Within-Trial Evaluation of Medical Resources, Costs, and Quality of Life Among Patients With Type 2 Diabetes Participating in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL)

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OBJECTIVE

To compare medical resource use, costs, and health utilities for 14,752 patients with type 2 diabetes who were randomized to once-weekly exenatide (EQW) or placebo in addition to usual diabetes care in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL).

RESEARCH DESIGN AND METHODS

Medical resource use data and responses to the EuroQol 5-Dimension (EQ-5D) instrument were collected at baseline and throughout the trial. Medical resources and medications were assigned values by using U.S. Medicare payments and wholesale acquisition costs, respectively. Secondary analyses used English costs.

RESULTS

Patients were followed for an average of 3.3 years, during which time those randomized to EQW experienced 0.41 fewer inpatient days (7.05 vs. 7.46 days; relative rate ratio 0.91; $P = 0.05$). Rates of outpatient medical visits were similar, as were total inpatient and outpatient costs. Mean costs for nonstudy diabetes medications over the study period were ~$1,600 lower with EQW than with placebo ($P = 0.01$). Total within-study costs, excluding study medication, were lower in the EQW arm than in the placebo arm ($28,907 vs. $30,914; $P \leq 0.01$). When including the estimated cost of EQW, total mean costs were significantly higher in the EQW group than in the placebo group ($42,697 vs. $30,914; $P < 0.01$). With English costs applied, mean total costs, including exenatide costs, were £1,670 higher in the EQW group than the placebo group (£10,874 vs. £9,204; $P < 0.01$). There were no significant differences in EQ-5D health utilities between arms over time.

CONCLUSIONS

Medical costs were lower in the EQW arm than the placebo arm, but total costs were significantly higher once the cost of branded exenatide was incorporated.

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Diabetes mellitus imposes substantial clinical, social, and economic burdens globally. In 2017 alone, an estimated 5 million deaths were attributable to diabetes among ~ 451 million adults with the condition worldwide (1). Global health expenditures for patients with diabetes are roughly $850 billion per year (1).

People with type 2 diabetes are at increased risk of coronary heart disease and ischemic stroke, and have a higher risk of death from any cause and from cardiovascular causes (2,3). Suboptimal blood glucose control leads to microvascular and macrovascular complications, which represent main sources of direct and indirect medical expenditures and reduced health-related quality of life. Pharmacologic management options for type 2 diabetes have multiplied as the understanding of the underlying pathophysiology has evolved. Large-scale cardiovascular outcome trials, performed in order to assess the safety of new diabetes drugs, offer the opportunity to investigate both the clinical and economic impacts of these treatments. Data on resource use and quality of life are essential inputs into comparative effectiveness and cost-effectiveness analyses that may inform reimbursement decisions and health technology assessments. Because these assessments are crucial to governing patients' access to and cost-sharing for new drugs, private and public payers are increasingly demanding high-quality, unbiased, and comparative data on drugs used in routine medical practice, such as those generated from pragmatic randomized trials. Analyses of these data not only provide objective comparisons over moderately long time periods, which are of interest to many private payers, they also provide greater transparency about medical resource and health utility inputs applied in model-based cost-effectiveness analyses that project outcomes over longer time periods.

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL), a randomized, placebo-controlled pragmatic study, was designed to assess the long-term cardiovascular safety and efficacy of once-weekly exenatide (EQW), a glucagon-like peptide-1 receptor agonist (GLP-1 RA), in patients with type 2 diabetes who had or did not have previous cardiovascular disease (4,5). One of the prespecified objectives of the trial was to compare medical resource use by, direct medical costs of, and health-related quality of life of patients in the treatment arms observed during the follow-up period (4). Although EXSCEL was designed to maintain similar glycemic control in both study arms, we hypothesized that EQW would reduce medical resource use and improve health-related quality of life secondary to its previously documented beneficial effects on lipids, blood pressure, and weight, and fewer drug-related adverse events.

RESEARCH DESIGN AND METHODS

EXSCEL Trial Design and Results

The study design and results of the trial have been reported (4,5). Briefly, patients with type 2 diabetes with a glycated hemoglobin level of 6.5–10.0% (48–86 mmol/mol) and any level of cardiovascular risk were eligible for participation. Participants were randomly assigned to receive either 2 mg/week EQW or matching placebo in addition to usual diabetes care. The primary composite outcome was time to the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

A total of 14,752 patients from 35 countries were randomized into EXSCEL and included in the intention-to-treat (ITT) analysis; of these patients, 73.1% had a history of cardiovascular disease. Participants in both study groups were followed for a median of 3.2 years (mean 3.3 years). By the study's end, 44% of participants had discontinued the study medication (EQW 43.0%, placebo 45.2%), although follow-up continued after treatment was discontinued. Only 0.5% of patients were lost to follow-up.

EXSCEL showed that EQW was noninferior to placebo for the primary composite cardiovascular outcome (hazard ratio [HR] 0.91 [95% CI 0.83–1.00]; $P < 0.001$ for noninferiority). The numerical advantage of EQW over placebo, however, did not reach statistical significance ($P = 0.06$ for superiority). All-cause mortality was 6.9% in the EQW group and 7.9% in the placebo group (HR 0.86 [95% CI 0.77–0.97]), but this difference was only nominally statistically significant given the prespecified hierarchical testing. The rate of severe hypoglycemia did not differ significantly between treatment groups (risk ratio 0.85 [95% CI 0.67–1.08]).

Medical Resource Use and Quality-of-Life Data

A detailed cost and data analysis plan was developed and finalized in August 2016. It served to guide cost assignments for and statistical analyses of medical resource use, cost, and health utility data. Detailed data on medical resource use, including hospitalizations, major cardiovascular and noncardiovascular procedures, study visits, outpatient visits to usual diabetes care providers and other providers, concomitant cardiovascular and diabetes medications, and study medications, were collected by using the trial's case report form for all randomized patients at 1 week, at 2, 6, and 12 months, and every 6 months thereafter through the end of follow-up.

Admission and discharge dates and primary discharge diagnoses were collected for each hospitalization. Discharge diagnoses were recorded as one of 52 prespecified diagnoses or as free text. Daily doses and drug names were collected for concomitant diabetes medications, whereas concomitant cardiovascular medications were recorded by drug class. Specific start or stop dates were not collected. For the cost analysis, if reported drug use differed between two consecutive visits, the change in treatment was assumed to have occurred halfway between visits. Total study drug doses taken by participants were collected, accounting for intermittent and premature discontinuation.

The EuroQol 5-Dimension instrument (EQ-5D), a preference-based measure of health-related quality of life, was administered to patients at baseline; 1 week; 2, 6, and 12 months; and then every 6 months thereafter through the end of the study. Over the course of the trial, the 5-level version (EQ-5D-5L) was phased in to replace the 3-level version (EQ-5D-3L) as appropriate translations of the EQ-5D-5L became available. In order to manage the two versions, responses to the EQ-5D-5L were converted to EQ-5D-3L responses by using a crosswalk developed by the EuroQol Group (6). Responses on the five items of EQ-5D-3L were then converted to U.S. (7) and U.K. utility weights (8). After patients died, subsequent EQ-5D utilities were set to zero.

Cost Assignment

For the main U.S. and U.K. analyses, we applied a "fully-pooled, one-country costing" approach to assign costs (9). In the U.S. cost analysis, sources for unit costs included 2017 Medicare payments for inpatient and outpatient care, and wholesale

acquisition costs for concomitant medications, with a 23.1% discount applied to branded EQW in order to approximate net costs after rebates for a branded medication (10). For the English cost analysis, unit costs were sourced from the National Schedule of Reference Costs and the Prescription Cost Analysis database (11,12). We adjusted length of stay (LOS) to allow for differences in LOS between countries for the same discharge diagnosis, using an approach previously used in other large multinational trials (13,14). Details of cost assignments are included in the Supplementary Data. All costs incurred after the 1st year were discounted at 3% per year in the U.S. analysis and 3.5% per year in the U.K. analysis.

Statistical Analysis

Statistical analysis was guided by the agreed cost and data analysis plan, with an initial focus on reporting descriptive statistics, including means and SDs, and mean cumulative counts of hospitalizations per patient that account for censoring across time (15). Mean health utility weights across time were plotted by treatment group.

Generalized linear models were applied in order to compare medical resource use and costs between treatment arms by using PROC GLIMMIX in SAS/STAT software (version 9.4; SAS Institute); MEGLM in Stata software (see below) was used when GLIMMIX had convergence issues. All medical resource use and cost models were specified with treatment assignment as a fixed effect and log-transformed follow-up duration as an offset variable in order to account for varying durations of observation across patients. Countries were modeled as random intercepts in order to allow for different rates of medical resource use and costs in the placebo group across countries. For comparisons of medical resources, models were specified with negative binomial error distributions and log links. For cost comparisons, γ error distributions and log links were specified. Exponentiating the parameter estimates provided estimates of relative rates for resource use and means ratios for costs with exenatide relative to placebo.

Health utilities were analyzed by using multilevel mixed-effects linear regression models (MEGLM or MIXED) in Stata software (version 14.2; StataCorp LLC). Both countries and patients were modeled as random intercepts in order to account for the correlated measurements across time for each participant and the potential correlation of health utilities within countries. Normal error distributions were specified. Independent variables included baseline health utilities, treatment assignment, time since baseline, and a term representing the interaction between treatment and time.

Sensitivity Analysis

Sensitivity analyses included discounting costs of nonstudy concomitant diabetes and nondiabetes medications, not applying

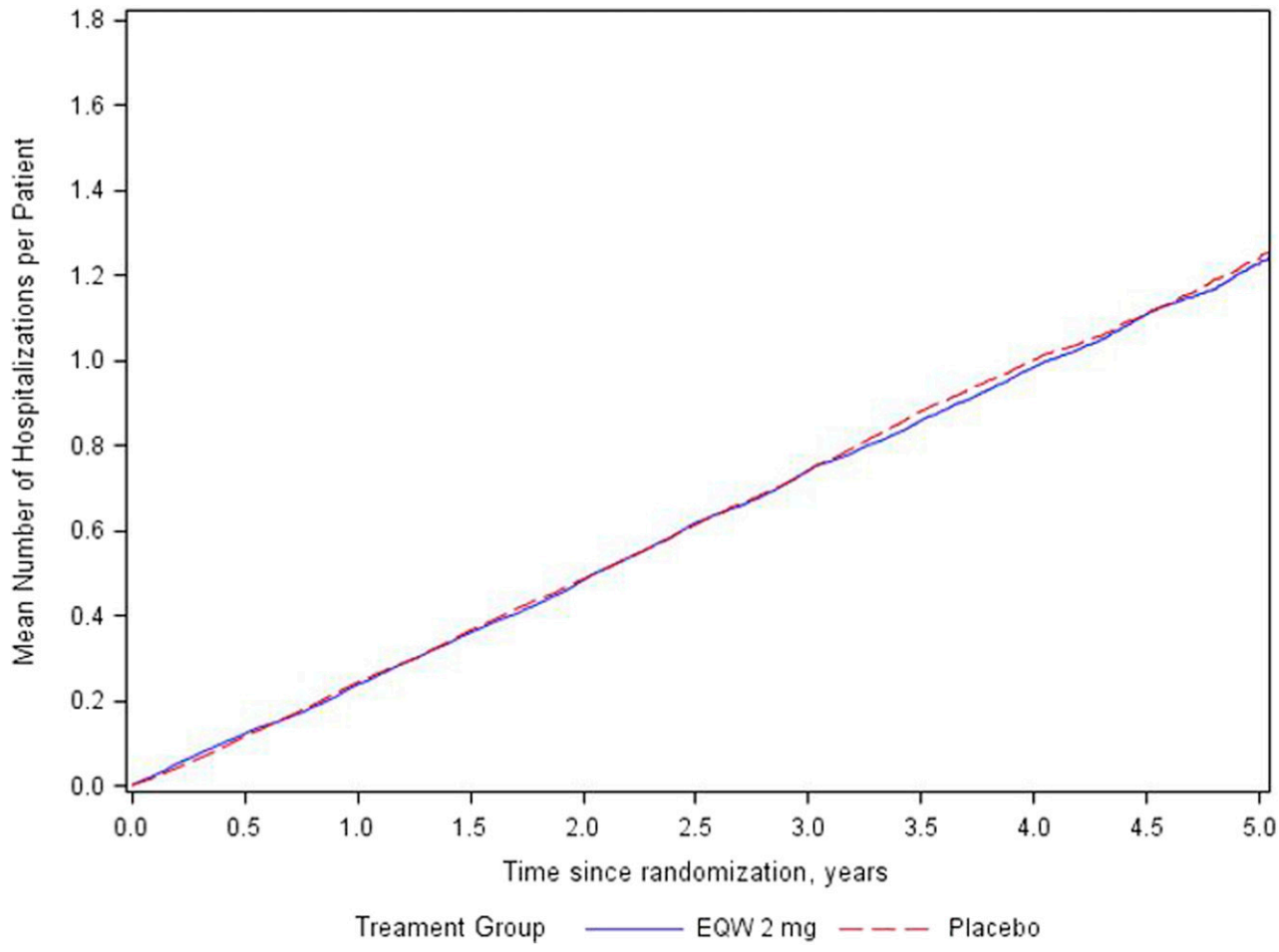

Figure 1—Mean cumulative number of hospitalizations over time by treatment group.

Table 1—Total medical resource use and costs throughout the trial

	EQW (n = 7,356)	Placebo (n = 7,396)	Difference (95% CI)*	Relative rate/means ratio (95% CI)	P value
Medical resource use					
All-cause hospitalizations	0.83 (1.68)	0.84 (1.62)	−0.01 (−0.06 to 0.05)	0.97 (0.91–1.03)	0.31
Inpatient days	7.05 (18.24)	7.46 (19.32)	−0.41 (−1.02 to 0.18)	0.91 (0.83–1.00)	0.05
Outpatient care visits	21.07 (23.26)	20.92 (23.55)	0.15 (−0.62 to 0.85)	0.99 (0.97–1.02)	0.66
Direct medical costs‡ (US$, 2017)					
Inpatient care	9,654 (25,051)	10,078 (26,016)	−424 (−1,290 to 384)	0.92 (0.83–1.02)	0.10†
Outpatient care	2,156 (1,872)	2,139 (1,910)	16 (−46 to 75)	1.01 (0.98–1.04)	0.68
Medications (excluding EQW)	17,098 (15,992)	18,698 (16,899)	−1,600 (−2,155 to 1,041)	0.91 (0.89–0.93)	<0.01
Diabetes medications	13,882 (14,592)	15,445 (15,295)	−1,564 (−2,068 to −1,069)	0.89 (0.87–0.92)	<0.01
Other medications	3,216 (3,610)	3,252 (3,876)	−36 (−157 to 82)	0.99 (0.96–1.02)	0.39
Total (excluding EQW)	28,907 (32,600)	30,914 (34,089)	−2,007 (−3,115 to −939)	0.92 (0.89–0.96)	<0.01
EQW	13,790 (8,374)	—	—	—	—
Total costs	42,697 (34,355)	30,914 (34,089)	11,782 (10,625–12,908)	1.39 (1.35–1.44)	<0.01
Direct medical costs§ (£, 2016)					
Inpatient care	5,021 (14,028)	5,204 (13,929)	−183 (−658 to 234)	0.92 (0.83–1.02)	0.10†
Outpatient care	1,313 (1,231)	1,293 (1,215)	20 (−19 to 56)	1.01 (0.98–1.03)	0.74
Medications (excluding EQW)	2,457 (2,558)	2,708 (2,913)	−251 (−346 to −162)	0.91 (0.89–0.93)	<0.01
Diabetes medications	1,640 (1,618)	1,823 (1,687)	−184 (−240 to −132)	0.89 (0.87–0.92)	<0.01
Other medications	817 (1,676)	885 (2,019)	−68 (−132 to −9)	0.96 (0.92–0.99)	0.03
Total (excluding EQW)	8,790 (15,024)	9,204 (14,970)	−414 (−906 to 95)	0.93 (0.88–0.99)	0.02
EQW	2,084 (1,254)	—	—	—	—
Total costs	10,874 (15,136)	9,204 (14,970)	1,670 (1,182–2,184)	1.18 (1.12–1.24)	<0.01

Data are mean (SD) unless otherwise indicated. *95% CIs are based on the bias-adjusted percentile method with nonparametric bootstrapping. †P value from the MEGLM procedure in Stata software. ‡Costs discounted at 3% per year. §Costs discounted at 3.5% per year.

a 23.1% discount to branded EQW, and limiting analyses to U.S. participants.

Subgroup Analysis

Subgroup analyses were limited to prespecified clinical and regional subsets examined for the primary clinical end point and were performed in order to evaluate whether certain groups of patients treated with EQW incurred different hospitalization rates and total costs.

RESULTS

Over a mean follow-up of 3.3 years across the 14,752 participants included in the ITT population, nearly 40% of participants in each treatment group were hospitalized at least once (EQW 38.5%, placebo 39.0%; $P = 0.50$). A total of 6,127 hospitalizations occurred among the 7,356 participants randomized to EQW; 6,202 hospitalizations occurred among the 7,396 participants randomized to placebo. The accumulation of hospitalizations was constant across time in both treatment groups (Fig. 1). The mean number of hospitalizations over the full follow-up period was 0.83 in the EQW arm and 0.84 in the placebo arm ($P = 0.31$) (Table 1). When accounting for the duration of hospitalizations, the mean cumulative number of inpatient days was lower in the EQW group (7.05 days) than in the placebo group (7.46 days; $P = 0.05$). Mean cumulative counts of outpatient visits were similar between the two groups: ~21 visits per participant over the follow-up period ($P = 0.66$).

Medications were the largest contributor to total costs in both study groups in the U.S. analysis. Mean costs for nonstudy diabetes medications were significantly lower in the EQW arm ($17,098) than in the placebo arm ($18,698)—a savings of $1,600 ($P < 0.01$), which was driven by lower nonstudy diabetes medication costs. The mean cost of study medication over the duration of the trial was $13,790 per patient in the EQW arm. Inpatient costs averaged $9,654 for patients randomized to EQW and $10,078 for patients randomized to placebo ($P = 0.10$). Mean costs for outpatient visits were similar in both groups, totaling roughly $2,100, of which ~$550 represented costs for study-related clinic visits. When summing costs for nonstudy medications, outpatient visits, and hospitalizations, mean total costs were $2,007 (8%) less in the EQW arm than in the placebo group ($28,907 vs. $30,914; $P < 0.01$). With study medications included in the EQW arm, total costs were $42,697—39% higher than costs in the placebo arm ($P < 0.01$).

When medical resources were valued using English costs, inpatient costs were the biggest cost driver in both groups, and the difference in inpatient costs remained, with a mean of £5,021 per patient in the EQW arm and £5,204 per patient in the placebo arm (Table 1). Mean costs for nonstudy medication were £251 lower in the EQW group ($P < 0.01$). Mean total costs for medical resources, excluding exenatide, were 7% lower in the EQW group ($P = 0.03$). When the cost of exenatide (£2,084 per patient) was added, however, total mean costs for the EQW group were 18% (£1,670 per patient) higher than those for the placebo group ($P < 0.01$).

At baseline, significant proportions of patients in both study groups reported at least some level of problem for each of the five domains represented in the EQ-5D: mobility (44.8%), self-care (14.1%), usual activities (31.7%), pain and discomfort (56.2%), and anxiety and depression (32.0%). Despite the prevalence of reported problems across the domains, mean EQ-5D utilities were 0.90 in both study groups at baseline and were similar in both groups during the follow-up period. Both treatment groups

showed similar overall declines in utility over time with U.S. and U.K. utility weights (Fig. 2*A* and *B*). Findings from the multilevel mixed-effects linear regression model confirmed these findings, revealing that mean utility scores did not significantly differ between treatment groups over time ($P > 0.05$), and that there was a significant negative time effect (−0.0004 per month with U.S. utility weights and −0.0006 per month with U.K. utility weights; both $P < 0.001$), indicating that health-related quality of life decreased over time in both groups. These findings were robust when adding covariates representing the history of cardiovascular events or BMI at baseline to the demographic covariates included in the base models (see Appendix in Supplementary Data).

Sensitivity Analysis

When costs for concomitant medications were reduced by 23.1% in order to reflect discounts on list prices, the difference in concomitant medication costs decreased from $1,600 to $1,233. When the discount was not applied to branded EQW, study drug costs increased from $13,790 to $17,932 in the EQW group. When limiting the analysis to the 3,164 participants enrolled at U.S. sites who were included in the ITT analysis, the findings from the EQ-5D regression analysis were similar to those for the full trial cohort. Approximately 47% of U.S. patients in each treatment group were hospitalized at least once. The mean numbers of hospitalizations and inpatient days per U.S. patient were not different between the two groups, even though fewer patients in the EQW group died (9.4% in the EQW group; 11.5% in the placebo group). Over the trial follow-up period, among U.S. patients, inpatient care costs averaged $12,736 for those receiving EQW and $12,862 for those receiving placebo; total costs were $52,441 in the EQW group, $11,361 greater than costs for placebo.

Subgroup Analysis

Effects of EQW on hospitalizations and total within-trial costs by prespecified subgroup are presented in Table 2.

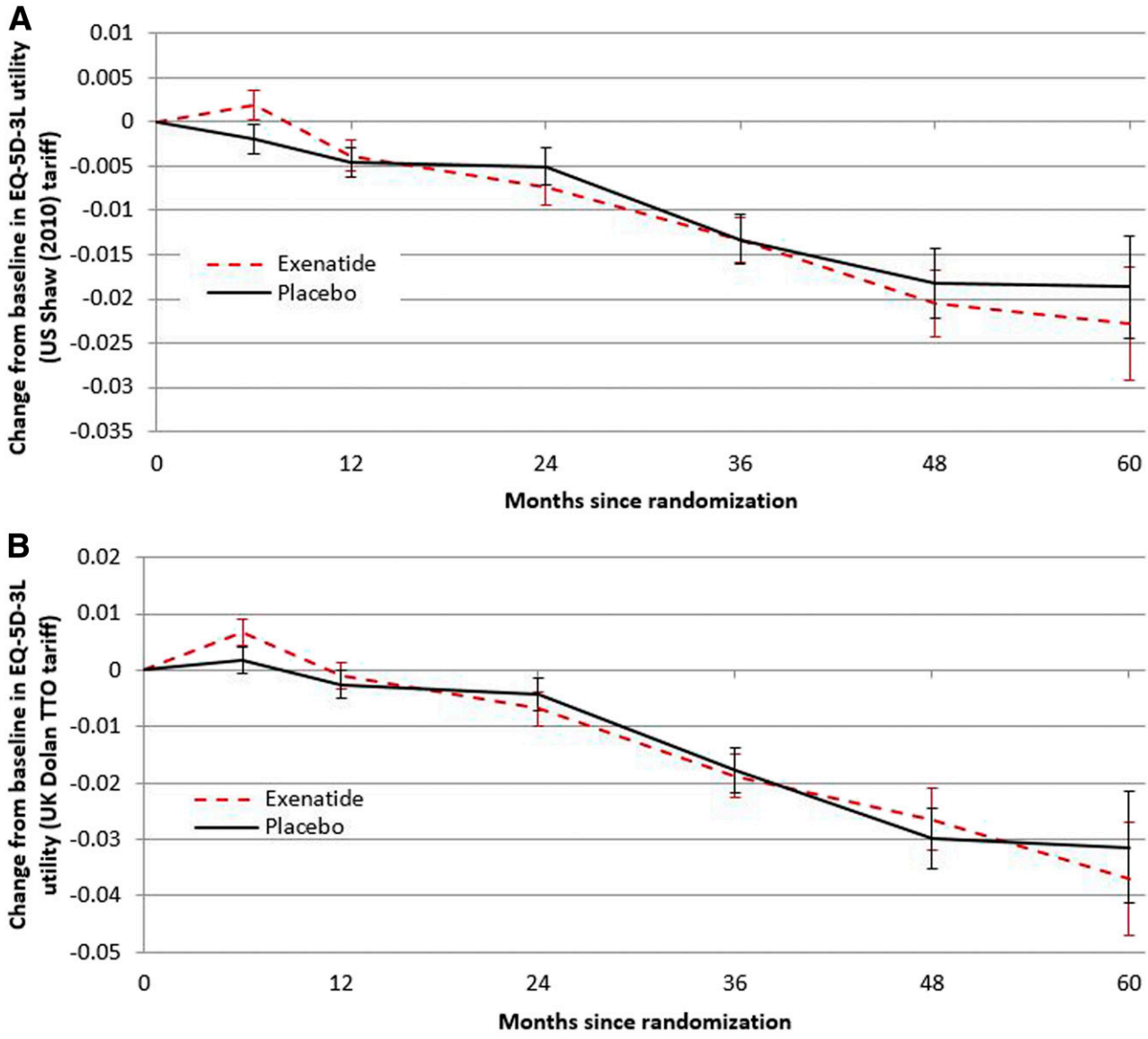

Figure 2—Change in EQ-5D utility from baseline: U.S. weights (*A*) and U.K. weights (*B*). Error bars represent standard errors. TTO, time trade-off.

Table 2—Impact of EQW on all-cause hospitalizations and total costs, including study medication costs, by subgroup

		All-cause hospitalizations			Total U.S. costs			Total U.K. costs		
Subgroups	Patients (*n*)	Relative rate ratio (95% CI)	*P* value*	*P* value†	Relative rate ratio (95% CI)	*P* value*	*P* value†	Relative rate ratio (95% CI)	*P* value*	*P* value†
Age (years)										
<65	8,813	1.02 (0.94–1.12)	0.59	0.76	1.44 (1.38–1.50)	<0.01	0.01	1.22 (1.14–1.31)	<0.01	0.27
≥65	5,939	0.92 (0.84–0.99)	0.04		1.33 (1.27–1.40)	<0.01		1.13 (1.05–1.22)	<0.01	
<75	13,502	0.97 (0.91–1.03)	0.32		1.41 (1.36–1.45)	<0.01		1.20 (1.13–1.26)	<0.01	
≥75	1,250	0.99 (0.85–1.16)	0.90		1.28 (1.15–1.42)	<0.01		1.06 (0.91–1.22)	0.46	
Sex										
Male	9,149	0.97 (0.90–1.05)	0.49	0.89	1.38 (1.33–1.43)	<0.01	0.36	1.17 (1.09–1.25)	<0.01	0.58
Female	5,603	0.97 (0.87–1.07)	0.53		1.42 (1.35–1.50)	<0.01		1.21 (1.11–1.31)	<0.01	
BMI (kg/m^2)										
<30	5,363	0.94 (0.85–1.04)	0.27	0.74	1.45 (1.38–1.53)	<0.01	0.02	1.18 (1.08–1.29)	<0.01	0.97
≥30	9,239	0.98 (0.91–1.05)	0.55		1.36 (1.31–1.42)	<0.01		1.18 (1.10–1.26)	<0.01	
Duration of diabetes (years)										
<5	2,012	0.78 (0.65–0.94)	0.01	0.85	1.45 (1.31–1.60)	<0.01	<0.01	1.03 (0.87–1.21)	0.76	0.59
5 to <15	7,266	1.02 (0.93–1.11)	0.67		1.47 (1.41–1.53)	<0.01		1.24 (1.15–1.33)	<0.01	
≥15	5,421	0.97 (0.88–1.06)	0.50		1.30 (1.24–1.37)	<0.01		1.15 (1.07–1.25)	<0.01	
Congestive heart failure										
Yes	2,389	1.05 (0.92–1.19)	0.50	0.26	1.40 (1.30–1.51)	<0.01	0.67	1.23 (1.09–1.38)	<0.01	0.64
No	12,362	0.96 (0.90–1.02)	0.19		1.40 (1.36–1.45)	<0.01		1.17 (1.11–1.24)	<0.01	
Insulin use at baseline										
Yes	6,836	0.96 (0.89–1.05)	0.38	0.77	1.28 (1.23–1.33)	<0.01	<0.01	1.13 (1.05–1.21)	<0.01	0.02
No	7,916	0.98 (0.90–1.07)	0.65		1.60 (1.52–1.67)	<0.01		1.26 (1.17–1.36)	<0.01	
Geographic region										
Europe	6,788	0.93 (0.86–1.01)	0.09	0.12	1.42 (1.35–1.48)	<0.01	<0.01	1.20 (1.12–1.30)	<0.01	0.16
North America	3,708	0.99 (0.88–1.12)	0.86		1.25 (1.18–1.33)	<0.01		1.12 (1.01–1.23)	0.03	
Latin America	2,727	0.93 (0.78–1.10)	0.39		1.46 (1.34–1.59)	<0.01		1.11 (0.96–1.28)	0.15	
Asia Pacific	1,529	1.20 (0.99–1.45)	0.06		1.55 (1.43–1.69)	<0.01		1.36 (1.19–1.55)	<0.01	
History of CV event										
Yes	10,782	0.95 (0.89–1.02)	0.13	0.15	1.36 (1.31–1.41)	<0.01	<0.01	1.15 (1.08–1.22)	<0.01	<0.01
No	3,970	1.07 (0.93–1.22)	0.36		1.54 (1.45–1.64)	<0.01		1.34 (1.21–1.50)	<0.01	

CV, cardiovascular. **P* values for treatment assignment for each subgroup. †*P* values for interactions between treatment arm and continuous measurement for age, BMI, and duration of diabetes, and between treatment arm and categorical subgroup for sex, history of heart failure, insulin therapy at baseline, and geographic region.

Hospitalization rates were significantly lower in the EQW group than in the placebo group for patients aged 65 years and older ($P = 0.04$) and among individuals who had had diabetes for fewer than 5 years at randomization ($P = 0.01$). However, tests of statistical interaction between treatment assignment and either age ($P = 0.76$) or duration of diabetes were not statistically significant ($P = 0.85$). Total U.S. costs excluding study medication costs were consistently lower in the EQW group. With the study medication costs included, however, total costs were consistently higher in the EQW group than in the placebo group for all subgroups. Total English costs, including study medication costs, also were consistently higher in the EQW group than in the placebo group for all subgroups except patients aged 75 years and older ($P = 0.46$), individuals who had had diabetes for fewer than 5 years at randomization ($P = 0.76$), and participants enrolled from Latin America ($P = 0.15$).

CONCLUSIONS

EXSCEL provides insights into the incremental effects of branded EQW on medical resource use, costs, and health utilities when the drug is added to usual diabetes care for patients with type 2 diabetes who have or do not have preexisting cardiovascular disease. Based on EQ-5D health utilities, both study groups experienced similar reductions in health-related quality of life during the follow-up period. We observed that participants randomized to EQW experienced approximately a half-day reduction in inpatient days over the course of the trial. It seems that the nominally significant reduction in mortality in the EQW group (6.9% vs. 7.9% mortality in the placebo group; $P < 0.05$) reported in the EXSCEL trial contributed to the reduction in the number of inpatient days. When excluding hospitalizations during which patients died, there remained a significant difference in the mean number of inpatient days between groups (EQW 6.77 days; placebo 7.02 days; $P = 0.05$). Nevertheless, the statistically significant reduction in the number of inpatient days in the main analysis did not translate into significantly lower inpatient costs, because of the variability in total inpatient costs. Costs for nonstudy diabetes medications also were significantly lower in the EQW group, but these cost savings were more than offset by the higher cost of branded exenatide, leading to significantly higher total costs with EQW than with placebo across the study period.

Higher total costs were expected when adding branded exenatide to usual care, given that clinicians were advised to

individualize care using predominantly generic medications in order to allow participants to achieve clinically appropriate glycated hemoglobin targets (5). EXSCEL also revealed a nominally significant reduction in all-cause mortality with EQW, but this did not translate into discernable economic benefit in this within-trial evaluation. Nevertheless, the trial offers an objective reporting of comparative, directly observed medical resource use and directly reported health status (using the EQ-5D) that is free from the selection bias that can plague nonrandomized comparisons.

Our analysis has some limitations. First, by the study's end, although only 0.5% of trial participants were lost to follow-up, ~40% of participants in both treatment arms had discontinued the study medication. Some of those participants transitioned from the study drug to open-label use of GLP-1 RAs and to the use of noninjectable agents such as dipeptidyl peptidase 4 inhibitors and sodium–glucose cotransporter 2 inhibitors. Although we accounted for these transitions when determining costs of concomitant nonstudy medications, greater transition from active study medication to open-label GLP-1 RA therapies would have narrowed the cost savings estimated for diabetes medications taken concomitantly with EQW and may also have affected hospitalization rates. Nevertheless, the cost of additional concomitant medications in the placebo arm did not offset the cost of EQW.

From a methods perspective, we adhered to good practice recommendations, including prospective collection of resource use and health utilities data and the development of a detailed cost and data analysis plan (9,16,17). It should be noted that if we had not adjusted for differences in LOS across countries when assigning inpatient costs, countries with longer stays would have had more influence on cost comparisons; this may account for the lack of a significant difference in inpatient costs despite a half-day reduction in the number of inpatient days (18). We also applied hierarchical generalized linear regression methods to control for between-country factors that affect baseline rates of resource use and costs.

This within-trial cost analysis revealed that adding EQW to usual care significantly reduced the number of inpatient days and produced lower costs for concomitant diabetes medications than for usual care alone. These findings can be useful to planners projecting costs and outcomes who may also be accounting for the drug transitioning to generic status, when its cost would be expected to decrease precipitously.

The trial also revealed a nominally significant reduction in all-cause mortality with EQW and nonsignificant reductions in other cardiovascular events and risk factors. This within-trial cost analysis does not account for these benefits or extrapolate beyond the end of the trial; an economic evaluation estimating the lifetime cost-effectiveness of EQW will be reported separately.

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Author Contributions. S.D.R. interpreted the findings and wrote the initial draft of the manuscript. S.D.R., Y.L., H.A.D., F.B., J.L., and A.M.G. drafted the cost and data analysis plan. S.D.R., A.M.G., and R.R.H. designed the study during the trial planning period. Y.L. assigned costs to medical resource use, programmed the statistical analyses of the medical resource use and cost data, generated tables and figures, and edited the manuscript. H.A.D., F.B., J.L., and A.M.G. provided English cost weights, programmed the statistical analysis of the EQ-5D data, interpreted the findings, and reviewed and edited the manuscript. S.M.G., B.K., and E.W. provided information about the clinical trial, interpreted the results, and reviewed and edited the manuscript. R.J.M., N.J.P., M.A.B., R.R.H., and A.F.H. were clinical investigators in the trial: they collected data, reviewed diagnosis-related group codes assigned to hospitalizations, reviewed the analysis plan, interpreted results, and reviewed and edited the manuscript. S.D.R. and A.M.G. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability. All requests and enquiries concerning access to data should be directed to the study's primary investigator (R.R.H.).

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References

1. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018;138:271–281

2. Sarwar N, Gao P, Seshasai SR, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies [published correction appears in Lancet 2010;376:958]. Lancet 2010; 375:2215–2222

3. Tancredi M, Rosengren A, Svensson A-M, et al. Excess mortality among persons with type 2 diabetes. N Engl J Med 2015;373:1720–1732

4. Holman RR, Bethel MA, George J, et al. Rationale and design of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) trial. Am Heart J 2016;174:103–110

5. Holman RR, Bethel MA, Mentz RJ, et al.; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228–1239

6. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012;15: 708–715

7. Shaw JW, Pickard AS, Yu S, et al. A median model for predicting United States population-based EQ-5D health state preferences. Value Health 2010;13:278–288

8. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095–1108

9. Reed SD, Anstrom KJ, Bakhai A, et al. Conducting economic evaluations alongside multinational clinical trials: toward a research consensus. Am Heart J 2005;149:434–443

10. Department of Health and Human Services, Office of Inspector General. Medicaid rebates for brand-name drugs exceeded Part D rebates by a substantial margin [Internet], 2015. Available from https://oig.hhs.gov/oei/reports/oei-03-13-00650.pdf. Accessed 17 January 2019

11. NHS Digital. Prescription cost analysis, England - 2016 [Internet], 2017. Available from http://www.content.digital.nhs.uk/catalogue/PUB23631. Accessed 29 January 2019

12. National Health Service England, Department of Health. Reference costs 2015-16 [Internet]. Available from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/577083/Reference_Costs_2015-16.pdf. Accessed 17 January 2019
13. Reed SD, Kaul P, Li Y, et al. Medical resource use, costs, and quality of life in patients with acute decompensated heart failure: findings from ASCEND-HF. J Card Fail 2013;19:611–620
14. Reed SD, Li Y, Leal J, et al.; TECOS Study Group. Longitudinal medical resources and costs among type 2 diabetes patients participating in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). Diabetes Obes Metab 2018;20:1732–1739
15. Dong H, Robison LL, Leisenring WM, Martin LJ, Armstrong GT, Yasui Y. Estimating the burden of recurrent events in the presence of competing risks: the method of mean cumulative count. Am J Epidemiol 2015;181:532–540
16. Ramsey SD, Willke RJ, Glick H, et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. Value Health 2015;18:161–172
17. Drummond M, Barbieri M, Cook J, et al. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. Value Health 2009;12:409–418
18. Reed SD, Friedman JY, Gnanasakthy A, Schulman KA. Comparison of hospital costing methods in an economic evaluation of a multinational clinical trial. Int J Technol Assess Health Care 2003;19:396–406