ClinicoEconomics and Outcomes Research

Dovepress

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ORIGINAL RESEARCH

Increase in direct diabetes-related costs and resource use in the 6 months following initiation of insulin in patients with type 2 diabetes in five European countries: data from the INSTIGATE study

This article was published in the following Dove Press journal:
ClinicoEconomics and Outcomes Research
19 December 2012
Number of times this article has been viewed

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Background: The purpose of this study was to describe the resource use and associated direct costs of diabetes care for patients with type 2 diabetes mellitus in the 6 months before and after initiation of insulin therapy.

Methods: INSTIGATE is a prospective, noninterventional, multicenter study of patients with type 2 diabetes who were initiating insulin for the first time as part of their usual care in 2006. The study was conducted in France, Germany, Greece, Spain, and the UK, and observed the course of diabetes therapy for up to 6 months. Direct medical costs were evaluated from the national health care system (third-party payer) perspective at 2006 prices.

Results: Of the 1153 patients with type 2 diabetes, 1051 (91.2%) had follow-up visits in the 6 months after insulin initiation and were included in the cost analysis. In all countries in our study, mean total direct costs per patient increased in the 6-month follow-up period, compared with the 6-month period prior to insulin initiation, and ranged from €577 in Greece to €1402 in France. The incremental cost of adding insulin treatment ranged from €81 in France to €471 in Spain.

Conclusion: In all countries, the mean total direct cost of care for diabetes increased after starting insulin. The breakdown of total direct costs by expenditure category varied considerably across countries, reflecting differences in resource use patterns, prices of medical resources, and different health care systems.

Keywords: type 2 diabetes mellitus, costs, resource use, insulin

Introduction

Diabetes mellitus represents a serious public health problem despite many advances in its treatment over the past few decades, and is a growing burden on global economies.[1] The clinical effectiveness of insulin therapy in patients with type 2 diabetes mellitus is well established, and clinical guidelines recommend initiation of insulin (or glucagon-like peptide-1 receptor agonists) for the many patients who are not adequately controlled using oral antidiabetic drugs.[2] However, according to the International Diabetes Federation audit findings, data on real-world health care resource utilization and costs associated with insulin use in European countries are limited.[1,3] The International Diabetes Federation has called for reliable data on diabetes and its associated costs.[1,3]

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A 2002 publication estimated (using 1999 values) the total direct medical cost of type 2 diabetes in eight European countries to be €29 billion a year (at an average annual cost per patient of €2834). Hospitalizations accounted for the greatest proportion (55%) of these costs, whereas the costs of oral antidiabetic drugs and insulin accounted for only 7% of the total health care costs.[4] Results of another analysis, performed at a similar time in the US, showed that the initiation of insulin therapy initially increased disease-related and total health care expenditures in patients with type 2 diabetes, but that this was offset by a consistent and substantial decrease in both these health care expenditures during the next 7 months.[5] By 9 months after initiation of insulin, total health care expenditures were reduced by 40% from levels before initiation. However, since these publications, there have been significant changes to the treatment options for patients with type 2 diabetes, notably with the introduction of the long-acting insulin analogs. Further, we have little understanding of how, in a European setting, the direct costs associated with utilization of health care resources differ before and after initiation of insulin therapy.

The observational INSTIGATE study was designed to assess the direct costs associated with initiation of insulin therapy in patients with type 2 diabetes and to describe the resource utilization, quality of metabolic control, clinical outcomes, and health-related quality of life following initiation of insulin therapy in five European countries. Clinical outcomes at 6 months from this study have recently been reported.[6] This paper aims to describe the resource use and associated direct costs of diabetes care, and between-country differences in direct costs and those patient and disease characteristics associated with total direct cost, for patients with type 2 diabetes in the 6 months before and after initiation of insulin therapy.

Materials and methods

Study design

INSTIGATE is a prospective, noninterventional, multicenter observational study of patients with type 2 diabetes who were initiating insulin for the first time as part of their usual care in 2006. The study was conducted in France, Germany, Greece, Spain, and the UK, and observed the course of diabetes therapy following insulin initiation for 6 months, and up to 24 months in some countries. The investigators were general practitioners, endocrinologists, diabetologists, and internal medicine specialists from primary and secondary care centers having a large number of patients with type 2 diabetes starting insulin therapy. Patient visits occurred during the normal course of care and all treatment choices were made by the physician and patient. Details on study design and baseline patient characteristics, as well as preliminary results for diabetes-related resource utilization and costs in German patients, have been published recently.[7,8]

Study population

All eligible patients with type 2 diabetes according to prespecified inclusion criteria were invited to participate in this study in 2006, and consenting patients were recruited at geographically distinct sites across the participating countries. Study participants were required to be aged 18 years or older with a diagnosis of type 2 diabetes and initiating insulin therapy for the first time within the normal course of care (not simultaneously participating in a study that included an investigational drug or procedure), and to have sufficient understanding of the primary language of the country. All patients participating in the study gave written informed consent for the release of their information according to local regulations. Patients received no compensation for participation in the study. Each participating country met local regulatory and ethics requirements, including, where relevant, regulatory notifications, reviews, and approvals for this type of noninterventional and observational study.

Participant physicians

Across all countries, participating study centers were those that routinely dealt with a large number of patients with type 2 diabetes. Investigators were health care professionals who were either responsible for initiating insulin therapy or were actively involved in the routine management of patients initiating insulin after referral to a diabetes specialist. Centers could provide primary or secondary care, depending on normal treatment practice for insulin initiation in that country. Therefore, diabetologists and general practitioners were selected by a stratified random procedure from two databases (Cegedim specialist and general practitioner databases) in France, only specialists were associated with the study in Germany, and investigators were nonrandomly selected from diabetologists, endocrinologists, internal medicine specialists, and primary care physicians who treated patients with diabetes in other countries.

Data collection

At baseline, ie, at the time of insulin initiation, investigators provided data for each patient on sociodemographics, history of diabetes, clinical status of diabetes, metabolic syndrome, and significant comorbidities, in addition to

diabetes-related medical resource utilization data for the previous 6 months, collected via a retrospective chart review. Patients were then followed prospectively for 6 months, and investigators reported clinical outcomes and diabetes-related medical resource utilization at two visits, approximately 3 and 6 months after insulin initiation. For those patients who missed a follow-up visit, physicians had the option to collect data by phone interview and/or regular mail. Information on diabetes-related medical resource utilization included visits/phone calls/consultations with health care professionals, hospitalizations for acute and long-term diabetes-related complications and hypoglycemia, treatment with insulin, any oral antidiabetic drugs, and blood glucose monitoring. Health care professionals were general practitioners and nurses, diabetologists/endocrinologists, specialists in internal medicine, specialist nurses, ophthalmologists, dieticians, and podiatrists. Investigators were compensated (at minimum rate) for the time associated with the data documentation for this study.

Cost assessment

Direct medical costs were evaluated from the national health care system (third-party payer) perspective at 2006 prices. UK costs were converted to Euros using the 2006 average annual exchange rate (£1 = €1.4666). Direct nonmedical costs (eg, transportation costs) and indirect costs (eg, productivity losses) were not assessed in this study. The different components of direct medical costs assessed in this study were as follows: visits/phone calls to health care professionals; insulin; blood glucose testing strips; oral antidiabetic drugs; and hospitalizations (as defined earlier). In France, unit cost data for physician visits/phone calls/consultations were obtained from published sources.[9] A national survey of hospitals provided data on inpatient costs.[10] Drug prices from the Vidal database[11] were used for calculating the average daily cost of medications from pack sizes, strength, and dosage. The cost of blood glucose monitoring was based on the cost of the blood glucose test strip, the lancet material, and the blood glucose monitor, and calculated using data from the Liste des Produits et des Prestations of the National Health Insurance Funds.[12] The assessment of costs for physician visits/phone calls/consultations in Germany was based on the uniform evaluation standard of physicians accredited by the National Association of Statutory Health Insurance.[13] Diagnosis-related groups were used to assign hospitalization costs.[14] Costs for oral antidiabetic drugs, insulin, and blood glucose monitoring were derived from the average pharmacy retail price.[15] Unit cost data for physician visits/phone calls/consultations, hospitalizations, and blood glucose monitoring in Spain were obtained from the Oblikue database.[16] Per diem costs were used for calculating the cost of hospitalization. Medication prices were taken from Catálogo de Especialidades Farmaceuticas, and average cost per day was calculated from pack sizes, strength, and dosage.[17] In the UK, unit costs of physician visits/phone calls/consultations and hospitalizations were sourced from the National Schedule of Reference Costs by the Department of Health, and the Unit Costs of Health and Social Care compiled by the Personal Social Services Research Unit.[18,19] The cost of insulin, oral antidiabetic drugs, and blood glucose monitoring was calculated based on drug and test strip prices detailed in the British Pharmaceutical Formulary.[20] Unit costs for Greece, to our knowledge, were not publicly available at the time of our study and were sourced directly from the National Board of Trade, Ministry of Health, and Integrated Management Strategy.

Statistical analyses

The primary objective of this study was to assess the direct costs associated with the first 6 months of insulin therapy in patients with type 2 diabetes mellitus at a country level. Sample size was preplanned in the protocol and based on information available at that time. Approximately 250 patients per country were calculated to provide adequate precision for the estimation of mean direct costs, assuming that 10% of data collected may be incomplete or inadequate for use.

All analyses were descriptive and exploratory, and were carried out in patients with both baseline and 6-month follow-up data. Continuous variables were summarized by their mean and standard deviation or, when there was high variability (such as for data on costs), by their median and interquartile range; categorical variables by percentages based on the total number of patients per country. Missing data were not imputed. All analyses were conducted using SAS software version 9.1.3 (SAS Institute Inc, Cary, NC).

Results

Sociodemographic characteristics

Of the 1172 patients with type 2 diabetes included in the study at baseline, 21 were excluded from further analyses because only limited baseline values were entered and no information was provided concerning the use of insulin during the entire study period. Data for two additional patients in Germany were entered after the baseline database lock and were included in post-baseline analyses. Thus, in total, 1153 patients with type 2 diabetes from France, Germany, Greece, Spain, and the UK were included in the study.

Table 1 Demographics and clinical characteristics at baseline (time of insulin initiation) for patients with a visit 6 months after insulin initiation, by country and overall, and for patients who were excluded from analyses

	Patients with a visit 6 months after insulin initiation						Excluded patients
	France	Germany	Greece	Spain	UK	Overall	Overall
Total number of patients	152	233	256	188	222	1051	102
Mean (SD) age, years	64.7 (11.3)	61.2 (12.4)	66.0 (10.1)	65.3 (11.8)	59.8 (11.0)	63.3 (11.6)	62.7 (14.4)
Male, % of patients	60.5	59.2	53.5	57.4	63.1	58.5	56.9
Mean (SD) BMI, kg/m^2	29.4 (6.2)	30.4 (5.8)	28.1 (4.7)	29.7 (5.6)	32.2 (6.5)	29.9 (5.9)	29.6 (7.2)
Mean (SD) waist circumference, cm	101.4 (16.3)	106.3 (13.2)	100.4 (14.6)	100.3 (17.1)	103.5 (16.8)	102.2 (15.5)	98.6 (15.9)
Mean (SD) time since diagnosis, years	12.7 (8.0)	6.7 (7.2)	11.6 (7.0)	10.7 (7.0)	8.0 (5.6)	9.7 (7.3)	10.0 (8.4)
Mean (SD) HbA_{1c} at insulin initiation, %	9.5 (1.9)	9.2 (2.0)	9.6 (1.6)	9.2 (1.6)	10.2 (1.6)	9.6 (1.8)	9.9 (2.3)

Abbreviations: SD, standard deviation; BMI, body mass index; HbA_{1c}, glycated hemoglobin.

Of these, 1051 (91.2%) had follow-up visits in the 6 months after insulin initiation and were included in the current analysis. The baseline sociodemographic characteristics of these patients are summarized in Table 1, both by country and overall. The demographic characteristics of patients who entered the study, and for whom 6-month data were available, are as expected for patients with type 2 diabetes; they did not differ substantially between countries or from those of patients who withdrew from the study before month 6 (Table 1). The mean time since diagnosis varied between 6.7 years (in Germany) and 12.7 years (in France) (Table 1).

Insulin regimens and oral antidiabetic drugs

As illustrated in Table 2, the insulin regimen at initiation varied across countries. In France, Greece, Spain, and the UK, where most patients were initiated on a basal only or mixture only regimen, the percentage distribution of insulin regimens remained relatively stable over time. In Germany, a large number of patients were initiated on a short-acting only regimen and many had moved to a basal bolus regimen by 6 months. In all countries, and across treatment regimens, the mean total daily dose of insulin (measured as IU or IU/kg) increased during the study period.

Table 2 Insulin regimen and total daily dose at insulin initiation (baseline) and 6 months thereafter (follow-up), by country

	France			Germany		
Total number of patients	**152**			**233**		
Insulin regimen and dose, mean (SD)	**Baseline**	**6 months**	**Change**	**Baseline**	**6 months**	**Change**
Long/intermediate only						
Patients, %	84.2	77.0		12.0	9.0	
Total daily dose, IU	17.1 (9.2)	25.0 (17.4)	8.2 (15.4)	7.2 (4.4)	12.6 (9.2)	5.2 (7.3)
Total daily dose, IU/kg	0.212 (0.107)	0.299 (0.188)	0.086 (0.178)	0.085 (0.051)	0.154 (0.107)	0.064 (0.085)
Mixture only						
Patients, %	9.2	8.6		9.4	9.4	
Total daily dose, IU	30.3 (13.2)	44.5 (30.9)	13.1 (25.2)	16.5 (5.4)	35.0 (24.5)	19.7 (23.0)
Total daily dose, IU/kg	0.399 (0.221)	0.511 (0.332)	0.126 (0.276)	0.201 (0.064)	0.421 (0.268)	0.231 (0.252)
Short-acting only						
Patients, %	0.7	0.0		50.2	33.0	
Total daily dose, IU	18.0 (–)	N/A	N/A	24.5 (11.1)	39.8 (24.7)	16.1 (20.6)
Total daily dose, IU/kg	0.320 (–)	N/A	N/A	0.279 (0.134)	0.429 (0.241)	0.164 (0.199)
Basal/bolus						
Patients, %	5.9	9.2		23.6	40.8	
Total daily dose, IU	51.6 (16.2)	57.9 (25.0)	8.7 (20.2)	31.4 (15.0)	56.0 (34.8)	24.9 (34.8)
Total daily dose, IU/kg	0.629 (0.170)	0.641 (0.184)	0.046 (0.197)	0.384 (0.209)	0.610 (0.341)	0.233 (0.362)
Other[a]						
Patients, %	0.0	3.9		4.7	5.6	
No insulin						
Patients, %	0.0	1.3		0.0	2.1	

Notes: [a]Data are not presented for these patients because of the small numbers.
Abbreviations: SD, standard deviation; IU, international units; –, data not available/could not be calculated; N/A, not applicable.

The largest mean increases in the total daily dose of insulin were reported in Germany and the UK, and small increases were reported in Spain.

The use of oral antidiabetic drugs was higher in France, Germany, Greece, and Spain following insulin initiation, with the largest difference seen in Spain, where 71.3% of patients were prescribed oral antidiabetic drugs in the 6 months after insulin initiation, compared with 58.5% in the 6 months prior to the baseline visit (Tables 3 and 4). In the same time frame, the use of oral antidiabetic drugs in the UK changed from use in 78.4% of patients prior to insulin initiation to use in 75.2% of patients after insulin initiation. Very few patients in any country were receiving more than two oral antidiabetic drugs (Table 3). The most commonly used oral antidiabetic drug in all countries was metformin, which was usually administered alone or with a sulfonylurea (Table 3).

Resource utilization

Diabetes-related medical resource utilization in the 6 months before insulin initiation, and in the 6 months thereafter, is summarized in Table 4. The distribution of types of health care professional contact differed between the countries (Table 4), the difference being driven, in part, by the range of participating clinicians.

Overall, the distribution of diabetes-related medical resource utilization varied across countries both at baseline and during the 6 months after insulin initiation. No consistent patterns of change could be detected across the five countries, either in terms of the magnitude or direction of change in individual resources measured, with the exceptions of visits to general practitioners (which appeared to decrease), interactions with specialist nurses (which increased), and blood glucose monitoring (which increased).

The mean number of visits or consultations with health care professionals appeared to be higher after insulin initiation, changing from 6.1 to 10.0 visits in the 6 months before insulin initiation to 7.7 to 18.8 visits thereafter, in all countries except the UK, where the mean number of visits was 7.9 and 6.5 at these times, respectively; the largest apparent change was reported in France (+9.9), and this was mainly driven by the mean increase in number of visits to primary care nurses (+9.7) which, in turn, was driven by a small number of patients with very frequent contacts.

Only a small proportion of patients (3.2% to 8.2%) had hospital admissions at baseline in all countries except France, which had a hospitalization rate of 28.3%. In the 6 months following insulin initiation, this rate was more than halved in France and remained small in the other countries (1.3% to 5.3%). Median length of stay appeared to show little

Greece			Spain			UK		
256			188			222		
Baseline	6 months	Change	Baseline	6 months	Change	Baseline	6 month	Change
48.4	46.1		68.1	67.0		38.7	33.8	
23.6 (12.4)	29.4 (14.6)	5.7 (10.6)	16.9 (8.1)	19.4 (9.6)	2.4 (5.3)	13.3 (7.9)	36.3 (29.7)	23.7 (28.72)
0.305 (0.166)	0.374 (0.189)	0.069 (0.140)	0.221 (0.108)	0.248 (0.109)	0.027 (0.070)	0.138 (0.067)	0.349 (0.253)	0.217 (0.259)
30.1	30.5		20.7	20.7		53.6	54.5	
38.3 (12.1)	46.8 (14.5)	7.9 (10.4)	30.6 (14.7)	36.4 (20.6)	4.9 (9.9)	24.2 (11.2)	42.2 (23.5)	17.1 (23.1)
0.503 (0.171)	0.598 (0.183)	0.086 (0.131)	0.380 (0.195)	0.452 (0.262)	0.059 (0.117)	0.274 (0.124)	0.449 (0.214)	0.155 (0.222)
6.6	6.3		8.0	6.9		0.9	0.9	
40.2 (23.1)	45.1 (27.4)	5.9 (8.0)	22.7 (7.9)	23.5 (10.1)	1.7 (3.4)	17.0 (9.9)	33.0 (12.7)	16.0 (22.6)
0.533 (0.242)	0.564 (0.273)	0.037 (0.081)	0.322 (0.108)	0.323 (0.123)	0.023 (0.040)	0.177 (0.111)	–	–
12.1	14.1		2.1	2.1		5.0	9.0	
39.0 (18.0)	50.5 (20.2)	11.7 (15.1)	24.0 (9.5)	38.8 (14.3)	3.0 (–)	24.6 (5.0)	51.2 (30.3)	25.5 (29.0)
0.504 (0.165)	0.639 (0.222)	0.144 (0.223)	0.358 (0.210)	0.556 (0.204)	0.027 (–)	0.264 (0.076)	0.548 (0.252)	0.343 (0.287)
2.7	3.1		1.1	2.7		0.9	1.4	
0.0	0.0		0.0	0.5		0.9	0.5	

Table 3 Oral antidiabetic drug use during the 6 months before insulin initiation (baseline) and during the 6 months thereafter, by country and overall

	France		Germany		Greece		Spain		UK		Overall	
	152		233		256		188		222		1051	
	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months
Ongoing/new medications, n, % of patients												
0	18.4	13.8	59.2	57.9	57.4	46.5	41.5	28.7	21.6	24.8	41.8	36.5
1	38.2	34.9	37.3	38.6	30.5	41.4	41.5	44.7	57.7	59.0	40.8	44.1
2	39.5	46.1	3.4	3.4	10.9	10.5	16.5	26.1	19.4	14.9	16.2	17.8
3	3.9	5.3	0	0	1.2	1.6	0.5	0.5	1.4	1.4	1.2	1.5
Most common medications, % of patients												
Metformin	18.4	14.5	33.0	33.0	19.9	25.0	26.1	26.6	45.9	49.5	29.2	30.7
Metformin + sulfonylurea	28.3	31.6	1.7	1.3	8.2	6.3	11.7	17.0	16.2	12.2	12.0	12.0
Metformin + other	3.3	6.6	1.7	2.1	1.6	3.1	4.3	6.9	2.7	2.7	2.6	4.0
Metformin + sulfonylurea + other	4.0	4.6	0	0	1.2	1.6	0.5	0.5	0.9	0.9	1.2	1.4
Sulfonylurea	13.2	13.2	2.1	2.1	9.0	12.1	9.0	9.6	10.4	8.6	8.4	8.8
Sulfonylurea + other	5.9	6.6	0	0	0.4	0.4	0.5	1.6	0.9	0.5	1.3	1.4
Other	8.6	9.2	2.1	3.4	2.4	5.1	6.4	9.0	1.4	0.9	3.7	5.1

change between the two study periods in all countries except Germany, where it was halved. However, the numbers of patients contributing to these data were small at all times.

Direct medical costs

Diabetes-related total direct costs and their components are summarized in Table 5. Both before and after starting insulin, the country distributions for the total direct cost of diabetes per patient exhibited high variability (Figure 1), as shown by the large standard deviations of the mean, and wide interquartile ranges around the medians. This was largely a result of the different hospitalization rates and the high cost of hospitalization in each country (Table 5). The breakdown of total direct costs by expenditure category also varied considerably across countries at both time periods measured, reflecting differences in the resource use pattern and regimens, and in the prices of medical resources (Table 5). However, at 6 months after initiation of insulin, resource use patterns had changed (Table 5), and both mean and median total direct costs per patient had increased, in all countries in our study, compared with the 6-month period prior to insulin initiation (Table 5). Mean total direct costs during the 6-month follow-up period ranged from €577 per patient in Greece to €1402 per patient in France, with the mean incremental cost of adding insulin treatment ranging from €81 in France to €471 in Spain (Table 5).

In all countries, both the absolute cost of oral antidiabetic drugs, the proportion of total costs attributed to these medications were lower during the 6 months after insulin initiation than in the baseline period (Table 5). Blood glucose monitoring costs also increased in all countries between the two periods, particularly in Germany, and generally contributed a greater proportion of the total costs (Table 5). However, in Spain, the contribution of blood glucose monitoring to mean total costs changed from 15.2% to 13.8%. In this country, mean hospitalization costs increased, whereas in all other countries, mean hospitalization costs decreased (absolutely and as a proportion of total costs, Table 5). The mean cost of specialist care for glycemic control increased in the 6 months after insulin initiation in all countries; this increase ranged from 20% in France to 177% in Germany (Table 5).

Discussion

The main purpose of this paper is to provide comprehensive direct cost estimates for type 2 diabetes-related treatment in patients who initiated insulin for the first time in five European countries, ie, France, Germany, Greece, Spain, and the UK.

Table 4 Diabetes-related resource utilization during the 6 months prior to insulin initiation (baseline) and during the 6 months thereafter, by country

	France		Germany		Greece		Spain		UK	
	n = 152		n = 233		n = 256		n = 188		n = 222	
	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months
Visits to and consultations with HCPs										
Patients with ≥1 visit/consultation, %	99.3	97.4	99.1	100.0	98.0	96.9	96.8	98.4	99.1	97.7
Mean (SD) visits/consultations	8.9 (8.5)	18.8 (38.1)	10.0 (7.3)	13.3 (7.1)	6.1 (4.6)	7.7 (6.0)	9.1 (6.0)	11.3 (7.7)	7.9 (3.7)	6.5 (4.2)
Phone calls to HCPs										
Patients with ≥1 phone call, %	14.5	17.1	41.2	62.7	28.9	28.1	14.9	18.1	29.7	79.3
Mean (SD) phone calls	0.7 (2.4)	2.2 (9.3)	1.6 (3.5)	2.4 (3.0)	1.4 (3.7)	2.7 (9.2)	0.5 (1.5)	0.9 (2.4)	0.7 (1.5)	5.0 (4.9)
Visits to general practitioners										
Patients with ≥1 visit, %	87.5	80.9	94.0	83.7	57.4	52.3	86.7	84.0	78.8	48.6
Mean (SD) visits	3.2 (2.3)	3.5 (4.9)	4.4 (4.7)	2.4 (2.2)	1.8 (2.5)	1.8 (3.0)	3.4 (3.1)	3.7 (3.3)	2.0 (2.0)	1.0 (1.4)
Phone calls to general practitioners										
Patients with ≥1 phone call, %	12.5	13.8	34.3	16.7	27.3	23.0	13.8	14.4	6.8	7.2
Mean (SD) phone calls	0.5 (1.6)	1.0 (3.6)	0.9 (1.7)	0.4 (1.1)	1.3 (3.6)	2.1 (8.6)	0.3 (0.9)	0.4 (1.2)	0.2 (0.9)	0.2 (0.7)
Visits to primary care nurses										
Patients with ≥1 visit, %	15.1	23.0	13.7	13.3	5.1	4.7	58.5	65.4	61.7	40.1
Mean (SD) visits	1.7 (6.2)	11.4 (35.3)	0.4 (1.2)	0.4 (1.2)	0.1 (0.5)	0.2 (1.1)	2.6 (3.4)	3.4 (4.1)	1.3 (1.6)	0.6 (0.9)
Phone calls to primary care nurses										
Patients with ≥1 phone call, %	5.3	3.9	9.9	6.9	1.6	2.7	10.1	12.2	3.2	6.8
Mean (SD) phone calls	0.2 (1.1)	0.9 (5.8)	0.5 (1.9)	0.1 (0.5)	0.0 (0.3)	0.1 (1.3)	0.2 (0.8)	0.5 (1.4)	0.0 (0.2)	0.1 (0.5)
Consultations with diabetologists/endocrinologists										
Patients with ≥1 consultation, %	75.0	71.1	77.7	97.0	73.8	81.3	59.0	59.0	80.6	50.9
Mean (SD) consultations	1.4 (1.3)	1.5 (1.5)	2.2 (2.6)	3.2 (2.2)	1.9 (1.7)	3.1 (2.4)	1.0 (1.1)	1.2 (1.3)	1.0 (0.7)	0.7 (1.0)
Consultations with internal medicine/other specialists										
Patients with ≥1 consultation, %	44.7	40.1	27.0	27.9	51.6	47.7	42.6	51.1	25.7	20.3
Mean (SD) consultations	0.7 (1.1)	0.9 (1.8)	0.6 (1.2)	0.7 (1.8)	1.2 (1.7)	1.3 (2.3)	0.7 (1.0)	1.1 (1.5)	0.4 (0.9)	0.4 (1.1)
Visits to specialist nurses										
Patients with ≥1 visit, %	17.1	21.1	54.9	91.4	4.3	6.6	28.7	32.4	78.4	82.4
Mean visits	0.4 (1.2)	0.5 (2.0)	1.3 (1.8)	5.0 (3.8)	0.1 (0.3)	0.1 (0.5)	0.5 (0.9)	0.9 (1.6)	1.4 (1.2)	2.1 (1.9)
Phone calls to specialist nurses										
Patients with ≥1 phone call, %	0.7	2.6	12.0	50.6	1.6	6.3	0.5	1.6	22.5	76.6
Mean (SD) phone calls	0.0 (0.2)	0.3 (3.0)	0.2 (0.8)	1.9 (2.8)	0.0 (0.2)	0.4 (1.8)	0.0 (0.1)	0.0 (0.1)	0.4 (1.2)	4.6 (4.8)
Consultations with dieticians/ophthalmologists/chiropodists/podiatrists										
Patients with ≥1 consultation, %	65.1	46.7	55.4	60.5	62.1	62.5	48.4	50.0	77.0	68.9
Mean (SD) consultations	1.5 (1.8)	0.9 (1.5)	1.2 (1.8)	1.6 (2.2)	1.2 (1.8)	1.3 (1.7)	0.8 (1.2)	1.0 (1.4)	1.9 (1.9)	1.7 (1.9)
OAD usage										
Patients with a new/ongoing OAD, %	81.6	86.2	40.8	42.1	42.6	53.5	58.5	71.3	78.4	75.2
Patients receiving metformin, %	53.9	57.2	36.5	36.5	30.9	35.9	42.6	51.1	65.8	65.3
Insulin usage										
Mean (SD) total daily dose, IU	20.4 (13.3)	31.9 (26.0)	23.6 (13.4)	45.3 (32.9)	31.5 (15.9)	39.5 (19.1)	20.3 (11.2)	24.1 (15.2)	20.0 (11.3)	41.9 (29.2)
Mean (SD) total daily dose, IU/kg	0.255 (0.165)	0.369 (0.253)	0.275 (0.168)	0.491 (0.319)	0.412 (0.202)	0.502 (0.232)	0.265 (0.148)	0.309 (0.186)	0.222 (0.123)	0.419 (0.237)

(*Continued*)

Table 4 (*Continued*)

	France		Germany		Greece		Spain		UK	
	n = 152		n = 233		n = 256		n = 188		n = 222	
	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months
Blood glucose monitoring										
Patients with blood glucose monitoring, %	86.2	98.0	76.4	99.6	96.5	99.6	78.2	91.0	95.0	98.2
Mean (SD) times/week[a]	11.5 (7.7)	16.0 (8.5)	9.0 (9.5)	20.8 (8.3)	6.5 (6.8)	8.1 (6.4)	6.8 (7.0)	8.1 (6.7)	9.0 (8.6)	12.0 (8.8)
Hospitalization due to diabetes										
Patients with ≥1 hospitalization, %	28.3	13.8	4.7	1.3	8.2	2.7	3.2	5.3	3.2	2.3
Mean (SD) total length of stay, days[b]	6.7 (4.1)	8.5 (14.6)	9.8 (5.1)	5.3 (1.5)	7.8 (4.3)	6.9 (4.7)	7.0 (4.4)	11.9 (10.5)	4.9 (2.3)	5.2 (6.1)
Median (Q1–Q3) total length of stay, days[b]	5.0 (4.0–10.0)	3.0 (1.0–7.5)	10.0 (5.0–13.0)	5.0 (4.0–7.0)	6.0 (5.0–10.0)	5.0 (3.0–10.0)	8.0 (3.0–10.0)	8.5 (5.0–13.0)	5.0 (3.0–7.0)	3.0 (2.0–4.0)
Hypoglycemia										
Patients with ≥1 episode of hypoglycemia, %	6.6[c]	27.0	3.9[c]	22.3	3.1[c]	29.7	6.4[c]	18.1	5.0[c]	38.3
Patients with ≥1 hospitalization due to hypoglycemia, %	0.0	0.7	0.0	0.4	0.4	0.0	0.5	0.5	0.0	0.5

Notes: [a]For patients who used blood glucose monitoring; [b]for patients who have been hospitalized; [c]in the past 3 months prior to baseline.
Abbreviations: HCP, health care professionals; SD, standard deviation; n, number; OAD, oral antidiabetic drug; IU, international units; Q1, lower quartile; Q3, upper quartile.

Our analysis indicates that health care diabetes-related resource utilization and direct costs for type 2 diabetes vary substantially between countries both before and after initiation of insulin. However, both mean and median direct costs per patient had increased in the 6-month follow-up period in all countries in our study, compared with the 6-month period prior to insulin initiation, in accordance with published data.[21]

The relatively high between-country variations in costs in our study might be due to differences in treatment patterns and care pathways, as well as to country-specific price level effects and purchasing power parities. For example, the frequency of reported macrovascular comorbidities at baseline was lowest in Greece,[7] which may help to explain why mean direct costs per patient were lower than in other countries. Spain showed the highest increase in mean direct costs associated with adding insulin to therapy, with average resource consumption increasing across all resource components, except for oral antidiabetic drug use. Although it is possible that the relatively low cost increase we observed in France was a result of high preinsulin costs, the actual reasons for this finding are unknown and may be multifactorial, including variables such as self-monitoring or hospitalization rates.

Patterns of resource use and associated costs were not consistent across the five countries included in our study, nor were changes in usage or costs consistent across countries, either in terms of magnitude or direction of change in individual resources measured. Nevertheless, some changes in specific resources and their costs were almost universally observed. For example, although the proportion of patients using oral antidiabetic drugs increased by 3%–26% in all countries except the UK (where it decreased by 4%), both the absolute and proportion of mean total cost of oral antidiabetic drugs were lower during the 6 months after insulin initiation than in the baseline period in each of the five countries. Not unexpectedly, because of increased usage, blood glucose monitoring costs increased in all countries between the two periods. However, in Spain, the contribution of blood glucose monitoring to total costs tended to be lower in the 6 months after insulin initiation, possibly because the increase in hospitalization costs seen in this country affected the overall distribution of costs. In all other countries, hospitalization costs decreased. The mean cost of specialist care for glycemic control also increased in all countries, possibly because of the increase in visits and phone calls to specialist nurses that was consistently observed.

A limitation of this study is that the sample may not be representative of the population initiating insulin across all countries. Although diabetologists and primary care physicians were randomly selected from a database in France,

Table 5 Direct costs of diabetes care per patient from the perspective of national health care systems during the 6 months prior to insulin initiation (baseline) and during the 6 months thereafter, by country in Euros

	France		Germany		Greece		Spain		UK	
	n = 152		n = 233		n = 256		n = 188		n = 222	
	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months
Consultation with general practice professionals[a]										
Mean (SD) cost	108 (135)	277 (645)	111 (127)	60 (58)	11 (17)	14 (34)	134 (117)	159 (147)	103 (95)	54 (68)
Median (Q1–Q3) cost	67 (45–134)	67 (45–134)	76 (38–114)	44 (19–81)	4 (0–16)	4 (0–12)	99 (53–196)	123 (49–217)	79 (40–148)	40 (0–79)
% of total mean direct cost	8.2	19.8	19.2	6.2	2.2	2.4	21.0	14.3	15.0	7.0
Specialist care for glycemic control[b]										
Mean (SD) cost	97 (85)	116 (129)	66 (66)	183 (100)	13 (10)	19 (15)	106 (89)	148 (125)	96 (63)	193 (134)
Median (Q1–Q3) cost	83 (41–128)	83 (41–143)	48 (12–94)	165 (115–225)	12 (8–16)	16 (8–25)	105 (53–158)	110 (55–215)	83 (61–123)	171 (101–264)
% of total mean direct cost	7.3	8.3	11.4	19.0	2.6	3.3	16.6	13.3	14.0	25.0
Oral antidiabetic drugs										
Mean (SD) cost	242 (193)	160 (140)	125 (137)	39 (72)	288 (300)	76 (165)	162 (164)	87 (119)	268 (382)	66 (92)
Median (Q1–Q3) cost	177 (99–352)	117 (58–247)	80 (19–176)	0 (0–67)	196 (76–454)	16 (0–84)	97 (35–257)	46 (0–124)	151 (98–373)	40 (15–75)
% of total direct cost	18.3	11.4	21.6	4.1	58.3	13.2	25.4	7.8	39.1	8.5
Insulin										
Mean (SD) cost	N/A	211 (138)	N/A	229 (155)	N/A	251 (137)	N/A	180 (102)	N/A	206 (134)
Median (Q1–Q3) cost	N/A	181 (124–268)	N/A	197 (118–302)	N/A	221 (155–331)	N/A	153 (111–222)	N/A	179 (110–258)
% of total direct cost	N/A	15.0	N/A	23.8	N/A	43.5	N/A	16.2	N/A	26.6
Blood glucose monitoring										
Mean (SD) cost	95 (79)	171 (84)	131 (174)	402 (166)	125 (135)	196 (149)	97 (123)	153 (142)	98 (99)	152 (86)
Median (Q1–Q3) cost	67 (19–135)	171 (110–229)	38 (10–266)	397 (290–526)	60 (40–140)	149 (69–307)	55 (9–127)	111 (48–223)	80 (23–160)	155 (85–203)
% of total direct cost	7.2	12.2	22.6	41.8	25.3	34.0	15.2	13.8	14.3	19.7
Hospitalization										
Mean (SD) cost	721 (1413)	431 (2254)	127 (639)	20 (171)	48 (185)	14 (100)	108 (715)	339 (1880)	46 (283)	37 (344)
Median (Q1–Q3) cost	0 (0–379)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
% of total direct cost	54.6	30.7	21.9	2.1	9.7	2.4	16.9	30.5	6.7	4.8
Other diabetes-related treatment[c]										
Mean (SD) cost	58 (68)	35 (56)	21 (36)	29 (44)	5 (7)	5 (6)	33 (49)	43 (80)	76 (74)	66 (73)
Median (Q1–Q3) cost	45 (0–81)	0 (0–45)	14 (0–14)	14 (0–35)	4 (0–8)	4 (0–8)	0 (0–42)	12 (0–42)	56 (16–116)	40 (0–92)
% of total direct cost	4.4	2.5	3.6	3.0	1.0	0.9	5.2	3.9	11.1	8.5
Mean (SD) total direct cost	1321 (1538)	1402 (2422)	579 (708)	961 (388)	494 (391)	577 (290)	639 (786)	1110 (1966)	686 (488)	773 (513)
Median (Q1–Q3) total direct cost	641 (417–1373)	804 (578–1181)	423 (238–683)	896 (742–1115)	428 (218–659)	538 (370–718)	521 (333–734)	699 (518–1043)	602 (435–812)	712 (528–893)
Mean incremental cost after addition of insulin		81		382		83		471		87

Notes: [a]Includes visits and phone calls to general health care professionals; [b]includes visits and phone calls to following specialists: diabetologists, endocrinologists, internists, and specialist nurses; [c]includes visits and phone calls to dieticians, ophthalmologists, chiropodists, and podiatrists.

Abbreviations: SD, standard deviation; Q1, lower quartile; Q3, upper quartile; N/A, not applicable; n, number.

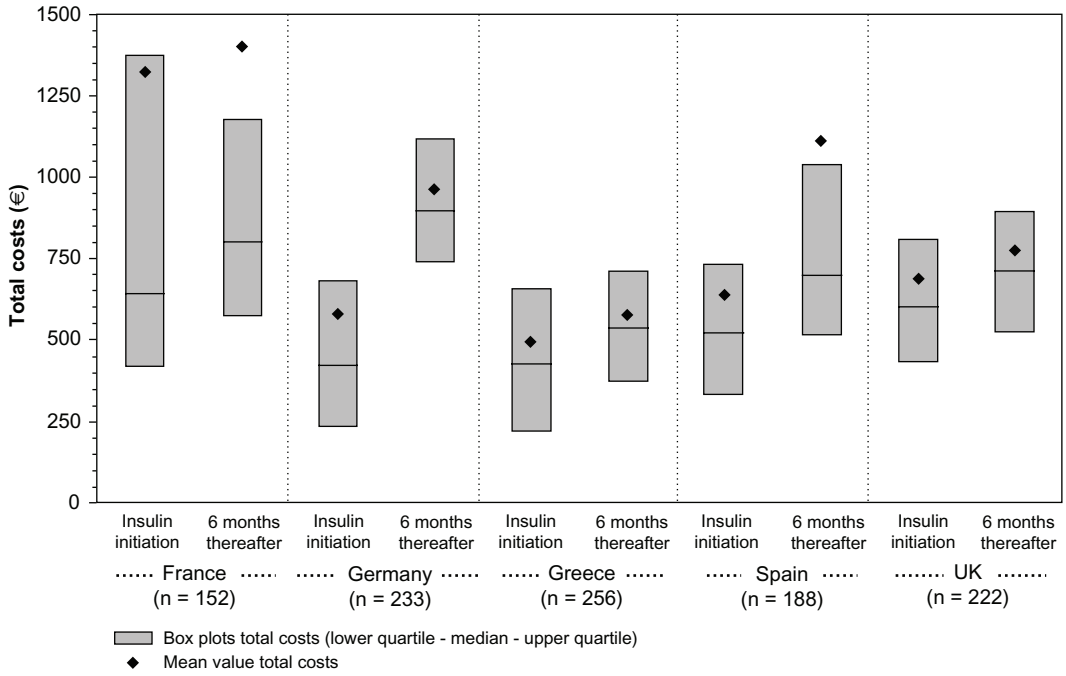

Figure 1 Total direct cost of diabetes care before and after insulin initiation. Total direct cost of diabetes care per patient from the perspective of national health care systems during the 6 months prior to insulin initiation (baseline) and during the 6 months thereafter, by country.
Notes: Box plots present total direct costs as lower quartile, median, and upper quartile. (♦) mean total direct costs.

making it likely that the French population was representative, in other countries physicians were not randomly selected, and in Germany, only diabetologists participated in the study. In this latter instance, the choice of diabetologists as the only participants may have influenced resource utilization, because they are likely to choose more complex insulin regimens that are associated with a higher training expenditure, a likelihood supported by our finding of a markedly different distribution of insulin regimens in Germany, compared with the other countries. Another possible limitation of our study is that, although most data were collected prospectively, the data before initiation of insulin therapy were collected retrospectively using reviews of patient records. However, this retrospective data collection has the advantage of reflecting real-world resource use in patients with type 2 diabetes.

According to results from the CODE-2 study, the largest study on diabetes-related resource use to date, mean yearly direct medical costs per patient with type 2 diabetes treated with insulin alone or in combination with oral antidiabetic drugs in 1999 were €5913 in France, €4997 in Germany, €2309 in Spain, and €2676 in the UK.[10] These costs are higher than those reported in the INSTIGATE study, due perhaps to differences in study methodology (eg, retrospective design in the CODE-2 study versus retrospective and prospective data collection components in the INSTIGATE study), the time when the studies were conducted (CODE-2 in 1999 versus INSTIGATE in 2006), and the patients included (INSTIGATE involved a subpopulation of patients with type 2 diabetes initiating insulin, whereas CODE-2 included a broader sample of patients with type 2 diabetes). Therefore, some patients in the CODE-2 study may have had diabetes for longer and hence experienced more advanced complications, which are known to increase direct medical costs.

There is little available information regarding the current costs of diabetes in Europe, particularly at a level that is detailed enough to be useful for decision-makers, and data regarding the cost of initiation of insulin therapy are even more limited. However, it is expected that, at least initially, insulin therapy will increase resource utilization and direct costs because of both the cost of insulin itself and the need to teach patients how to manage such therapy optimally. The results of our study support this supposition in the five European countries of France, Germany, Greece, Spain, and the UK. Therefore, despite the limitations discussed, our study provides important health economic insight regarding direct cost estimates over the 6 months prior to and 6 months after insulin initiation in patients in five European countries in 2006, helping to meet the data gap identified by the International Diabetes Federation.[1,3]

It has been reported that health care costs for patients with type 2 diabetes initially increase when insulin therapy is initiated, but that this is followed by an overall decrease

in long-term health care expenditure.[20] Analysis of 2-year follow-up data on costs from the INSTIGATE study is planned and will be published in due course, helping to determine if the initial increase in costs is sustained in the longer term.

Conclusion

The mean total direct cost of diabetes care increased after starting insulin in all countries. Differences in resource use patterns, prices of medical resources, and different health care systems likely contributed to the high variability in total direct costs by expenditure category across countries. Further data will determine if the increased costs seen in this study are sustained over a 2-year follow-up period, or whether the increases are related to changes in treatment patterns associated with insulin initiation and are then followed by a decrease in long-term expenditure.

Acknowledgments

We are grateful to M Benroubi, A Charles, A Liebl, and K Meadows (members of the INSTIGATE Advisory Board), coordinating center staff, and clinical investigators for their support in this study.

Disclosure

HTS was employed by Eli Lilly and Company at the time of the study, and is now employed by GlaxoSmithKline plc. AS was employed by Eli Lilly and Company at the time of the study, and is now employed by Sixcess Limited. CN and CS-M are employees of Eli Lilly and Company. The INSTIGATE study was funded by Eli Lilly and Company and supported by Amylin Pharmaceuticals Inc. Funding for preparation of the manuscript was provided by Eli Lilly and Company. Medical writing support was provided by L Breitscheidel and M Merito (Kendle GmbH, Germany), and Caroline Spencer (Rx Communications, UK). The other authors have no conflicts of interest to declare.

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