Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Health-related quality-of-life implications of cardiovascular events in individuals with type 2 diabetes mellitus: A subanalysis from the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-TIMI 53 trial

Andrew H. Briggs [a,*], *Deepak L. Bhatt* [b], *Benjamin M. Scirica* [b], *Itamar Raz* [c], *Karissa M. Johnston* [d], *Shelagh M. Szabo* [d], *Klas Bergenheim* [e], *Jayanti Mukherjee* [f], *Boaz Hirshberg* [g], *Ofri Mosenzon* [c]

[a] *Health Economics & Health Technology Assessment, Institute of Health & Wellbeing, University of Glasgow, 1 Lilybank Gardens, Glasgow G12 8RZ, United Kingdom*

[b] *TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA*

[c] *Diabetes Unit, Hadassah Hebrew University Hospital, PO Box 12000, Jerusalem 91120, Israel*

[d] *Broad Street Health Economics & Outcomes Research, 4016 Glen Dr, Vancouver V5V 4T3, Canada*

[e] *AstraZeneca, 431 83 Molndal, Sweden*

[f] *Bristol-Myers Squibb, 5 Research Parkway, Wallingford, CT 06492, USA*

[g] *MedImmune, One Medimmune Way, Gaithersburg, MD, 20878, USA*

ARTICLE INFO

Article history:
Received 14 June 2016
Received in revised form
10 December 2016
Accepted 29 December 2016
Available online 23 January 2017

Keywords:
Health-related quality of life
Cardiovascular
Diabetes mellitus

ABSTRACT

Background: The impact of cardiovascular complications on health-related quality-of-life (HRQoL) in type 2 diabetes mellitus has not been clearly established. Using EQ5D utility data from SAVOR-TIMI 53, a large phase IV trial of saxagliptin versus placebo, we quantified the impact of cardiovascular and other major events on HRQoL.

Methods: EQ5D utilities were recorded annually and following myocardial infarction (MI) or stroke. Utilities among patients experiencing major cardiovascular events were analyzed using linear mixed-effects regression, adjusting for baseline characteristics (including EQ5D utility), and compared to those not experiencing major cardiovascular events. Mean utility decrements with standard errors (SE) were estimated as the difference in utility before and after the event.

Findings: The mean EQ5D utility of the sample was 0.776 at all time points, and did not differ by treatment. However, mean baseline and month 12 utilities among those with a major cardiovascular event were 0.751 and 0.714. Mean utilities were 0.691 within 3 months of, 0.691 3–6 months after, and 0.714 6–12 months after, a major cardiovascular event. Cardiovascular event-specific utility decrements were 0.05 (0.007) for major cardiovascular events over the same time periods. Decrements of 0.051 (0.012; myocardial infarction), 0.111 (0.022;

* Corresponding author.
E-mail address: andrew.briggs@glasgow.ac.uk (A.H. Briggs).

http://dx.doi.org/10.1016/j.diabres.2016.12.019

stroke), 0.065 (0.014; hospitalization for heart failure) 0.019 (0.024; hospitalization for hypoglycemia) were estimated; all coefficients were statistically significant.
Interpretation: Consistent with clinical outcomes reported elsewhere, saxagliptin did not improve HRQoL. Cardiovascular complications were associated with significantly decreased HRQoL, most substantial earlier after the event.
Funding: BMS/AZ.

1. Introduction

Type 2 diabetes mellitus (T2DM) and its management can have a dramatic impact on the health-related quality of life (HRQoL) of those afflicted, in particular, among those who develop microvascular and macrovascular complications [1–4]. However, the exact HRQoL impact of macrovascular complications, including major cardiovascular events, among patients with T2DM has not been clearly established. Many of the estimates of the impact of cardiovascular events on HRQoL in T2DM come from cross-sectional studies [1–4]; which were not able to adequately consider the HRQoL impact of pre-existing T2DM and its complications, how these measures change over time, and the additive impact of multiple or recurrent cardiovascular events. The United Kingdom Prospective Diabetes Study (UKPDS), for example, established that while the occurrence of major cardiovascular events could be shown to adversely impact HRQoL, intensive blood glucose control did not improve it [3]. That study group also reported utility [5] values for T2DM health states after major cardiovascular events in T2DM based on a cross-sectional survey of patients as the trial drew to a close [6]. Although macrovascular complications in T2DM are severe, they remain relatively rare; robust measures from a large international sample of patients with T2DM would be helpful to better understand their HRQoL impact.

Saxagliptin (Onglyza, AstraZeneca and Bristol-Myers Squibb) is a selective dipeptidyl peptidase 4 (DPP-4) inhibitor that improves glycemic control compared to placebo [7]. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) – Thrombolysis in Myocardial Infarction (TIMI) 53 multicentre randomized controlled phase IV trial evaluated the safety and efficacy of saxagliptin with respect to cardiovascular outcomes in patients with T2DM who are at risk for cardiovascular events. Although DPP-4 inhibition with saxagliptin improved glycemic control, it did not significantly increase or decrease the rate of major cardiovascular events in the SAVOR-TIMI 53 trial, other than heart failure [8,9]. Given that almost 10% of the SAVOR-TIMI 53 population experienced an ischemic cardiovascular event over the follow up-period, and that SAVOR-TIMI 53 was specifically powered to rigorously evaluate their frequency, the SAVOR-TIMI 53 trial dataset represents a unique opportunity to further explore the burden of cardiovascular events among those with T2DM. In the SAVOR-TIMI 53 trial, the occurrence of composite endpoints describing ischemic and overall cardiovascular events was equivalent in the saxagliptin and placebo arms. However, the proportion of patients hospitalized for heart failure was statistically significantly higher in the saxagliptin arm (3.5% vs. 2.8%; $p = 0.007$). While the proportion of those hospitalized for hypoglycemia was numerically higher in the saxagliptin arm, this difference was not statistically significant (0.6% vs. 0.5%; $p = 0.33$).

In addition to the clinical data collected with the SAVOR-TIMI 53 trial, regular HRQoL data, in the form of the the EuroQoL-5 dimension (EQ-5D) multi-attribute survey,[10] were also collected. Assessments were conducted at baseline, during routine assessments, and also following a major clinical event. These longitudinal data from a large population of patients may help to understand the impact of major cardiovascular events on HRQoL in T2DM, considering baseline HRQoL status.

The objectives of this analysis were to describe the HRQoL of the SAVOR-TIMI 53 trial population; compare mean utilities over time according to treatment arm; quantify the impact of major cardiovascular events on EQ5D utilities; and compare utilities over time among those experiencing, and not experiencing, major cardiovascular events. As an exploratory objective, we also evaluated the impact of hospitalization for heart failure or hypoglycemia on EQ-5D utilities.

2. Methods

2.1. *SAVOR-TIMI 53 trial conduct*

This is a secondary analysis of HRQoL data collected as part of SAVOR-TIMI 53. SAVOR-TIMI 53 included 16,492 patients with documented T2DM and either a history of previous cardiovascular events or multiple risk factors for vascular disease, enrolled from 788 sites worldwide and followed for a median of 2.1 years, randomized 1:1 to saxagliptin or placebo. Both patients who had prior treatment with glucose-lowering medication (with the exception of incretin-based therapy), and treatment-naive patients, were enrolled. The full eligibility criteria and further details of the study conduct have been reported previously [8]. The primary efficacy and safety endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke. The secondary efficacy endpoint included the primary composite endpoint plus hospitalization for heart failure, coronary revascularization, or unstable angina [8]. For the HRQoL analyses reported here, the secondary endpoint from SAVOR-TIMI 53 was used, to incorporate any HRQoL impacts of hospital-

ization for heart failure, which was of particular interest; this event was also considered individually. Together, the events comprising the secondary endpoint from SAVOR-TIMI 53 were termed, 'major cardiovascular events'. While not included in the composite endpoint, hospitalized hypoglycemic events are of clinical interest, and the HRQoL impact of these events was also assessed by comparing HRQoL assessments before and after such an event.

2.2. *Health-related quality of life impact assessment*

As part of the routine assessments within SAVOR-TIMI 53, data from the EuroQOL-5 dimension (EQ-5D) survey were collected. The EQ-5D survey measures HRQoL impacts for five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on three levels of 1 (no impact), 2 (moderate impact) and 3 (severe impact). Combinations of responses to the domain questions result in 243 unique health states to which respondents can be assigned; this can be formally synthesized to a single utility value on a scale of 0 (corresponding to being dead) to 1 (representing full health). The EuroQol group's UK-specific value set was used to generate utility values based on the domain scores [11].

EQ-5D assessments were performed at baseline, 12 months, 24 months, and study completion; and at semi-annual visits, among patients who had experienced non-fatal myocardial infarction or ischaemic stroke since their previous visit (Fig. 1). Although the SAVOR-TIMI 53 protocol indicated EQ-5D administration linked to the incidence of an event, there may have been up to six months' lag time between the event and the administration of the instrument. For non-ischemic events and hypoglycemic events, additional dedicated EQ-5D assessments were not performed, and subsequent EQ-5D data were not available until the following routine scheduled assessment.

In addition to and at the same time as the EQ-5D, all patients also completed the EQ-5D visual analogue scale (VAS).

2.3. *Analysis*

The baseline characteristics of the sample and the frequency of EQ-5D data measurement were summarized. Continuous variables were characterized by means and 95% confidence intervals. Categorical variables were characterized by frequency and percent distributions, and statistically compared between groups using a chi-squared test. Categorical distributions of scores on individual EQ-5D domains were tabulated, and EQ-5D utility values summarized; overall, at each individual visit, and following a major cardiovascular event. EQ-5D utility data were summarized both in terms of the mean absolute utility value specific to the health states of interest; but also as utility decrements, or the difference in utility score between health states, reflecting the incremental HRQoL impact of major cardiovascular events on utility. Some individuals had multiple events, and utilities were all measured relative to the most recent cardiovascular event.

Mixed effects regression models were fit, including individual-level intercepts to account for the longitudinal data structure in which individuals contributed multiple, potentially correlated, observations. We fit an additive linear mixed model, and explanatory variables included: treatment arm, trial visit number, age, sex, baseline utility, and a time-dependent variable for history of a cardiovascular event. A covariate describing participant race was also considered, but as the estimated coefficients were both statistically non-significant and small in absolute value race was excluded from the final models. EQ-5D measurements may have occurred up to six months after a major cardiovascular event, and up to one year after hospitalized hypoglycemic events, such that, depending on the ongoing implications of the event, its impact may be partially or fully missed by the EQ-5D measure. To account for this, time between EQ-5D measurement and cardiovascular event was included as a categorical variable, stratified into categories of <3 months, 3–6 months, and 6–12 months.

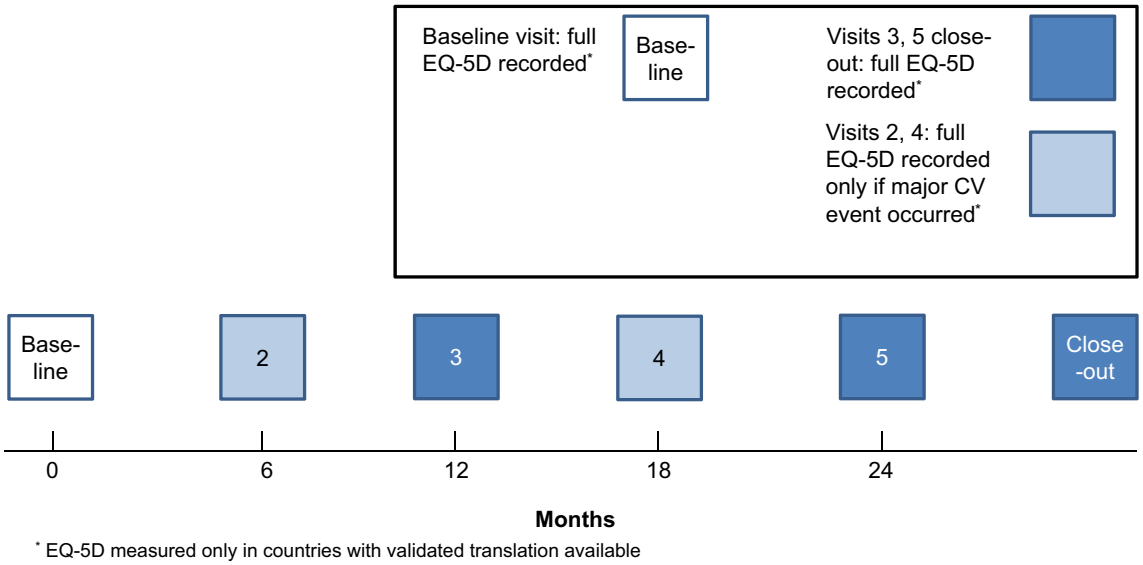

Fig. 1 – Schematic describing SAVOR protocol for EQ-5D data collection. Major cardiovascular (CV) events include elements of primary composite endpoint: fatal CV event, non-fatal myocardial infarction, non-fatal ischaemic stroke.

As an exploratory analysis to assess the added impact of additional cardiovascular events on utility, a simple linear regression model was fit describing utility measures elicited following any cardiovascular event, with an exploratory variable indicating the number of previous cardiovascular events.

2.4. Role of the funding source

This study was funded by AZ/BMS, and co-authors from AZ/BMS participated in the in study activities as outlined in the Contributors section. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Description of the sample

Baseline clinical and demographic characteristics are presented by treatment arm in Table 1. In addition to the routine EQ-5D measurements collected at baseline, 12 months, 24 months, and at the closeout visit, 594 additional measurements were collected among 535 trial participants at the semi-annual visit following a major cardiovascular event (Table 1). In all, 1437 (8.7%) of the population met the inclusion criteria of experiencing a major cardiovascular event during SAVOR-TIMI 53 and having at least one subsequent EQ-5D survey administered. The EQ-5D survey was administered within 3 months of the event in 549 individuals (3.3%), from 3 to 6 months from the event in 438 individuals (2.7%), and within 6–12 months of the event in 741 individuals (4.5%) (see Table 2).

In the primary SAVOR-TIMI 53 analysis, 2093 individuals experienced the secondary composite cardiovascular endpoint. While the requirement imposed here of having an EQ-5D survey administered following the event resulted in a smaller number of events included, the distribution of events between the saxagliptin and placebo treatment arms was similar in both samples. Note that 656 individuals experienced a major cardiovascular event but did not have a subsequent EQ-5D measurement, and 529 individuals died of cardiovascular causes, suggesting that a majority of the excluded individuals did not contribute EQ-5D results due to cardiovascular death.

Hospitalization for heart failure occurred in 373 individuals with a subsequent EQ-5D result, while 79 individuals were hospitalized with a hypoglycemic event and a subsequent EQ-5D result.

3.2. EQ5D utility results

Mean utility values did not vary by treatment arm, and were virtually unchanged over the time horizon of the SAVOR-TIMI 53 trial. Mean EQ-5D utilities were 0.776 at baseline and all subsequent time points; and the width of all confidence intervals was within ±0.01 (Fig. 2). Therefore, there was no evidence that saxagliptin was associated with a difference in HRQoL relative to placebo. Despite this lack of difference in utilities between the treatment arms, cardiovascular events had a substantial impact on HRQoL and utilities.

Mean utility values at baseline are presented in Fig. 3, stratified by whether an individual experienced a major cardiovascular event by the end of the trial. The mean baseline utility of 0.778 (95% CI: 0.775–0.783) was significantly higher among those who never experienced a major cardiovascular event compared to those who experienced a major cardiovascular event during SAVOR-TIMI 53 (0.751 (0.739–0.763)). A mean utility decrement of 0.050 (SE = 0.007) was observed

Table 1 – Baseline clinical and demographic characteristics (*n*, %).

	Overall (*n* = 16,488)	Saxagliptin (*n* = 8279)	Placebo (*n* = 8209)
Male sex	11,034 (66.9)	5511 (66.6)	5523 (67.3)
Age at diagnosis (mean, SD)			
18–39 years	1 (0.0)	1 (0.01)	0 (0.0)
40–59 years	4030 (24.4)	2031 (24.5)	1999 (24.4)
⩾60 years	12,457 (75.6)	6247 (75.5)	6210 (75.6)
Time since diagnosis (years median, interquartile range)	10.3 (5.3–16.7)	10.3 (5.3–16.7)	10.3 (5.3–16.6)
Baseline HbA1c			
Major cardiovascular event during SAVOR and subsequent EQ-5D measurement	1437 (8.7)	731 (8.8)	706 (8.6)
Hospitalization for heart failure during SAVOR and subsequent EQ-5D measurement	373 (2.2)	214 (2.6)	159 (1.9)
Hospitalization for hypoglycemia during SAVOR and subsequent EQ-5D measurement	79 (0.5)	45 (0.5)	34 (0.4)
Myocardial infarction during SAVOR and subsequent EQ-5D measurement	415 (2.5)	205 (2.5)	210 (2.6)
Stroke during SAVOR and subsequent EQ-5D measurement	208 (1.3)	112 (1.4)	96 (1.2)
Timing of cardiovascular event compared to EQ5D elicitation[*]			
<3 months	549 (3.3)	282 (3.4)	267 (3.3)
3 < 6 months	438 (2.7)	219 (2.6)	219 (2.7)
6 < 12 months	741 (4.5)	386 (4.7)	355 (4.3)

[*] Individuals experiencing more than one major cardiovascular event could appear in more than one time category.

Table 2 – Number of EQ-5D measurements recorded by visit in the SAVOR trial.

	Overall	Saxagliptin	Placebo
Baseline	16,480	8,277	8,203
12 months	14,336	7,230	7,106
24 months	6,831	3,480	3,351
Closeout*	13,954	7,036	6,918
Following major cardiovascular event	1,437	731	706
Within 3 months of event	549	282	267
Within 3–6 months of event	438	219	219
Within 6–12 months of event	741	386	355
Additional elicitation outside of routine trial visits	535	253	282

* Mean time to closeout visit: 23.8 months.

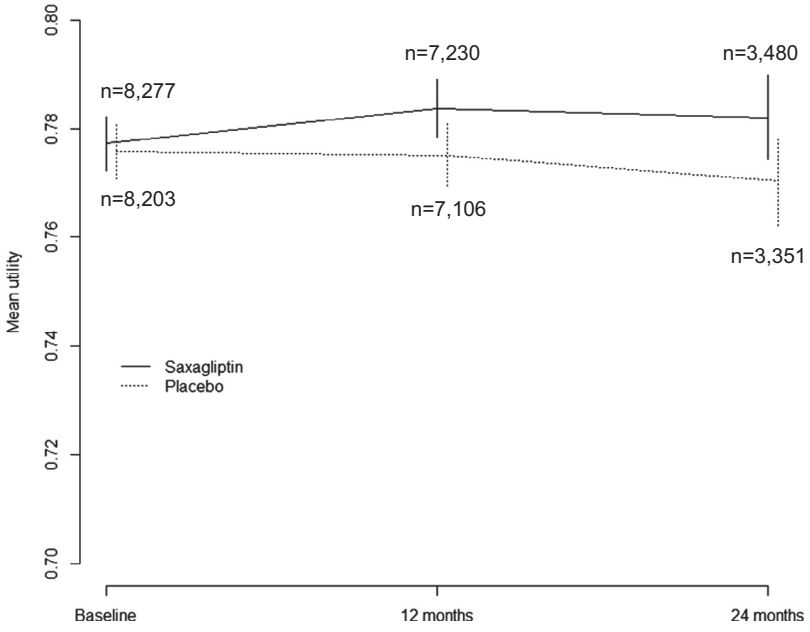

Fig. 2 – Mean EQ-5D utility values over time, according to treatment arm, among the SAVOR trial population.

among the 1437 individuals with EQ-5D results available after a first major cardiovascular event. A utility decrement of 0.065 (SE = 0.014) was observed among individuals after hospitalization for heart failure ($n = 373$), compared to 0.051 (SE = 0.012) after myocardial infarction ($n = 415$) and 0.111 (SE = 0.022) after stroke ($n = 208$). A utility decrement of 0.019 (SE = 0.024) was observed following a hypoglycemic event while hospitalized ($n = 79$).

For major cardiovascular events, the HRQoL and utility impact was most substantial in the initial post-event period; mean utility values among the subgroup of individuals experiencing a major cardiovascular event, are presented in Fig. 4 by time since the event. Mean utility was observed to decrease immediately after the event, and then gradually increase, although it did not return to baseline by 12 months. Further decreases were then observed at 24–30 months post-event, which may reflect long-term clinical consequences of the event, although relatively small sample sizes at this time point, and corresponding wide variability, limits the interpretation of observed trends. A clear temporal trend was not observed for hospitalized hypoglycemic events (*data not shown*), although the sample size was notably smaller which limited the power for analysis.

Results of the normal (identity link) generalized linear mixed model are reported in Table 3, and coefficients illustrate the additive impact of each variable on utility values. Increasing age was associated with a statistically significant decrease, and male sex associated with a significant and notable absolute increase of 0.033, in utility. After accounting for individual-level trends via random effects, baseline HRQoL was still associated with a statistically significant increase in utility: a 0.1 increase on the utility scale was associated with an estimated additive increase of 0.056. History of a cardiovascular event had a significant negative impact on utility, with the magnitude of the impact increasing with proximity to the event. On the additive scale, the decrease in utility ranged from 0.035 for events occurring 6–12 months prior to EQ-5D elicitation, to 0.057 for events occurring within 3 months prior to EQ-5D elicitation.

The impact of major cardiovascular events on utility values waned with greater time since the event. After a cardiovascular event, mean utilities were 0.691, 0.691, and 0.714

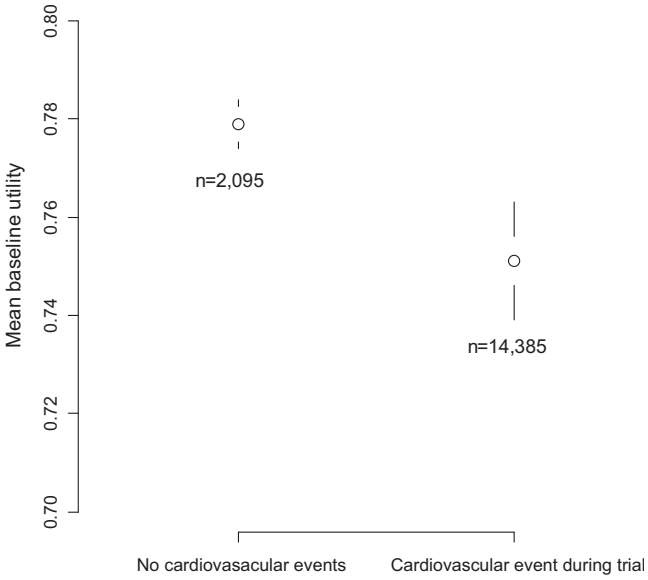

Fig. 3 – Mean baseline EQ-5D utility values and 95% confidence interval, according to CV event status, among the SAVOR trial population.

(within 3 months, 3–6 months, and 6–12 months after the event, respectively). Predicted utility values were similar between saxagliptin and placebo *(data not shown)*. Utilities were similar across trial visits, and the only notable difference was a trend towards lower utilities on follow-up measurements, which is expected as such measurements were triggered by major clinical events.

3.3. EQ5D utilities and domain scores following a cardiovascular event

The distributions of EQ-5D domain at baseline and closeout in the overall SAVOR-TIMI 53 population, and at baseline and following a major cardiovascular event in those that experienced them, are presented in Table 4. Among those who ever experienced a major cardiovascular event during the trial, EQ5D domain distributions were less favorable at baseline compared to the overall population, particularly for the mobility, pain/discomfort, and usual activities domains. Domain scores dropped even further after experiencing a major cardiovascular event. For the mobility domain, among those who ever experienced a cardiovascular event during the trial, the proportion reporting at least a moderate impact increased from 49.5% at baseline, to 54.4% following a cardiovascular event, compared with 42.1% of the overall population at baseline.

In the exploratory regression analysis of utility following subsequent major cardiovascular events, the intercept was 0.753 ($p < 0.001$), with a coefficient for number of cardiovascular events of −0.038 ($p < 0.001$), indicating an additional utility decrement of 0.038 for each additional event experienced.

The findings from the analyses of the EQ-5D VAS data were consistent with those of the EQ-5D for all outcomes assessed.

In addition to the linear regression model presented here, a gamma generalized linear model for utilities, in which covariates were modeled to have a multiplicative rather than additive effect, was also considered and fit to the data. For clarity, only the linear model results are presented here, as results were generally consistent across the two models, and diagnostics indicated a better fit for the linear model.

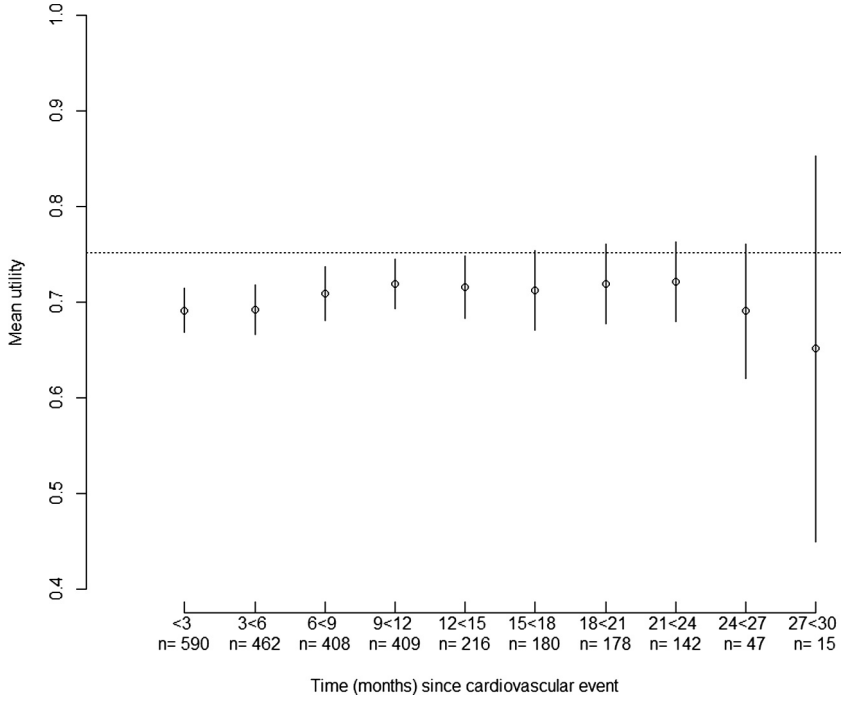

Fig. 4 – Mean (±95% confidence interval) EQ-5D utility values over time since a cardiovascular event, among the subgroup of the SAVOR trial population who experienced a major cardiovascular event.

Table 3 – Mixed effects linear regression results of EQ-5D converted utility values at all recorded visits in the SAVOR trial (UK tariffs)[*], n = 16,457 individuals included.

Variable	Estimated coefficient (additive on utility scale)	Standard error	p-Value
Intercept	0.375	0.012	<0.001
Visit			
12 month (reference)	0	NA	NA
24 month	−0.009	0.002	<0.001
Closeout	−0.005	0.002	0.008
Additional elicitation following cardiovascular event	−0.023	0.008	0.003
Treatment arm			
Placebo (reference)	0	NA	NA
Saxagliptin	0.006	0.003	0.129
Age (years)	−0.001	0.000	<0.001
Sex			
Female (reference)	0	NA	NA
Male	0.033	0.003	<0.001
Baseline utility	0.560	0	<0.001
History of cardiovascular event			
None (reference)	0	NA	NA
<3 months	−0.057	0.008	<0.001
3 < 6 months	−0.043	0.009	<0.001
6 < 12 months	−0.035	0.007	<0.001
History of on-trial hypoglycemic event			
No history (reference)	0	NA	NA
History	−0.027	0.020	0.157

[*] UK-specific value sets for health states were applied to EQ-5D results in order to derive utility values relevant to a UK population.

While the assumption of normal distribution within the linear model does statistically allow for utility predictions greater than 1.0, given the distribution of the data and variability, this was not a practical concern.

4. Discussion

Macrovascular complications, including the development of cardiovascular disease, are a major source of burden for individuals with T2DM [12]. However, the exact magnitude of this burden has not been established, particularly with respect to patient-reported outcomes such as HRQoL. The SAVOR-TIMI 53 trial provided a unique opportunity to examine the relationship between cardiovascular events and HRQoL in individuals with T2DM, given its large sample size and considerable follow-up period, and that the trial was powered to rigorously evaluate the frequency of cardiovascular events in a T2DM population [8,13]. The SAVOR-TIMI 53 trial protocol included measurement of EQ-5D data from participants at baseline, throughout study follow-up, and within 6–12 months following cardiovascular events. As a result, sufficient data were available to compare HRQoL outcomes in individuals who did and did not experience cardiovascular events, and over time to assess the temporal impact of an event on subsequent HRQoL.

While consistent with SAVOR-TIMI 53 trial results reported elsewhere for clinical events [13], that saxagliptin did not significantly improve HRQoL, cardiovascular events were associated with a significant decrease in HRQoL that was most substantial in the initial post-event period. After adjusting for age, sex, treatment arm, and baseline HRQoL, utility decrements associated with cardiovascular events were 0.059 within 3 months of the event, 0.045 3–6 months after the event, and 0.037 6–12 months after the event; the statistically significant reductions in health state utility observed initially following a cardiovascular event dampened over time. These findings highlight the need to elicit utilities proximal to the occurrence of the events of interest, in order to accurately and comprehensively quantify the HRQoL burden. Applying these utility decrements for 12 months after the event, results in an estimated reduction of approximately half a month of quality-adjusted life. When this total decrement in quality-adjusted life years is applied to the difference in major cardiovascular event rates across treatment arms (8.8% vs. 8.6%), the treatment effect per individual is estimated to be 0.000089 quality-adjusted life years, consistent with the finding reported here of no significant association between treatment and HRQoL.

These analyses also demonstrated that individuals who experience cardiovascular events have poorer baseline function and HRQoL, compared to those who did not experience cardiovascular events. This is consistent with other studies, in which similar trends have been noted[6]. The less favorable EQ5D scores (particular for mobility, pain/discomfort and usual activities) and lower mean baseline EQ5D utilities document HRQoL impairments prior to the occurrence of the index event, and highlight the importance of adjusting utilities for baseline health status. The analyses conducted

Table 4 – The *n* (%) of SAVOR subjects reporting each EQ-5D domain score at baseline and closeout; and at baseline and after a major event, among the subgroup of SAVOR subjects experiencing cardiovascular events (*n* = 2568 post-event measures in 1437 individuals – note that 1424 have measures at baseline).

		Overall population (*N* = 16,488*)				Those experiencing cardiovascular events (*N* = 2,568)			
		Baseline		Overall		Baseline		After cardiovascular event	
Domain	Level	*n*	%	*n*	%	*n*	%	*n*	%
Mobility	1	9,460	57.9	8,053	59.4	719	50.5	1,171	45.6
	2	6,838	41.9	5,432	40	703	49.4	1,369	53.3
	3	40	0.2	83	0.6	2	0.1	28	1.1
Self-care	1	14,711	90	12,003	88.5	1,269	89.1	2,111	82.2
	2	1,524	9.3	1,429	10.5	146	10.3	409	15.9
	3	102	0.6	131	1	9	0.6	48	1.9
Usual activities	1	11,852	72.5	9,826	72.4	965	67.8	1,509	58.8
	2	4,191	25.7	3,424	25.2	428	30.1	913	35.6
	3	295	1.8	316	2.3	31	2.2	145	5.6
Pain/discomfort	1	7,727	47.3	6,729	49.6	604	42.4	1,036	40.3
	2	7,979	48.8	6,270	46.2	758	53.2	1,362	53
	3	631	3.9	568	4.2	62	4.4	171	6.7
Emotional	1	11,436	70	9,825	72.4	988	69.4	1,675	65.2
	2	4,586	28.1	3,491	25.7	407	28.6	822	32
	3	313	1.9	248	1.8	29	2.0	72	2.8

* Of 16,488 individuals providing any EQ-5D visit, not all individuals provided valid measures for all domains at all visits. For each individual domain and time point, the denominator for calculating percentages is taken to be the total number with a valid measurement for that domain at that time point).

here also identified a potential trend in reduced HRQoL associated with hypoglycemic events in individuals with T2DM, although the study was not specifically powered to study this population. Further investigating this association would be best addressed by a study designed to include a sufficient number of hypoglycemic events.

HRQoL findings for cardiovascular events in T2DM from SAVOR-TIMI 53 are generally consistent with those reported in other studies (below) of HRQoL impacts due to macrovascular complications in individuals with T2DM. The United Kingdom Prospective Diabetes Study (UKPDS) included more than 5000 newly-diagnosed diabetic patients[6]; because the population was not specifically recruited with respect to cardiovascular risk, relatively few events were observed. In the UKPDS, the observed HRQoL impact of cardiovascular events was greater than that observed for SAVOR-TIMI 53, although variability was substantial due to relatively small sample sizes, and the estimates observed in the present analyses were within the range of sampling error. While follow up in the UKPDS was longer (mean follow up time, ten years), SAVOR-TIMI 53 reflects a more contemporary and multinational population than that of the UKPDS, who were recruited between 1977 and 1991 only from the UK. Findings from the present study were consistent with those from three other smaller studies looking at utility decrements following cardiovascular events in diabetes, including another study conducted in 2048 individuals with type 1 or 2 diabetes mellitus and T2DM, which also reported a utility decrement of 0.058 associated with cardiovascular disease [1,2,4]. Within the temporal analyses conducted here, we considered the HRQoL impact by time since event occurrence, and found that impacts on utility were dampened over time. Nonetheless, HRQoL does not tend to return to pre-event levels within one year of the event. We also considered baseline utility for the subgroup of individuals who experienced a cardiovascular event and found it to be significantly lower than the population average, potentially due to ill health experienced in the time prior to the event. This was adjusted for in the statistical modeling to assess the utility impact of the event itself, independent of underlying health status.

The key strength of this study was the rich data source available, specifically, a large study of over 16,000 individuals with extensive follow-up data available. Based on trial inclusion criteria specifying a high cardiovascular risk patient population, this resulted in more than 2500 longitudinal utility elicitations conducted in more than 1400 individuals experiencing a cardiovascular event. The longitudinal nature of the data allowed for characterization of the changing HRQoL impact of a cardiovascular event over time. The collection of baseline utility data allowed for model adjustment by baseline HRQoL status, reflecting the fact that individuals who go on to experience cardiovascular events may have poorer HRQoL in advance of event occurrence related to increased risk factors, and allowing for this to be formally accounted for in the analysis.

Limitations to the study included that, for approximately half of all individuals experiencing a cardiovascular event, the most proximal subsequent utility measurement was 6–12 months following the event. However, more than 500 individuals contributed EQ-5D values within three months of an event, allowing for meaningful assessment of the initial impact of the event on HRQoL. The EQ-5D is a generic HRQoL instrument and while very useful for estimating utility values and allowing standardized comparisons across disease states,

it may not be sensitive to all disease-specific HRQoL impacts. While UK-specific tariffs were used to estimate EQ-5D utilities from the raw data, SAVOR-TIMI 53 was a multinational study with patients recruited at sites worldwide. Using other country-specific tariffs could therefore yield slightly different parameter estimates. Finally, there is the potential for misclassification of outcomes, based on timing of utility elicitations, and this potential bias could impact the results in either direction. Underestimation of utility decrements could occur if a true utility decrement both occurred and resolved between elicitations, such that it is never captured; while overestimation could occur if the utility elicitation occurred very shortly after the event, and the captured utility decrement is assumed until the following visit. In addition, detailed clinical data were not available to characterize the severity of cardiovascular events, so this level of clinical detail was not incorporated into the analysis.

Although these analyses of data from the SAVOR-TIMI 53 trial did not find that saxagliptin improved HRQoL, experiencing cardiovascular events was associated with a significant decrease in HRQoL most substantial in the initial post-event period. These data also suggest a potential relationship between hypoglycemic events and HRQoL; investigating this association would be best addressed by a study designed to include a sufficient number of hypoglycemic events.

Contributors

AHB, KMJ, SMS, and JM contributed to study design, analysis, interpretation, drafting, and critical review of the manuscript. DLB, BMS, IR, and OM contributed to study design, data collection, data interpretation, and critical revision of the manuscript. BH contributed to study design, data collection, data interpretation, and critical revision of the manuscript. KB contributed to study design, analysis, data interpretation, and critical revision of the manuscript.

Declaration of interests

AHB reports personal fees from BMS and AstraZeneca during the conduct of the study; and personal fees from AstraZeneca and BMS, outside the submitted work.

DLB reports grants from AstraZeneca and Bristol-Myers Squibb, during the conduct of the study; grants from Amarin, grants from AstraZeneca, grants from Bristol-Myers Squibb, grants from Eisai, grants from Ethicon, grants from Medtronic, grants from sanofi aventis, grants from The Medicines Company, other from FlowCo, other from PLx Pharma, other from Takeda, personal fees from Duke Clinical Research Institute, personal fees from Mayo Clinic, personal fees from Population Health Research Institute, personal fees and non-financial support from American College of Cardiology, personal fees from Belvoir Publications, personal fees from Slack Publications, personal fees from WebMD, personal fees from Elsevier, other from Medscape Cardiology, other from Regado Biosciences, other from Boston VA Research Institute, personal fees and non-financial support from Society of Cardiovascular Patient Care, non-financial support from American Heart Association, personal fees from HMP Communications, grants from Roche, personal fees from Harvard Clinical Research Institute, other from Clinical Cardiology, personal fees from Journal of the American College of Cardiology, other from VA, grants from Pfizer, grants from Forest Laboratories, grants from Ischemix, other from St. Jude Medical, other from Biotronik, other from Cardax, other from American College of Cardiology, other from Boston Scientific, outside the submitted work.

BMS reports grants from AstraZeneca and Bristol-Myers Squibb, during the conduct of the study; grants from AstraZeneca, grants from Daichi-Sankyo, grants from Poxel, grants from Gilead, grants from Eisai, grants from Merck, personal fees from Gilead, personal fees from Lexicon, personal fees from AstraZeneca, personal fees from Eisai, personal fees from St. Jude's Medical, personal fees from Boston Clinical Research Institute, personal fees from Biogen Idec, personal fees from University of Calgary, personal fees from Elsevier Practice Update Cardiology, personal fees from Forest Pharmaceuticals, personal fees from Dr. Reddy's Laboratory, personal fees from Boehringer Ingelheim, from Covance, from GE Healthcare, from GlaxoSmithKline, from Merck, outside the submitted work.

IR reports personal fees from AstraZeneca/Bristol Myers Squibb, during the conduct of the study; personal fees from Eli Lilly & Co, Merck, Sharlp & Dohme Ltd, NovoNordisk, Sanofi, Orgenesis, SmartZyme Innovation Ltd, Labstyle Innovations Ltd, Boehringer Ingelheim, personal fees from AstraZeneca/Bristol-Myers Squibb (AZ/BMS), Insuline Medical, Gili Medical, Kamada Ltd, FuturRx Ltd, Nephrogenex Inc, Diabetes Medical Center (Tel Aviv, Israel), personal fees from AZ/BMS, Eli Lilly & Co., Johnson & Johnson, MSD Ltd, Novartis Pharma AG, NovoNordisk Inc, Sanofi, Teva, Boehringer Ingenheim, personal fees from Insuline Medical, Labstyle innovations, smartZye innovation Ltd, Orgenesis, Glucome Ltd., outside the submitted work.

KMJ has no competing interests to declare. At the time of the conduct of this work, KMJ was employed by ICON plc.

SMS has no competing interests to declare. At the time of the conduct of this work, SMS was employed by ICON plc.

KB is an employee of AstraZeneca and owns stock in AstraZeneca.

JM is an employee of Bristol-Myers Squibb and owns stock in Bristol-Myers Squibb.

BH is an employee of AstraZeneca.

OM reports grants from Astra Zeneca, during the conduct of the study; grants and other from Astra Zeneca, grants and other from Novo Nordisk, other from Sanofi, other from Eli Lilly, other from MSD, other from Boehringer Ingelheim, other from Novartis, outside the submitted work.

Conflict of interest

The analysis reported here was supported by funding to ICON plc, a contract research organisation, from BMS. KMJ and SMS were employed by ICON at the time of the analysis and AHB has received consulting fees from ICON plc. JM is an employee of BMS.

Acknowledgments

Executive Committee: Eugene Braunwald (Study Chair), Deepak L. Bhatt (Co-Principal Investigator), Itamar Raz (Co-Principal Investigator), Jaime A. Davidson, Robert Frederich (non-voting), Boaz Hirshberg (non-voting), Ph. Gabriel Steg.

REFERENCES

[1] Wexler DJ, Grant RW, Wittenberg E, Bosch JL, Caqliero E, Delahanty L, et al. Correlates of health-related quality of life in type 2 diabetes. Diabetologia 2006;49(7):1489–97.
[2] Solli O, Stavem K, Kristiansen IS, et al. Health-related quality of life in diabetes: the associations of complications with EQ-5D scores. Health Qual Life Outcomes 2010;8(18).
[3] UK Prospective Diabetes Study (UKPDS) Group. Quality of life in type 2 diabetes patients is affected by complications but not be intensive policies to improve blood glucose or blood pressure control (UKPDS 37). Diabetes Care 1999;22 (7):1125–36.
[4] Coffey JT, Brandle M, Zhou H, Marriott D, Burke R, Tabaei BP, et al. Valuing health-related quality of life in diabetes. Diabetes Care 2002;25(12):2238–43.
[5] Torrance GW. Measurement of health state utilities for economic appraisal. J Health Econ 1986;5(1):1–30.
[6] Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making 2002;22(4):340–9.
[7] Frederich R, Alexander JH, Fiedorek FT, Donovan M, Berglind N, Harris S, et al. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. Postgrad Med 2010;122(3):16–27.
[8] Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369(14):1317–26.
[9] Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. The design and rationale of the saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus-thrombolysis in myocardial infarction (SAVOR-TIMI) 53 study. Am Heart J 2011;162(5):818–25.
[10] EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 1990;16 (3):199–208.
[11] Szende Agota, Oppe Mark, Devlin Nancy, editors. EQ-5D value sets: inventory, comparative review and user guide. EuroQol group monographs, vol. 2.
[12] Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabetes 2008;26:77–82.
[13] Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014;130(18):1579–88.