utility [13]. Loss to follow-up over the study duration was estimated to be 20% at 6 months (i.e. the second survey) and maintained for the duration of the study.

Baseline characteristics, qualifying event type, death (if noted in health records), and patient-reported causes of change in health during the study period were tabulated and analysed using simple summary statistics (proportions, means, standard deviations [SDs], and ranges).

HRQoL was assessed using linear regression analysis to examine change in utility between timepoints and by multivariable linear regression analysis stratified by qualifying CV event and controlling for variables (i.e. age, sex, weight, type 2 diabetes mellitus [T2DM] status, smoking status, wheelchair use, and causes of changes in health) and interactions between variables. The calculated β, standard error, 95% confidence intervals, and *p*-values were tabulated, and the utility decrements associated with baseline characteristics and patient-reported causes of change in health were calculated and presented by qualifying event.

Regression analyses were conducted by patient group (prospectively identified patients, retrospectively identified patients, and combined patient groups) and survey time point. EQ-5D was used as the dependent variable with all other variables entered as independent variables. Backward elimination stepwise regression models were utilised with non-statistically significant variables removed one at a time; for consistency qualifying event,

gender, age, and weight were forced variables entered into the model irrespective of their statistical significance.

This study was approved by the National Institute for Social Care and Health Research (NISCHR) Research Ethics Service (RES), Rec reference: 10/WSE03/37, IRAS project ID: 61628.

Results

A total of 2,103 patients returned surveys; 1,350 (64.2%) prospectively identified patients and 753 (35.8%) retrospectively identified patients. Most patients in the prospective group were enrolled from Cardiff (48.4%) with Peterborough and Barnet recruiting 30.3% and 21.3% of patients, respectively. Overall survey response rate at baseline was 62.0%, with follow-up response rates ranging 66.3% to 70.6% (Table 1).

Baseline characteristics

Baseline characteristics of the patient group by qualifying event are shown in Table 2. Of the 2,103 patients enrolled, 1,176 (55.9%) had an MI, 898 (42.7%) had UA, and 29 (1.4%) had a stroke. Approximately one-quarter of patients had been diagnosed with type 2 diabetes mellitus at the time of completion of their initial survey (Table 2).

Patients reported wheelchair use at baseline and at each follow-up survey. Wheelchair use was reported in 6.3% of patients at baseline and varied from 5.1% at Month 6 to 6.2% at Month 18 (Table 2).

The majority of patients enrolled (86.9%) were not current smokers at the time of completing their initial study survey. Cardiff (12.6%) had the highest proportion of smokers followed by Peterborough (10.5%) and Barnet (6.3%).

Outcomes

Health utility: EQ-5D index scores

As shown in Table 3, mean EQ-5D scores increased from baseline to Month 6, then subsequently decreased through Month 12 and Month 18, before increasing again at Month 24.

Mean EQ-5D scores was lowest in the stroke subgroup, ranging from 0.448 (SD 0.425) at Month 18 to 0.527 (SD 0.403) at Month 24. Mean EQ-5D was highest in the MI group, ranging from 0.690 (SD 0.290) at baseline to 0.708 (SD 0.322) at Month 18.

Utility over time

Table 4 shows changes in utility over time. Although decreases in utility were observed between each timepoint, none of these decreases were statistically significant (p=0.267 to 0.785).

Change in utility with secondary events

The numbers of patients reporting an event that significantly affected their health, as assessed in each follow-up survey, are shown in Table 5. Joint and CV disease events were the most common event types influencing self-reported health. The ~12% of further CV events over the 24 months of follow up is consistent whatever the follow up duration available. This rate may be somewhat low for an average follow up of 24 months, compared to ACS registries such as GRACE [4].

Changes in utility associated with baseline characteristics, wheelchair use, and secondary health events, as determined by multivariate regression analysis, are shown in Table 6. For discussion and presentation of regression model results, the initial survey was estimated to have been completed 1 month after the qualifying event.

Baseline characteristics (e.g. qualifying event, gender) were forced into the regression analysis model regardless of their significance to evaluate their effect over time. Changes in health due to secondary events were not included in the regression analysis model if they were not statistically significant. For example, cancer and complications of diabetes did not have a statistically significant effect on utility, most likely due to the small number of occurrences (cancer) or the effect on utility (complications of diabetes) not being significantly greater than already incurred by having the disease (baseline T2DM status).

Adjusted EQ-5D scores over time for study participants whose qualifying event was an MI or UA are shown in Figure 1; stroke patients were excluded due to the small number of patients. The utility point estimated at months 6, 12, 18 and 24 are contrasted with mean utilities for individuals aged 68 years without complications derived from the English Health Survey [14].

Male patients who experienced an MI had a mean utility score of 0.692 at Month 1 after the event and 0.649 at Month 6, before increasing to 0.727 at Month 12, 0.782 at Month 18, and 0.765 at Month 24 all lower than the general population mean of 0.886 (Figure 1). In patients with UA mean utility was 0.649 at Month 1 after the event decreasing to 0.614 at Month 6, before increasing to 0.688 at Month 12 and 0.761 at Month 18, before decreasing to 0.65 at Month 24; again, all lower than the general population mean.

Discussion

Several utility values are available to represent health states in patients with ACS [15]. However, many such values do not take into account the time between the CV event and the utility assessment. This limits interpretation of the impact of the event and the resulting quality of life implications, which can occur acutely and chronically following the event. In the current study, regression analyses indicated a modest increase utility from 1-month after the initial event (i.e. at initial survey completion) to month 24 months, although significant differences in utility were not detected between baseline and subsequent Month 6, 18, 12, and 24 timepoints. It is noteworthy that health utility remained significantly lower than population norms for age-matched subjects without complications. Wheelchair use, current smoking, and secondary mental and joint health events were associated with the greatest utility decrements (>0.250 decrease). The effect of these baseline characteristics and secondary events were more profound than baseline T2DM status. The number of stroke patients enrolled in the study was inadequate for any conclusions to be made regarding this group.

A potential limitation of the study was that CV history (aside from the qualifying event) was not available and that secondary or subsequent clinical events were captured via self-reporting rather that via-health records. Nevertheless, the high patient response to study surveys allowed for the collection of valuable utility information which could be examined in the context of initial CV events that characterised participants' ACS. In addition, the limited number of sites could introduce characteristic biases, such as the smoking rate differences

seen. We have not looked for or adjusted for social class demographic differences between the sites, but these may be present given the average survival ages for the three regions is known to differ. Study patient death was likely underreported as only those deaths documented in hospital records were included. Furthermore, patients whose poor health or undocumented death precluded survey completion would have inappropriately biased results toward better utility. The study did not ask investigators to chase patient status if questionnaires were unreturned.

Conclusion

This real-world, survey based, study indicates that health utility decreases following a CV event, although some improvement occurs over the subsequent 24 months. If we assume a general population quality of life baseline from published data, this level of quality of life score is not approached by our study group as a whole.

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Transparency

Declaration of funding

This study was sponsored by Roche Products Ltd. The non-interventional nature of the study means that it was not registered on any commonly used clinical trial databases.

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Declaration of financial/other relationships

Joshua Ray and Simon Shutler are employed (and paid) by F. Hoffmann-La Roche, Basel, Switzerland. Irwin Tran is employed (and paid) by Roche Products Ltd, Welwyn Garden City, UK. The other authors declare no financial/other relationships.

Author contributions

All authors were involved in the conception and design, analysis and interpretation of the data, drafting of the paper and revising it critically for intellectual content, and the final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

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Table 1. Survey response by time point

	Patients	Total
Baseline	Identified as eligible	2,179
	Surveyed	2,179
	Responded	1,350 (62.0%)
6 months	Surveyed	2,096
	Responded	1,389 (66.3%)
12 months	Surveyed	2,287
	Responded	1,597 (69.8%)
18 months	Surveyed	2,386
	Responded	1,685 (70.6%)
24 months	Surveyed	2,536
	Responded	1,732 (68.3%)

Table 2. Baseline patient characteristics

	Survey post event					
Characteristic	**1 month**	**6 months**	**12 months**	**18 months**	**24 months**	**MI**
Combined n	**1,350**	**1,298**	**1,473**	**1,508**	**1,539**	**1,176**
Mean age, years ± SD	68.3 ± 12.3	69.0 ± 11.8	68.8 ± 11.9	68.8 ± 11.6	68.3 ± 11.5	67.4 ± 12.
(range)	(24–97)	(36-96)	(26-97)	(26-97)	(34-96)	(24–97)
Male, *n* (%)	1,428 (67.9)	891 (68.6)	1,010 (68.6)	1,031 (68.4)	1,059 (68.8)	828 (70.4
Mean body weight, kg ± SD	80.5 ± 17.3	80.5 ± 16.4	80.5 ± 17.2	80.5 ± 17.4	80.6 ± 17.0	79.8 ± 16.
(range)	(29 – 200)	(29 – 189)	(39 – 200)	(29 – 200)	(39 – 200)	(29 – 189
Smoking status, *n* (%)						
Smoker	151 (11.2)	128 (9.9)	143 (9.7)	149 (9.9)	151 (9.8)	134 (11.4
Non-smoker	1,173 (86.9)	1,162 (89.5)	1,322 (89.7)	1,352 (89.7)	1,383 (89.9)	1,031 (87.
Unknown	26 (1.9)	8 (0.6)	9 (0.6)	7 (0.5)	5 (0.3)	11 (0.9)
Type 2 diabetes, *n* (%)						
Yes	345 (25.6)	328 (25.3)	356 (24.2)	362 (24.0)	353 (22.9)	345 (29.3
No	979 (72.5)	962 (74.1)	1,108 (75.2)	1,136 (75.3)	1,171 (76.1)	911 (77.5
Unknown	26 (1.9)	7 (0.5)	9 (0.6)	10 (0.7)	15 (1.0)	20 (1.7)
Wheelchair use, *n* (%)	85 (6.3)	66 (5.1)	84 (5.7)	94 (6.2)	87 (5.7)	55 (4.7)

MI, myocardial infarction; SD, standard deviation; UA, unstable angina.

Table 3. Mean EQ-5D index scores

		Mean (SD) EQ-5D score by qualifying event		
Timepoint	**Mean (SD) EQ-5D score for all patients**	**MI**	**UA**	**Stroke**
0 months	*n*=1257	*n*=702	*n*=535	*n*=20
	0.659 (0.307)	0.690 (0.290)	0.623 (0.322)	0.496 (0.362)
6 months	*n*=1298	*n*=733	*n*=552	*n*=13
	0.672 (0.320)	0.702 (0.309)	0.637 (0.327)	0.525 (0.427)
12 months	*n*=1473	*n*=817	*n*=635	*n*=21
	0.669 (0.333)	0.708 (0.322)	0.625 (0.339)	0.498 (0.374)
18 months	*n*=1508	*n*=844	*n*=647	*n*=17
	0.659 (0.344)	0.692 (0.337)	0.622 (0.344)	0.448 (0.425)
24 months	*n*=1539	*n*=888	*n*=635	*n*=16
	0.665 (0.346)	0.706 (0.336)	0.611 (0.352)	0.527 (0.403)

MI, myocardial infarction; UA, unstable angina.

Table 4. Unadjusted change in EQ-5D score over time

Time period (first – second timepoint)	*n*	Mean EQ-5D (SD) First timepoint	Mean EQ-5D (SD) Second timepoint	Change over time (SD)	*p*-value
0–6 months	1031	0.684 (0.288)	0.682 (0.316)	–0.002 (0.237)	0.785
6–12 months	1096	0.694 (0.307)	0.687 (0.326)	–0.008 (0.225)	0.267
12–18 months	1246	0.679 (0.329)	0.672 (0.341)	–0.007 (0.226)	0.272
18–24 months	1277	0.679 (0.336)	0.674 (0.346)	–0.004 (0.222)	0.501
0–24 months	920	0.690 (0.294)	0.684 (0.349)	0.005 (0.277)	0.551

EQ-5D, EuroQoL 5-Dimensions questionnaire; SD, standard deviation.

Table 5. Patients reporting secondary health events

Secondary health event	Month 6	Month 12	Month 18	Month 24
Total No. responding	1,298	1,473	1,508	1,539
Patients reporting event (%)				
CV disease	12.6	12.5	12.3	11.9
Mental	1.9	2.6	2.7	3.1
Eye/ear	4.2	5.9	5.8	5.5
Respiratory	7.3	8.0	8.6	8.3
Digestive	6.2	6.6	6.9	7.0
Joint	21.9	26.1	29.1	29.7
Injury	2.8	2.8	2.8	2.2
Nervous	1.1	1.1	1.5	1.4
Infection	5.8	5.8	6.8	6.6
Cancer	3.3	2.3	3.2	3.4
Diabetes complications	10.2	8.2	9.4	9.1
Other	5.2	6.1	7.1	7.3

CV, cardiovascular.

Table 6. Adjusted EQ-5D utility scores

	Month 1[a]	Month 6	Month 12	Month 18	Month 24
EQ-5D	0.767	0.703	0.785	0.801	0.801
Prospective	–	0.143	0.088	0.055	0.073
MI	0	–	–	–	–
Angina	–0.043	–0.035	–0.039	–0.021[b]	–0.047
Stroke	–0.136	–0.028[b]	–0.197	–0.128[b]	0.026[b]
Female	–0.075	–0.054	–0.058	–0.019[b]	–0.036
Age	–0.002	–0.003	–0.002	–0.001[b]	–0.002
Weight	–0.002	–0.001	–0.001	–0.001[b]	0.000[b]
Diabetes	–0.106	–0.061	–0.072	–0.074	–0.063
Smoker	–0.149	–0.088	–0.109	–0.130	–0.116
Wheelchair	–0.363	–0.236	–0.276	–0.285	–0.351
CVD	–	–0.111	–0.113	–0.127	–0.090
Mental	–	–0.291	–0.192	–0.226	–0.307
Eye/ear	–	–	–	–0.115	–
Respiratory	–	–0.174	–0.127	–0.064	–
Digestive	–	–0.110	–	–	–
Joint	–	–0.174	–0.215	–0.206	–0.230
Injury	–	–	–0.129	–0.108	–
Nervous	–	–	–0.218	–0.146	–0.161
Infection	–	–	–	–0.092	–0.107
Diabetes	–	–	–	–	–
Cancer	–	–	–	–	–
Other	–	–0.085	–0.073	–0.108	–0.112

CVD, cardiovascular disease; EQ-5D, EuroQoL 5-Dimensions questionnaire; MI, myocardial infarction.

[a]For discussion and presentation of regression model results, the initial survey was estimated to have been completed 1 month after the qualifying event.

[b]Utility decrement or increase not considered significant.

Figure

Figure 1. Adjusted EQ-5D by qualifying event over time. Note: Results of the English Health Survey (2003 publication) for individuals aged 68 years were used as a pre-event baseline. Initial survey completion estimated to have occurred 1 month after the qualifying event. EQ-5D, EuroQoL 5-Dimensions questionnaire