

**Longitudinal Medical Resources and Costs Among Type 2 Diabetes Patients Participating
in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)**

Running title: Medical Resource Use and Costs in TECOS

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Abstract

Aims: TECOS, a cardiovascular safety trial of 14,671 patients with type 2 diabetes and cardiovascular disease, demonstrated sitagliptin was non-inferior to placebo for the primary composite cardiovascular outcome when added to best usual care. This study tested hypotheses that medical resource use and costs differed between these two treatment strategies.

Materials and Methods: Medical resource use information was collected on case report forms throughout the trial and valued using US costs: Medicare payments for hospitalizations, medical procedures, and outpatient visits, and wholesale acquisition costs (WAC) for diabetes-related medications. Hierarchical generalized linear models were used to compare resource use and US costs, accounting for variable intercountry practice patterns. Sensitivity analyses included resource valuation using English costs for a UK perspective.

Results: There were no significant differences in hospitalizations, inpatient days, medical procedures, or outpatient visits during follow-up (mean and median 3.0 years in both groups). Hospitalization rates appeared to diverge after 2 years, with lower rates among sitagliptin vs. placebo-treated patients with at least 2.5 years (relative rate, 0.90 [95%CI: 0.83–0.97], $P=0.01$). Mean medical costs, exclusive of study medication, were \$11,937 in the sitagliptin and \$12,409 in placebo arm ($P=0.06$). Mean sitagliptin costs based on undiscounted WAC were \$9,978 per patient. Differential UK total costs including study drug costs were smaller (£911), primarily due to lower mean costs for sitagliptin (£1,072).

Conclusions: Lower hospitalization rates across time with sitagliptin slightly offset sitagliptin treatment costs over 3 years in type 2 diabetes patients at high risk for cardiovascular events.

Key Words: diabetes; sitagliptin; dipeptidyl peptidase-4 inhibitor; costs; cost analysis

Trial Registration: ClinicalTrials.gov identifier: NCT00790205

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The economic implications of type 2 diabetes are immense. Disability-adjusted life-years associated with diabetes increased globally by 29% between 2005 and 2015.¹ Estimated global health expenditures for diabetes ranged from \$612 billion to \$1.10 trillion per year in 2014.² These extraordinary numbers are expected to grow as the number of people with diabetes worldwide is projected to rise from 415 million in 2015 to 642 million by 2040.³

Patients with type 2 diabetes have rates of coronary heart disease and ischemic stroke that are two-fold higher than patients without type 2 diabetes, even after adjusting for traditional risk factors.⁴ Although there is evidence of long-term declines in the excess risk of death and cardiovascular outcomes in persons with type 2 diabetes,⁵ death rates due to vascular causes and non-vascular causes, including cancer and infectious diseases, remain significantly higher among individuals with type 2 diabetes.⁶ Numerous therapeutic strategies are available to improve glycemic control with the goal of reducing morbidity and mortality, but questions about potential adverse effects on major cardiovascular events have been raised,^{7,8} leading regulators to require large-scale cardiovascular safety trials of new type 2 diabetes treatments.^{9,10} These trials typically strive for equivalent levels of glycemic control between study arms to isolate the potential direct impact of the study drug on major adverse cardiovascular events, from possible indirect effects attributable to better glycemic control.

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), a placebo-controlled cardiovascular safety study, was designed to test the impact of adding sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, to usual care in patients with type 2 diabetes and established cardiovascular disease who did not receive other DPP-4 inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists.¹¹ A prespecified secondary objective was to compare medical resource use by treatment arm incurred during the trial. As an extension, we valued all

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3 medical resources using US cost weights and compared direct medical costs between study arms.
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5 As a sensitivity analysis, we also valued medical resources using English cost weights, to
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7 evaluate the results in a different setting.
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10 11 12 **RESEARCH DESIGN AND METHODS** 13

14 *TECOS Trial Design and Results* 15

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17 Eligible patients had a history of cardiovascular disease. Baseline glycated hemoglobin (HbA_{1c})
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19 range for enrollment was 6.5-8.0% (48–64 mmol/mol). Patients were randomized to either
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21 placebo or sitagliptin (100 mg or 50 mg daily, depending on renal function). The primary
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23 endpoint was time to first cardiovascular-related death, nonfatal myocardial infarction, nonfatal
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25 stroke, or hospitalization for unstable angina. The study was powered to demonstrate non-
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27 inferiority of sitagliptin added to usual care vs. usual care alone, with 90% power to exclude a
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29 30% increased risk of cardiovascular events with sitagliptin-based care.¹¹ The protocol for the
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31 study was approved by the ethics committees associated with all participating trial sites, and all
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33 participants provided written informed consent.
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38 In TECOS, the intention-to-treat analysis population included 14,671 randomized
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40 participants from 38 countries. Participants in both study groups were followed for a mean of 3.0
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42 years (sitagliptin, 3.01 [SD=0.96]; placebo, 2.99 [SD=0.97]).¹² Approximately one-quarter of
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44 participants in both arms discontinued study medication prior to the end of follow-up (sitagliptin,
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46 26.1%; placebo, 27.5%). Despite the aim of equal glycemic control between groups, mean HbA_{1c}
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48 levels were on average 0.3% lower with sitagliptin (95% confidence interval [CI], –0.32 to
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50 –0.27). Sitagliptin was shown to be noninferior to placebo for the primary composite
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52 cardiovascular outcome (hazard ratio [HR]: 0.98; 95%CI: 0.88-1.09; *P* for noninferiority
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<0.001). All-cause mortality was similar in both arms (HR: 1.01; 95%CI: 0.90-1.14). The proportion of patients initiating insulin during the trial was significantly lower in the sitagliptin group (9.7%) compared to the placebo group (13.2%; $P < 0.001$). Severe hypoglycemia occurred in 2.0% of patients randomized to sitagliptin compared with 1.7% of patients randomized to placebo (HR: 1.13; 95%CI: 0.89-1.44).

Economic Evaluation

Academic health economics teams from the Duke Clinical Research Institute and the University of Oxford Health Economics Research Centre led and performed the economic evaluation. An analysis plan finalized on August 7, 2015, was used to guide cost assignment and planned statistical analysis.

Medical Resource Use and Cost Assignment

Data on medical resource use including hospitalizations, cardiovascular procedures, study visits, outpatient visits to usual diabetes care providers or other providers, concomitant medications, and study drug were collected at 4, 8, and 12 months, then every 6 months through study end.

For each hospitalization, admission and discharge dates were recorded, along with the primary discharge diagnosis documented as one of 32 prespecified diagnoses or free text. All major cardiovascular and renal procedures were recorded, as were specific procedures for management of congestive heart failure, cardiac ischemic event, stroke/transient ischemic attack, and pancreatitis.

Numbers of treatment days on study drugs were derived from trial records, accounting for intermittent discontinuations. Information for other diabetes medicines included drug name and

daily dose, but start and stop dates were not collected, hence drug use recorded as ‘yes’ was assumed to continue until ‘no’ was recorded at a subsequent visit.

Cost Assignment

Costs were assigned to medical resource use reported for all patients in the trial. US hospital cost assignment was based on Medicare reimbursement rates for corresponding Diagnosis-Related Group (DRG) codes assigned to prespecified discharge diagnoses and procedures (Supplemental Tables 1 and 2) and high-frequency free-text discharge diagnoses recorded in TECOS. To account for systematic differences in length of stay across patients in different countries with the same diagnosis, we applied an approach to inpatient cost assignment used in another large multinational trial.¹³ For each DRG code, cost per inpatient day was estimated by dividing the 2015 Medicare reimbursement by the median length of stay published by the Centers for Medicare and Medicaid Services,¹⁴ then merged with hospitalizations using the assigned DRG code. We then adjusted lengths of stay recorded for hospitalizations outside the United States to approximate the length of stay had the patient been treated at a US facility. This was done by calculating the ratio of mean length of stay across all hospitalizations in the United States to the mean length of stay in each non-US country participating in TECOS. The resulting country-specific ratio was multiplied by the length of stay for each hospitalization record and the DRG-specific daily inpatient cost.

The 2015 Medicare Physician Fee Schedule was used to estimate costs for physician services using Current Procedural Terminology codes (Supplemental Tables 3 and 4).¹⁵ Daily costs for concomitant diabetes medications were provided by Merck & Co., Inc., based on 2015 wholesale acquisition costs (WAC) published by First Databank, which represent the

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3 manufacturer's published list price to wholesalers and may not represent actual transactional
4 prices.¹⁶ Since generic drugs were available from multiple manufacturers, the lowest and highest
5 costs for specific daily doses of concomitant diabetes drugs were developed. Lowest costs for
6 generic drugs were used in the base-case analysis. The daily cost assigned for sitagliptin was
7 \$11.02 across all doses. All costs incurred beyond the first year were discounted at 3% per year.
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17 *Statistical Analysis*
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19 Descriptive statistics, including proportions, means, standard deviations, and medians,
20 summarized counts of medical resource use and costs by treatment group. Mean cumulative
21 counts of hospitalizations per patient that account for censoring across time were plotted,¹⁷ and
22 annual hospitalization rates were computed by dividing the total number of hospitalizations for
23 each treatment group in each year by the total duration of follow-up in the corresponding year.
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31 To account for the nested structure of the multinational trial data, generalized linear
32 mixed models were used to compare counts of medical resource use between treatment groups
33 using SAS's PROC GLIMMIX with Laplace estimation (SAS Institute, Version 9.4). The
34 models included treatment assignment as the independent variable, with the log of each
35 participant's duration of follow-up as an offset variable to adjust for differences in observation
36 time. Treatment assignment was modeled as a fixed effect and countries were modeled as
37 random intercepts, to allow rates of medical resource use and costs in the placebo group to vary
38 across countries while modeling the relative impact of sitagliptin as a fixed effect across
39 countries. To compare medical resource use counts (hospitalizations, inpatient days, and
40 outpatient visits), the models were specified with negative binomial error distributions and log
41 links. Models to compare diabetes drug-days relied on normal distributions and identity links.
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For cost comparisons, gamma error distributions and log links were used. The exponentiated parameter estimates from these models represent relative rates (RR) for resource use and means ratios for costs. To provide additional descriptive information about treatment effects on resource use and costs on an absolute scale, differences in mean counts were computed and corresponding 95%CIs were estimated using the bias-corrected percentile method based on 1000 nonparametric bootstrap replications.¹⁸

Sensitivity Analysis

Several sensitivity analyses were performed to evaluate the impact of alternative methods and assumptions on study findings. First, in lieu of assigning the lowest WACs reported for generic diabetes medications, the highest WACs were assigned. Second, when adjusting lengths of stay for hospitalizations outside the United States, we calculated the conversion ratios using median rather than mean lengths of stay. Third, we replicated the entire analysis using costs from England rather than the United States (see Supplemental Methods for details).

Subgroup Analysis

Subgroup analyses were performed to determine whether adding sitagliptin to usual care had a differential impact on all-cause hospitalizations. Selection of subgroups mirrored those that were prespecified or conducted for the primary clinical endpoint.¹²

Post-Hoc Analysis

Post-hoc analyses were performed to compare rates of hospitalizations between groups among patients with longer periods of follow-up.

RESULTS

Participants randomized to receive sitagliptin in addition to usual care were hospitalized 4,803 times compared with 5,168 times among participants randomized to receive placebo (Figure 1), representing 34.1% and 34.6% of participants, respectively ($P=0.26$) being hospitalized at least once over the 3-year follow-up period. The mean number of hospitalizations was 0.66 in the sitagliptin arm and 0.70 in the placebo arm (RR, 0.95 [95%CI: 0.90 to 1.02] $P=0.14$; Figure 1). Mean numbers of inpatient days were 5.50 days for the sitagliptin group and 5.74 days for the placebo group (Table 1; $P=0.94$). Mean counts of outpatient visits were 19.4 per participant in both groups ($P=0.85$). The mean number of concomitant diabetes drug-days was 1,635 and 1,673 per participant for the sitagliptin and placebo groups, respectively, or about 1.5 diabetes drugs per day per participant ($P=0.06$). When including sitagliptin, diabetes drug-days averaged 2.3 per day per participant among those randomized to the sitagliptin arm. The mean number of days on insulin therapy was 234 per participant in the sitagliptin arm compared to 241 days in the placebo arm ($P=0.26$).

Inpatient costs over the follow-up period averaged \$6,947 in the sitagliptin group and \$7,377 in the placebo group (Table 1). Outpatient care costs were approximately \$1,465 in both study groups. Mean total costs for medical resources, exclusive of sitagliptin, were \$11,937 in the sitagliptin group and \$12,409 in the placebo group. Mean costs for sitagliptin were estimated at \$9,978, resulting in total within-trial costs for the sitagliptin group of \$21,915.

Sensitivity Analysis

When concomitant diabetes medicines were assigned the upper (instead of lower) bound of prices across generic manufacturers, diabetes medications costs averaged \$4,126 in the sitagliptin arm vs. \$4,198 in the placebo arm, a difference of \$72. Using length-of-stay conversion ratios based on median (instead of mean) length of stay in the United States relative to other countries, estimated inpatient costs were \$901 higher in the sitagliptin group and \$931 higher in the placebo group. And, when resource use was valued using English costs, inpatient costs over the follow-up period averaged £2,629 in the sitagliptin group and £2,760 in the placebo group (Table 1). Outpatient care costs were £2,648 in the sitagliptin group and £2,654 in the placebo group. Mean total costs for medical resources, exclusive of sitagliptin, were £6,058 in the sitagliptin group and £6,219 in the placebo group. Mean costs for sitagliptin were estimated at £1,072, resulting in total within-trial costs for the sitagliptin group of £7,130, which was £911 higher than the placebo group ($P<.0001$).

Subgroup Analysis

Effects of sitagliptin on hospitalizations by subgroup are reported in Table 2. Only one interaction term was statistically significant at $P<0.05$, suggesting that younger patients (<75 years of age) may experience fewer hospitalizations when treated with sitagliptin. Within subgroups, just one P -value was <0.05 , occurring among patients with diabetes duration of 5 to <15 years.

Post-Hoc Analysis

Post-hoc analyses revealed that patients with at least 2.5 years of follow-up experienced a 10% lower rate of hospitalizations (i.e., RR, 0.90, $P=0.01$) when treated with sitagliptin compared to placebo (Table 3). This observation was maintained among smaller groups of patients with at least 3.0 and 3.5 years of follow-up.

CONCLUSIONS

TECOS randomized 14,671 patients across 38 countries to evaluate long-term safety of sitagliptin in patients with type 2 diabetes and pre-existing cardiovascular disease. Clinical findings confirmed that sitagliptin, when added to usual care (but excluding DPP-4 inhibitors and GLP-1 receptor agonists), is non-inferior to placebo plus usual care in regard to its impact on cardiovascular outcomes, including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina, and had no impact on the incidence of hospitalization for heart failure.¹⁹

TECOS allowed providers to help enrolled patients achieve individualized glycemic control goals with their choice of open-label antihyperglycemic agents excluding other DPP-4 inhibitors or GLP-1 receptor agonists, and as a randomized and blinded clinical trial, permits an internally valid evaluation of whether the addition of sitagliptin had an independent impact on medical resource use and associated costs. However, it should be noted that not all resources of relevance in type 2 diabetes (such as glucose testing strips) were measured. In addition, despite the aim of achieving glycemic equipoise, participants randomized to sitagliptin had mean HbA_{1c} values 0.3% lower on average than the placebo group, suggesting possible suboptimal addition of antihyperglycemic agents in the control arm during the study and commensurately lower

medication costs in that arm than had equal glycemic control been achieved. The study design also limited enrollment to HbA_{1c} levels of 6.5-8.0% at baseline, potentially restricting the opportunity to demonstrate effects of improved glycemic control, which may have reduced the generalizability of our findings.

Drug costs, monitoring costs and costs to manage drug-related side effects are essential components of an economic evaluation of sitagliptin. In our resource utilization study, we observed slightly fewer drug treatment days with concomitant diabetes drugs and fewer days on insulin in the sitagliptin arm, but little cost saving owing to the low cost of generic diabetes drugs and the modest absolute differences in total insulin use between arms given the proportion of patients (23%) using insulin at study entry. At the outset of the trial, we considered that sitagliptin might make it easier to achieve personalized glucose targets and reduce the number of outpatient visits relative to usual care plus placebo, but in practice the mean number of outpatient visits reported was nearly identical. However, it is possible that additional care for drug initiation or monitoring occurred during protocol-required visits that was not captured in the context of TECOS, which may have reduced the opportunity to observe additional differences in resource utilization between arms.

The 0.3% lower HbA_{1c} values in the sitagliptin arm may have contributed to several indications that the treatment lowered hospitalization rates. The 95%CI corresponding to the difference in mean hospitalizations between treatment arms excluded zero, consistent with a nominally significant finding at $P<0.05$, but the P -value from the prespecified hierarchical model to compare hospitalization rates in the primary analysis was not statistically significant. We also observed cases where mean costs in the sitagliptin arm were lower than in the placebo arm, yet means ratios were consistent with higher costs. These inconsistencies can be attributed to the

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resampling-with-replacement procedure employed with the standard approach to bootstrapping, whereas the modeling procedure accounts for correlations across patients enrolled within a country and adjusts for patient-level differences in duration of follow-up.

More compelling evidence is that all-cause hospitalization rates began to diverge in the second year of follow-up and continued through the fifth year. Evidence from previous long-term trials in diabetes suggests that changes in HbA_{1c} require long follow-up periods to observe cardiovascular benefits, and it has been hypothesized that a ‘metabolic memory’ may contribute to such effects.^{20,21} Post-hoc analyses suggest that hospitalization rates were about 10% lower among patients treated with sitagliptin. The net clinical and economic impact is dependent on the absolute hospitalization rate, which was 0.24 per patient-year for the placebo group, but varied widely across countries, ranging (in countries with ≥ 100 patients per arm) from 0.06 per patient-year in India to 0.57 per patient-year in New Zealand. The hospitalization rate for the placebo arm in the United States, where more than 1000 patients were randomized to placebo, was 0.34 per patient-year. At \$10,000 per hospitalization, a 10% reduction in hospitalizations would result in savings of \$335 per patient-year in the United States. By comparison, the annual cost of sitagliptin, based on the WAC, was estimated at about \$3,300. Discounts and rebates negotiated by payers are not transparent, but a recent report from the US Office of the Inspector General reports a mean rebate of 23.1% of the average manufacturer’s price for brand-name drugs paid by Medicaid.²² With this discount, treatment costs of approximately \$2,500 would be marginally offset with lower inpatient costs. In other jurisdictions, with higher rates of hospital admission and/or larger discounts and rebates for sitagliptin, the offset could be larger. In the UK cost analysis, lower annual costs of sitagliptin treatment (relative to the United States) combined with

savings in hospitalization costs (relative to the placebo group) reduced total incremental costs to about £300 per patient-year.

The present study is a resource utilization study conducted within a clinical trial and cannot be compared directly with cost-effectiveness analyses of sitagliptin, which typically estimate incremental lifetime costs and quality-adjusted life-years (QALYs) as the outcome measure. Previously published cost-effectiveness analyses have suggested that, when sitagliptin is compared with sulfonylureas in patients receiving metformin monotherapy, lifetime gains with sitagliptin range from 0.04 to 0.1 QALYs.²³ Using the upper end of that range, incremental lifetime costs with sitagliptin less than \$10,000 would maintain an incremental cost-effectiveness ratio of <\$100,000 per QALY. In a UK setting, lifetime costs with sitagliptin would have to be less than £2,000 to maintain an incremental cost-effectiveness ratio of <£20,000 per QALY.

Our findings raise some methodological issues associated with conducting economic evaluations using data from multinational clinical trials. First, assigning costs to medical resource use in such trials is complex.²⁴⁻²⁶ We applied a pragmatic approach, assigning US-based costs to medical resources used by patients from all countries, but adjusting inpatient length of stay to account for variations in practice patterns. We also applied UK costs in a sensitivity analysis to evaluate the impact of different price weights on the results. However, all approaches must recognize that practice patterns, and thus rates of medical resource use, can vary dramatically across jurisdictions. We also realize that the constraints of excluding GLP-1 receptor agonists and other DPP-4 inhibitors from usual care means that the results may be less generalizable to countries where these drugs are treatment options.

TECOS provides valuable large-scale pragmatic trial insights into the short- to mid-term incremental effects on medical resource use and costs when sitagliptin is added to usual care for

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type 2 diabetes patients with cardiovascular disease. We observed small reductions in insulin use and hospitalization rates when sitagliptin was added to usual care. These cost-savings slightly offset sitagliptin treatment costs over a 3-year period. The amount of drug cost offset in the US would be proportionately larger with greater discounts and rebates on the WAC for sitagliptin. As type 2 diabetes is a chronic, progressive and complex disease, further research is needed on the impact of DPP-4 inhibitor treatment on clinical outcomes, health care resource utilization and costs in broader diabetes populations such as those with higher HbA1c levels with and without pre-existing cardiovascular disease.

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Figure legend

Figure 1—Mean cumulative number of hospitalizations per patient and 95% confidence intervals by treatment group. See Table 3 for results by minimum follow-up duration.

Table 1—Medical resource use and costs throughout trial

	Sitagliptin (n=7332)	Placebo (n=7339)	Difference (95%CI)*	Relative rate/ Means ratio (95%CI)	P-value
Medical resource use					
All-cause hospitalizations	0.66 (1.29)	0.70 (1.43)	-0.05 (-0.09 to -0.01)	0.95 (0.90-1.02)	0.14
Inpatient days	5.50 (16.38)	5.74 (16.54)	-0.24 (-0.77 to 0.24)	1.00 (0.90-1.10)	0.94
Outpatient care visits	19.42 (17.36)	19.43 (17.35)	-0.01 (-0.52 to 0.58)	1.00 (0.98-1.02)	0.85
Diabetes drug-days**	1635 (833)	1673 (861)	-38 (-66 to -11)	0.99 (0.97-1.00)	0.06
Direct medical costs[†] (US\$, 2015)					
Inpatient care	6947 (19,935)	7377 (20,066)	-430 (-1109 to 168)	1.08 (0.97-1.21)	0.35
Outpatient care	1465 (1413)	1464 (1364)	1 (-39 to 50)	1.00 (0.97-1.03)	0.88
Diabetes medications	3524 (7644)	3567 (7623)	-43 (-269 to 216)	0.96 (0.91-1.02)	0.18
Total, excluding sitagliptin	11,937 (22,265)	12,409 (22,283)	-472 (-1193 to 247)	1.04 (1.00-1.09)	0.06
Sitagliptin	9978 (4527)	0 (0)			
Total Costs	21,915 (22,630)	12,409 (22,283)	9506 (8809 to 10,233)	1.79 (1.73-1.86)	<.001
Direct medical costs[‡] (English £, 2015)					
Inpatient care	2629 (19,935)	2760 (20,066)	-131 (-406 to 116)	1.05 (0.94-1.17) [¶]	0.20
Outpatient care	2648 (2287)	2654 (2294)	-6 (-73 to 73)	1.00 (0.97-1.03)	0.94
Diabetes medications	781 (870)	805 (868)	-24 (-50 to -5)	0.99 (0.96-1.02)	0.38
Total, excluding sitagliptin	6058 (8769)	6219 (9061)	-161 (-445 to 119)	1.02 (0.99-1.05)	0.22
Sitagliptin	1072 (485)	0 (0)			
Total Costs	7130 (8822)	6219 (9061)	911 (627 to 1201)	1.19 (1.16-1.23)	<.0001

Data are mean (SD) unless otherwise indicated.

* 95%CI's based on bias-adjusted percentile method with nonparametric bootstrapping. ** Represents the number of diabetes drugs per day summed across the follow-up period for each patient. [†] Costs discounted at 3% per annum. [‡] Costs discounted at 3.5% per annum. [¶] Rate ratio, 95%CI's, and *P*-value estimated using Stata's MEGLM command.

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Table 2—Impact of sitagliptin on all-cause hospitalizations by subgroup

Subgroups	Patient population	N	Relative rate (95%CI)	<i>P</i> -value; treatment assignment*	<i>P</i> -value; interaction term**
Age [†]	<65 years	6616	0.92 (0.83-1.02)	0.11	0.36 [‡]
	≥65 years	7735	0.98 (0.91-1.06)	0.65	
	<75 years	12,347	0.93 (0.87-1.00)	0.05	0.04 [‡]
	≥75 years	2004	1.09 (0.95-1.26)	0.23	
Sex [†]	Male	10,374	0.96 (0.90-1.04)	0.33	0.53
	Female	4297	0.94 (0.83-1.05)	0.26	
Body mass index	<30 kg/m2	7735	1.00 (0.91-1.09)	0.91	0.21 [‡]
	≥30 kg/m2	6799	0.92 (0.84-1.00)	0.06	
Duration of diabetes [†]	<5 years	2858	0.96 (0.82-1.13)	0.66	0.23 [‡]
	5 to <15 years	7511	0.91 (0.83-0.99)	0.03	
	≥15 years	4290	1.02 (0.91-1.13)	0.77	
Prior congestive heart failure	Yes	2643	0.99 (0.87-1.12)	0.87	0.42
	No	12,028	0.94 (0.88-1.01)	0.08	
Insulin therapy at baseline [†]	Yes	3408	0.96 (0.86-1.08)	0.48	0.63
	No	11,263	0.94 (0.88-1.01)	0.12	
Geographic region	Asia Pacific and Other	4565	0.98 (0.88-1.11)	0.78	0.53
	Eastern Europe	3965	0.92 (0.82-1.04)	0.18	
	Latin America	1471	1.13 (0.89-1.43)	0.33	
	North America	2594	0.90 (0.79-1.03)	0.13	
	Western Europe	2076	0.96 (0.82-1.12)	0.61	

**P*-values for treatment assignment for each subgroup.
***P*-values for interactions between treatment arm and categorical subgroup.
[†]Prespecified subgroups in trial protocol.
[‡]*P*-values for interaction terms for interactions between treatment group and continuous, linear variables representing are 0.32 for age, 0.07 for body mass index, and 0.18 for duration of diabetes.

Table 3—Hospitalization rates and relative impact of sitagliptin on all-cause hospitalizations by minimum follow-up duration

Duration of follow-up	N	Unadjusted*			Adjusted**	
		Sitagliptin	Placebo	Relative rate	Relative rate	P-value**
≥ 2 years	13,700	0.203	0.223	0.91	0.94 (0.88-1.01)	0.07
≥ 2.5 years	9674	0.200	0.227	0.88	0.90 (0.83-0.97)	0.01
≥ 3 years	7189	0.199	0.225	0.88	0.90 (0.83-0.98)	0.02
≥ 3.5 years	4440	0.183	0.213	0.86	0.89 (0.79-0.99)	0.03
≥ 4 years	2641	0.186	0.215	0.86	0.89 (0.77-1.02)	0.10

*Number of hospitalizations divided by patient-years of follow-up in each time interval.

** Adjusted relative rate and *P*-values from SAS GLIMMIX procedure representing relative impact of sitagliptin versus placebo, accounting for country-level correlation and adjusted for age, sex, prior CV disease and years since diabetes diagnosis.

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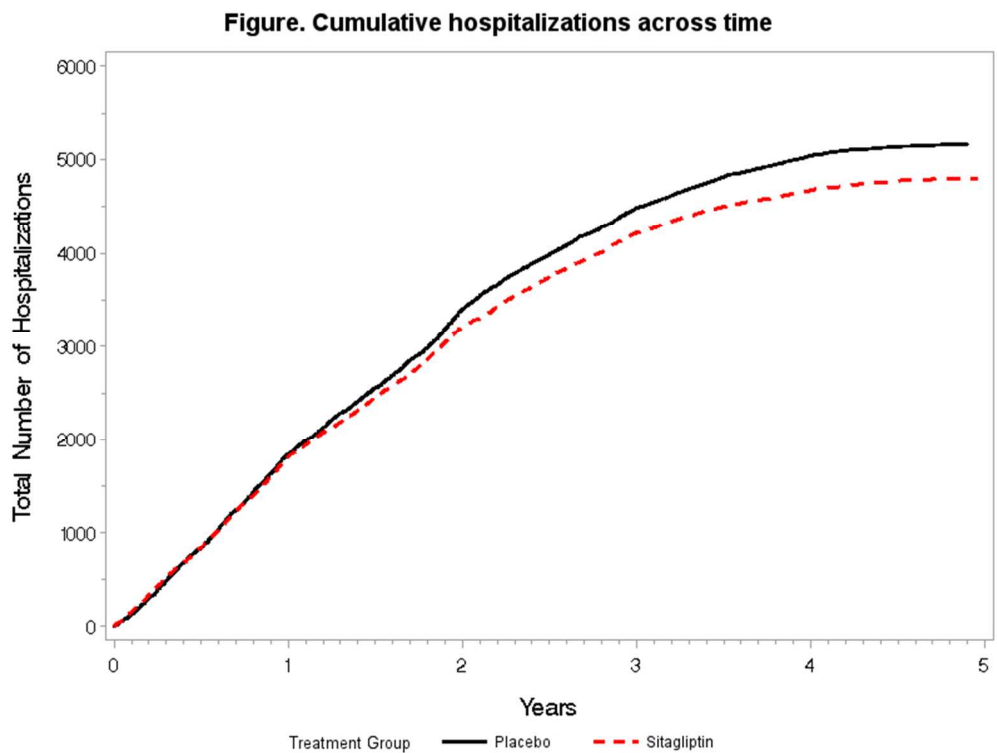


Figure 1
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ONLINE APPENDIX

Table 1. US DRG codes assigned to discharge diagnoses pre-specified in trial case report form

Pre-specified Discharge Diagnosis	DRG codes	DRG Description
Hypertension requiring inpatient treatment	305	Hypertension without MCC
Diabetes requiring inpatient treatment	638	Diabetes with CC
Diabetic neuropathy	74	Cranial and peripheral nerve disorders without MCC
Diabetic retinopathy	125	Other diseases of the eye without MCC
Diabetic nephropathy	699	Other kidney and urinary tract diagnoses with CC
Renal failure	683	Renal failure with CC
Scheduled cardiovascular procedure	N/A	Specific procedure identified using procedure information reported in CRF.
Heart failure	292	Heart failure and shock with CC
Unstable angina	311	Angina pectoris
Myocardial Infarction (MI)	280	Acute MI, discharged alive with MCC
Pulmonary embolism	176	Pulmonary embolism without MCC
Septicemia	872	Septicemia or severe sepsis without mv 96+ hours without MCC
Fracture of hip or pelvis	470	Major joint replacement or reattachment of lower extremity without MCC
Diverticulosis or diverticulitis	392	Esophagitis, gastroenteritis and miscellaneous digestive disorders without MCC
Gastrointestinal hemorrhage/obstruction	378	GI hemorrhage with CC
Peritonitis and intestinal abscess	372	Major gastrointestinal disorder and peritoneal infections with CC
Endocarditis	291	Acute and subacute endocarditis with MCC/
Presyncope/hypotension	312	Syncope and collapse
Syncope	312	Syncope and collapse
Stroke	65	Intracranial hemorrhage or cerebral infarction with CC
TIA	69	Transient ischemia
Acute bronchitis	203	Bronchitis and asthma without CC/MCC
Urinary tract infection	690	Kidney and urinary tract infections without MCC
Biliary tract disease	445	Disorders of the biliary tract with CC
Fluid & electrolyte disorders	641	Miscellaneous disorders of nutrition,

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		Metabolism and Fluids and Electrolytes without MCC
Cancer	999 [†]	Costs were assigned based on the top 12 DRG codes for cancers reported in the 2012 NIS data on the HCUP.net website
Depression	881	Depressive neuroses
Acute and subacute necrosis of liver	443	Disorders Of liver except malignancy, cirrhosis, alcoholic hepatitis without CC/MCC
Inflammatory disease of prostate	728	Inflammation of the male reproductive system without MCC
Acute pancreatitis	440	Diseases of pancreas except malignancy without CC/MCC
Skin and soft tissue infection	603	Cellulitis without MCC
Ophthalmologic/eye disease	125	Other diseases of the eye with/without MCC

DRG: Diagnosis-Related Group; MCC: major complications and comorbidities; CC: complications and comorbidities. To choose among the DRG codes corresponding to the diagnoses with MCC, with CC, or without CC/MCC, the DRG code most frequently represented in the 2012 Nationwide Inpatient Sample (NIS) was assigned.

[†]For the general diagnosis of ‘cancer’, a weighted daily reimbursement was computed across 12 cancer-related DRG codes with weights based on the number of discharges in the 2012 Nationwide Inpatient Sample. The 12 most frequent DRG codes were used because there was a discernible drop in the frequency of cancer-related codes after the first 12.

Table 2. US DRG codes for procedures included in trial case report form

Inpatient procedures	DRG codes	DRG description
Coronary artery bypass graft (CABG)	234	Coronary bypass w cardiac catheterization without MCC
Cardiac catheterization	287	Circulatory disorders except acute myocardial infarction, with cardiac catheterization without MCC
Percutaneous coronary intervention	251	Percutaneous cardiovascular procedure without coronary artery stent Without MCC
Amputation, above the knee	240	Amputation for circulatory system disorders except upper limb & toe without CC
Amputation, below the knee	256	Upper limb & toe amputation for circulatory system disorders with CC
Amputation, multiple digits	256	Upper limb & toe amputation for circulatory system disorders with CC
Revascularization of lower extremity artery	253	Other vascular procedures with CC
Surgical repair of abdominal aortic aneurysm	237	Major cardiovascular procedures with MCC
Intra-aortic balloon pump (IABP)	237	Major cardiovascular procedures with MCC
Left ventricular assist device (LVAD)	001	Heart transplant or implant of heart assist system with MCC
Pacemaker	243	Permanent cardiac pacemaker implant with CC
Transplant (heart)	001	Heart transplant or implant of heart assist system with MCC
Carotid intervention	36	Carotid artery stent procedure without CC/MCC
Carotid surgery	36	Carotid artery stent procedure without CC/MCC
Chronic peritoneal/hemodialysis	685	Admit for renal dialysis
Renal transplant	652	Kidney transplant

DRG: Diagnosis-Related Group; MCC: major complications and comorbidities; CC: complications and comorbidities.

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Table 3. Current Procedural Terminology (CPT) codes for physician services

CPT Code	CPT Code Description
99223	Initial hospital care, per day, for the evaluation and management of a patient, which requires these 3 key components: a comprehensive history; a comprehensive examination; and medical decision making of high complexity.
99239	Hospital discharge day management; more than 30 minutes.
99233	Subsequent hospital care, per day, for the evaluation and management of a patient, which requires these 2 key components: a comprehensive history; a comprehensive examination; and medical decision making of high complexity.
99213	Level 3 established outpatient visit requiring 2 of the following components: expanded problem focused history; expanded problem focused exam; low complexity medical decision making

Table 4. CPT codes for medical procedures collected in case report form

	CPT codes
Coronary Artery Bypass Graft (CABG)	33512
Cardiac Catheterization	93454
Percutaneous Coronary Intervention	92997
Amputation, above the knee	27590
Amputation, below the knee	27880
Amputation, multiple digits	26951
Revascularization of lower extremity artery	37228
Surgical repair of Abdominal Aortic Aneurysm	34802
Chronic Peritoneal/Hemodialysis/Dialysis	90935
Renal Transplant	50320, 50340, 50365
Intra-aortic balloon pump (IABP)	33967
Left ventricular assist device (LVAD)	33979
Pacemaker	33206
Transplant (heart)	33945 33940 33944
Ultrafiltration	90945
Hemofiltration	90935
Dialysis	90935
Thrombolysis	72975
Stress Test [†]	93350
ECG	93000
Carotid Intervention [‡]	37215
Carotid Surgery [‡]	37215
Head CT	70460
Head MRI	70552
Cerebral Angiography	70496
Lumbar Puncture	62270
Transesophageal Echocardiogram	93312
Head PET Scan	78607
Pancreas imaging (abdominal CT, MRI, or ultrasound) [§]	76700

[†]Stress test was not separately reimbursed in 2015. It was assumed that a recorded stress test was performed with echocardiography and assigned CPT® code 93350 (Echocardiography rest and cardiovascular stress test with interpretation and report).

[‡]CPT® code 37215 is for transcatheter placement of intravascular stent(s), cervical carotid artery, percutaneous; with distal embolic protection.

[§]CPT® code 76700 is for abdominal ultrasound.

SUPPLEMENTAL METHODS

Cost assignment for England

To do this, US medical DRG codes were converted into ICD-10-CM codes and used to cross-match the US DRGs into English Healthcare Resource Groups (HRGs) using the English Reference Cost HRG4+ Grouper Software. US procedure DRGs that had no associated ICD-10 code were matched to English HRGs using the UK Office of Population Censuses and Surveys (OPCS) Classification of Interventions and Procedures version 4 (OPCS-4) or directly into HRGs, where appropriate. For each HRG code, the cost per inpatient day was then estimated by dividing the 2015 Reference costs for the entire duration of an inpatient stay (i.e. spell costs) by the respective mean length of stay published by the Department of Health (1). In the UK setting, there are different unit costs for the same HRG conditional on being an elective or an emergency admission as well as a 1- ay stay or a longer stay. Hence, we averaged elective and emergency admission unit costs into a single unit cost using the number of admissions at HRG level published in England. Finally, when several HRGs were matched to a single US DRG, we estimated the weighted average cost per inpatient day using the number of admissions reported per HRG in England.

We used an analogous approach as applied for the US analysis to adjust lengths of stay for non-UK hospitalizations, by calculating the ratio of mean length of stay across all hospitalizations in the UK to the mean length of stay in each non-UK country participating in the trial, then multiplying the length of stay for each hospitalization by the country-specific conversion factor to approximate the length of stay if the patient had been treated in the UK. Costs per inpatient day were applied to estimate total inpatient costs. Admissions with adjusted lengths of stay of less than 1 day were costed as though they lasted 1 day.

Outpatient visits to usual diabetes care providers and other providers were valued using 2015 Reference costs. Daily costs for concomitant diabetes medications were calculated as the weighted average daily cost based on the total volume of different drugs of that dose and type prescribed in England in 2015, and thus represent a weighted mix of generic and proprietary drugs. The daily cost assigned for sitagliptin was £1.19 across all doses. All medical costs incurred beyond the first year were then discounted at the UK-approved rate of 3.5% per year.

Supplemental Reference

1. Department of Health. NHS reference costs 2014 to 2015. Available from
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