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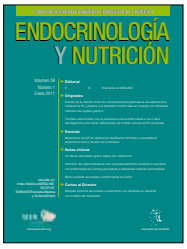

ORIGINAL ARTICLE

Direct health care costs in patients with type 2 diabetes mellitus six months after starting insulin treatment in Spain: The INSTIGATE Study

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KEYWORDS
Health care costs;
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Abstract
Background and objectives: The INSTIGATE study was designed to assess the direct health care costs incurred by patients with type 2 diabetes mellitus (T2DM) who start insulin therapy in Spain. It was a multicenter, observational, non-interventional, prospective study.
Methods: Direct costs per patient in standard clinical practice were assessed for 6 months before and after the start of insulin therapy from the perspective of the Spanish health care system. A total of 188 patients (42.6% women) with a mean age of 65.3 years, a mean body mass index of 29.7 kg/m^2, and a mean disease duration of 10.7 years were assessed.
Results: Before insulin therapy was started, the mean (standard deviation) values of various clinical parameters were: hemoglobin A1c (%), 9.22 (1.58); fasting plasma glucose (mmol/L), 12.03 (3.62); and total cholesterol (mmol/L), 4.90 (1.1). These values decreased after insulin therapy was started. Mean total direct health care costs per patient 6 months before and after insulin start were €639 and €1,110, respectively. Mean total costs 6 months after insulin was started included hospitalization costs (30.5%, €339), insulin (16.2%, €180), primary care (14.3%, €159), blood glucose monitoring (13.8%, €153), specialized care (13.3%, €148), oral antidiabetics (7.8%, €87), and other diabetes-related treatment (3.9%, €43).
Conclusions: The clinical outcomes of T2DM patients improved after insulin therapy was started. This improvement was associated with increases in resource utilization and direct health care costs in the first 6 months of insulin therapy.

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PALABRAS CLAVE
Costes sanitarios;
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Costes directos sanitarios en pacientes con diabetes mellitus tipo 2 a los seis meses de inicio del tratamiento con insulina en España: estudio INSTIGATE

Resumen
Antecedentes y objetivo: El estudio INSTIGATE tuvo como objetivo evaluar los costes directos sanitarios incurridos por pacientes con diabetes mellitus tipo-2 (DM2) que inician insulinoterapia en España. Es un estudio observacional, no intervencionista, prospectivo y multicéntrico.
Material y métodos: Se valoraron los costes directos por paciente, según la práctica clínica habitual, durante un período de 6 meses antes y después del inicio de la insulinoterapia. En total se evaluaron 188 pacientes (42,6% mujeres) con una edad media de 65,3 años, un índice de masa corporal medio de 29,7 kg/m^2 y una duración media de la enfermedad de 10,7 años.
Resultados: Antes de iniciar la insulinoterapia, la media (desviación estándar) de las variables clínicas fueron: % de hemoglobina-A1c 9,22 (1,58); glucosa plasmática en ayunas (mmol/L) 12,03 (3,62), y colesterol total (mmol/L) 4,90 (1,1). La media del total de los costes directos sanitarios por paciente 6 meses antes y después de iniciar el tratamiento con insulina fue de 639€ y 1.110€ respectivamente. Los costes medios totales a los 6 meses del inicio de la insulinoterapia comprendieron: costes de ingresos hospitalarios (30,5%; 339€), insulina (16,2%; 180€), asistencia en servicios de atención primaria (14,3%; 159€), monitorización de glucosa en sangre (13,8%; 153€), asistencia por parte de especialistas (13,3%; 148€), antidiabéticos orales (7,8%; 87€) y otros tratamientos relacionados con la diabetes (3,9%; 43€).
Conclusiones: Los resultados clínicos de este grupo de pacientes con DM2 mejoraron tras iniciar terapia con insulina. Esta mejoría se acompañó de aumentos en la utilización de recursos y de costes directos sanitarios durante los 6 primeros meses de insulinoterapia.

Introduction

Type 2 diabetes mellitus (T2DM) represents a significant public health problem. The expected worldwide increase in the number of people with T2DM from 170 to 360 millions in 2030 suggests that the direct health care costs attributable to T2DM will continue to increase[1].

In Spain, the estimated prevalence of diabetes mellitus is approximately 6.5% of the population aged 30 to 65 years[2]. The different studies conducted in Spain suggest a significant increase in prevalence of T2DM, which may be estimated at 10%-15%[3].

T2DM is among the most costly chronic disease[4]. According to Oliva et al., total direct health care costs incurred by T2DM patients in Spain in 2002 ranged from €2.4 to €2.67 billion, which represents approximately 6.3%-7.4% of public health care costs in Spain[5]. Both limited resources and the increasing pressure to reduce health care costs in Spain have resulted in an increasing number of studies focusing on the evaluation of the costs associated with T2DM and the factors influencing such costs. Studies assessing health care costs associated with T2DM from the Spanish health care perspective have estimated mean annual direct costs ranging from €381 to €2,504 per patient[5-8]. However, no data are available about resource utilization and direct treatment costs in patients with T2DM who start treatment with insulin in clinical practice in Spain. Moreover, little is known about the difference between direct costs associated with treatment of T2DM in a public health care setting in Spain incurred before and after insulin therapy has been started.

If cost data were available and factors affecting such costs were understood, the available resources could be better assigned. Updated estimates of costs related to clinical outcome data also represent an important basis for studies aimed at calculating disease costs and budget impact. These updated cost estimates are used in decision analysis models for the treatment of T2DM throughout the course of the disease[9-11]. For this reason, this study was designed to help fill the information gap regarding the clinical results and direct health care costs of T2DM treatment under real life conditions in a sample of Spanish patients starting insulin therapy.

Patients and methods

Study design

The INSTIGATE study was a 24-month multicenter, observational, non-interventional, prospective study that examined the normal course of diabetes treatment in adult patients with T2DM starting insulin therapy. The study was conducted in France, Germany, Greece, the United Kingdom, and Spain. Readers interested in additional details regarding study design, baseline characteristics of the 1,172 patients enrolled in the participating countries, and other related publications are referred to the previously published articles[12-14]. For the purposes of this manuscript, direct costs per patient were assessed from the perspective of the Spanish health care system for the 6 months prior and the 6 months following the start of insulin therapy.

Study population

T2DM patients who met the predefined inclusion criteria were sequentially enrolled during 2006 throughout Spain. Study participants (n = 224 at the start and n = 188 at 6 months) were aged 18 years or older, had been diagnosed with T2DM, were being treated according to standard practice, and first started insulin therapy in 2006; they were not participating in any study which included the use of an investigational drug at the time of enrolment into the INSTIGATE study, and had an adequate understanding of the Spanish language. All patients were given comprehensive information about the study and provided their written consent for the use of their data. Participants received no compensation for their participation in the study. The study was approved by the Spanish regulatory authorities and was conducted in accord with the applicable local ethical requirements.

Investigators participating in the study

The investigators participating in this study, 24 in total (9 endocrinologists, 8 internal medicine specialists, and 7 primary care physicians) were selected to ensure that they were representative of the physicians in charge of this type of patient in Spain. Primary and specialized care centers with T2DM outpatients starting insulin therapy were selected. The physicians provided sociodemographic data, as well as information about the history of diabetes, other diseases, treatment for diabetes, clinical results, and the utilization of resources related to diabetes. Data were collected at baseline (at the time insulin therapy was started) and during the visits which occurred 3 and 6 months later. All medical visits by patients were in accordance with standard clinical practice. Treatment decisions and combinations of insulin with oral antidiabetic drugs (OADs) were left to the physician's discretion. For participants missing a visit, investigators had the option of collecting patient data through a telephone interview with him/her and/or collecting data through the ordinary post. Investigators received financial compensation for participating in this study.

Data collection and cost assessment

Patients were followed up prospectively for 6 months from the start of insulin therapy. The following information relating to clinical results was collected at baseline and/or at subsequent visits: weight and abdominal circumference, the presence of medical complications, prior medical history of diabetes, and the clinical severity of diabetes expressed as glycosylated hemoglobin (HbA_{1c}) levels, fasting plasma glucose, lipid profile, and blood pressure.

Information was also collected about diabetes-related resource utilization (visits and telephone calls to health care professionals, hospitalizations, treatment with insulin and OADs, and blood glucose monitoring). Health care professionals included primary care physicians and nursing staff, diabetologists/endocrinologists, internal medicine specialists, specialized nursing staff, ophthalmologists, nutritionists, and podiatrists. Resource utilization was retrospectively assessed by reviewing clinical histories for the 6 months prior to starting insulin therapy. Direct costs were assessed from the perspective of the Spanish health care system using prices for the year of the study (2006). Data regarding costs incurred from physician visits, telephone calls or consultations, hospitalizations, and blood glucose monitoring were taken from a Spanish database[15]. The costs of visits, telephone calls, and consultations with health care professionals were based on unit costs per visit depending on the specialty. Daily costs were used to calculate the costs of hospital admission. Data collected about drugs included the name and dosage of the medicinal product. Medication costs were collected from the database of the General Council of Spanish Official Associations of Pharmacists[16], and average daily costs were calculated based on package size, presentation, and dosage. This study did not consider direct non-health care costs (e.g. ambulance transport) or indirect costs (e.g. productivity losses).

Analysis of results

All analyses were descriptive and exploratory. For continuous variables, the mean, standard deviation (SD), median, minimum, maximum, and quartiles were calculated. For categorical variables, absolute and percent frequencies were calculated. All calculations made for the 188 patients for which 6-month follow-up data were available are provided. Missing values have not been included. Data have not been extrapolated. All analyses were performed using SAS version 9.0 software (SAS Institute Inc, Cary, North Carolina, USA).

Results

Sociodemographic characteristics

Among the 224 patients enrolled into the study, 17 (7.6%) were excluded from the analysis because only their baseline data were available and there was no information about their use of insulin during the 6-month observation period. Of the remaining 207 patients, 19 did not return for the 6-month visit. Thus, 188 patients with a mean age of 65.3 years (standard deviation [SD], 11.8) at the start of insulin therapy attended a visit at 6 months and were therefore eligible for analysis. Table 1 shows the descriptive characteristics of these patients: there were more males (57.4%) than females; a majority of the study population was Caucasian, overweight (with a mean body mass index [BMI] of 29.7 kg/m^2), and with a mean diabetes duration longer than 10 years. At study start, almost 56% of patients were retired, and approximately 16% had a full-time job. Non-smokers and smokers (including current and former smokers) were almost equally represented in the study sample.

Disease severity and comorbidities

Before insulin therapy was started, the most recent mean HbA_{1c} value (SD) was 9.22% (1.6). At baseline, mean (SD) fasting blood glucose level was 12.0 (3.6) mmol/L, and mean HDL (high density lipoprotein) cholesterol and LDL

Table 1 Baseline characteristics of Spanish patients who participated in the INSTIGATE study.

Characteristics	Total No. = 188 (100%)
Age (years), mean [SD]	65.3 [11.8]
Sex	
Male/female, %	57.4/42.6
Ethnic group	
White/African/East Asian, %	98.4/1.1/0.5
Occupation	
Unemployed/full-time job/part-time job/retired/housework/other, %	2.7/16.0/3.2/55.9/21.8/0.5
Smoking	
Current smoker/former smoker/never smoked/unknown, %	10.6/35.6/51.6/2.1
Diabetes duration (years), mean (SD)	10.7 [7.0]
Macrovascular disease, any, %	38.3
Coronary artery disease, %	11.2
Chronic heart failure, %	10.6
Prior myocardial infarction, %	9.0
Stroke, %	7.4
Occlusive peripheral artery disease, %	6.4
Transient ischemic attack, %	4.8
Microvascular disease, any, %	16.5
Diabetic retinopathy, %	7.4
Diabetic neuropathy, %	3.7
Diabetic nephropathy, %	10.6
High blood pressure, %	63.8
Depression, %	12.8

SD: standard deviation.

(low density lipoprotein) cholesterol levels were 1.3 (0.4) and 2.8 (1.0) mmol/L respectively. The proportion of patients with at least one macrovascular comorbidity was 38.3%, and 16.5% of patients reported at least one microvascular comorbidity (Table 1). Of the patients with macrovascular complications, 29.2% had coronary artery disease, 23.6% a history of myocardial infarction, and 12.5% a history of transient ischemic attack. Among the patients with macrovascular complications, 16.7%, 27.8%, 4.2%, and 2.8% had had occlusive peripheral artery disease, chronic heart failure, a coronary artery bypass graft, or surgery for limb amputation respectively. In addition, 63.8% and 12.8% of the total study population reported high blood pressure and depression respectively (Table 1).

Resource utilization

Table 2 summarizes resource utilization data for both the 6 months prior and following the start of insulin therapy. As shown, the proportions of patients attending any health care professional changed little in the 6 months following the start of insulin therapy as compared to before the start of therapy. The proportion of patients seen by a primary care physician in the 6 months of follow-up was approximately 84%, while 59% of patients received specialized care for the treatment for T2DM or its complications. Overall, telephone calls to health care professionals were less common as compared to other resource categories (18.1% of patients). The mean number of visits to any health care professional increased from 9.1 per patient in the 6 months prior to the start of insulin therapy to 11.3 in the first 6 months after the start of insulin therapy. Six patients (3.2%) reported at least one diabetes-related hospital admission in the 6 months prior to insulin therapy, while 10 patients (5.3%) required admission during a 6-month period after therapy was started.

As regards medication, one OAD was prescribed before insulin therapy in 92% (n = 173) of all patients, and 77 patients (41.0%) were taking two OADs. With insulin therapy, 58.5% of patients continued taking some OAD, of which metformin was the most commonly used (42.6%). The proportion of patients who monitored their blood glucose

Table 2 Diabetes-related resource utilization 6 months before and 6 months after the start of insulin therapy.

Resource utilization by category	Total No. = 188 (100%)	
	Six months before the start of insulin therapy	Six months after the start of insulin therapy
Visits to HCPs		
Patients with ≥ 1 visit, %	96.8	98.4
Mean number (SD)	9.1 (6.0)	11.3 (7.7)
Telephone calls to HCPs		
Patients with ≥ 1 telephone call, %	14.9	18.1
Mean number (SD)	0.5 (1.5)	0.9 (2.4)
Visits to PCPs		
Patients with ≥ 1 visit, %	86.7	84.0
Mean number (SD)	3.4 (3.1)	3.7 (3.3)
Telephone calls to PCPs		
Patients with ≥ 1 telephone call, %	13.8	14.4
Mean number (SD)	0.3 (0.9)	0.4 (1.2)
Visits to diabetologists or endocrinologists		
Patients with ≥ 1 visit, %	59.0	59.0
Mean number (SD)	1.0 (1.1)	1.2 (1.3)
Oral antidiabetic drugs (OADs)		
Patients with new/continued OADs, %	58.5	71.3
Patients receiving metformin, %	42.6	51.1
Blood glucose monitoring		
Patients with blood glucose monitoring, %	78.2	91.0
Mean weekly number of strips per patient with blood glucose monitoring (SD)	6.8 (7.0)	8.1 (6.7)
Hospitalizations for diabetes		
Patients with ≥ 1 hospital admission, %	3.2	5.3
Mean total number of days (SD)	7.0 (4.4)	11.9 (10.5)

OADs: oral antidiabetic drugs; SD: standard deviation; n: number of patients; PAP: primary care physician; HCP: health care professional.

[a]The results shown in this table are based on the number of evaluable patients for each criterion.

levels increased from 78.2% to 91.0%, and mean monitoring frequency by patient increased from 6.8 to 8.1 times weekly. In the first 6 months of insulin therapy, the mean daily dose of insulin increased from 20.3 to 24.1 IU/day (from 0.265 to 0.309 IU/kg).

Direct health care costs

Table 3 shows the unit costs used to calculate direct costs per patient. The direct costs of treatment for T2DM in the six-month periods before and after the start of insulin therapy were €1,100 and €639 per patient respectively. Data shown in Table 4 reflect the subcategories of mean direct costs during the six-month periods prior and subsequent to the start of insulin therapy. Mean costs per patient associated with visits or telephone calls to health care professionals after the start of insulin therapy increased by 18.66% (general medical care) and 39.62% (specialist care). Mean costs related to blood glucose monitoring, hospital admission, and other diabetes-related treatment during the six-month period following the start of insulin therapy were also greater as compared to the period prior to insulin therapy. In addition, a reduction by almost a half was seen in mean costs per patient associated with OAD treatment in the six months following the start of insulin therapy. However, decreased OAD costs were compensated for by an increase in mean insulin cost per patient after insulin therapy was started. The key factors determining direct costs before insulin therapy was started were OADs, medical visits, and hospital admissions (25%, 21%, and 17% of mean

Table 3 Unit costs per resource unit.

Resource item	Unit costs (€)
Physician visits/telephone calls[a]	
PCP visit, cost per visit	24.68
Telephone call to PCP, cost per call	16.29
Visit to primary care nurse, cost per visit	16.25
Telephone call to primary care nurse, cost per call	10.58
Visit to diabetologist/endocrinologist, cost per visit	52.65
Visit to specialized nurse, cost per visit	27.82
Telephone call to specialized nurse, cost per call	18.36
Nutritionist visit, cost per visit	125.55
Ophthalmologist visit, cost per visit	42.02
Podiatrist visit, cost per visit	24.68
Hospitalizations	
One-day hospital stay for acute complications of diabetes	403.30
One-day hospital stay for chronic complications of diabetes	613.56
Emergency room visit with no overnight stay	114.26
Laboratory tests	
HbA_{1c}, cost per test	10.20
HDL, cost per test	2.24
Triglycerides, cost per test	0.84
Total cholesterol, cost per test	0.47
Fasting blood glucose, cost per test	0.45
Creatinine, cost per test	0.93
Reactive strip for testing urinary glucose	0.25
Reactive strip for testing blood glucose	0.70

HbA_{1c}: glycosylated hemoglobin; HDL: high density lipoprotein; PCP: primary care physician.
[a]Estimated unit costs of physician visits and telephone calls include the time spent by the health care professional.

direct costs per patient respectively). The start of insulin therapy resulted in a shift in the abovementioned factors. Specifically, hospital admissions, insulin therapy, and medical visits accounted for 31%, 16%, and 14% respectively of mean total costs per patient in the six months following the start of insulin therapy.

Clinical results

Six months after the start of insulin therapy, reductions were reported in levels of HbA_{1c}, plasma fasting glucose, LDL, triglycerides, and total cholesterol (Table 5). No significant changes from baseline were seen in weight, BMI, abdominal circumference, HDL, triglycerides, and creatinine during the six months of follow-up. A higher proportion of patients experienced hypoglycemic episodes after six months as compared to the three-month period before the start, but only one patient had to attend the hospital for a severe hypoglycemic episode after starting insulin therapy.

Discussion

Diabetes mellitus is a chronic disease that represents a worldwide risk for the health of people[17]. Diabetes mellitus and its associated comorbid conditions represent a significant burden for the Spanish economy[2,7]. Oliva et al. showed that costs per patient were up to 1.5-1.7-fold higher as compared to the Spanish population with no diabetes (from €1,290 to €1,476 per patient per year), representing from 6.3% to 7.4% of the total costs of the national health system[5]. According to Ballesta et al., annual direct costs of T2DM in a patient sample (n = 517) in southern Spain amounted to €2,504 per patient[7]. The CODE-2 study, conducted in Spain, reported the mean annual direct costs of T2DM patients (n = 1,004) as €1,304 per patient[18]. Because of the foreseeable increase in health care expenses associated with diabetes mellitus, the most significant factors accounting for resource utilization and costs associated with patients with T2DM should be identified. The abovementioned studies did not provide cost estimates for T2DM patients who started insulin therapy.

The INSTIGATE study provides data concerning the clinical results and direct health care costs of T2DM patients in the Spanish population under study based on actual data collected prospectively for 24 months after the start of insulin therapy, and retrospectively for the six months prior to the start of insulin therapy. To our knowledge, this is the only published study reporting the direct costs of T2DM patients who start insulin therapy in Spain.

This article provides the direct costs associated with the first six months of insulin therapy because this appeared to us to be a reasonable time for patients to become familiar with insulin administration and for any necessary adjustments in therapy to be made. In addition, the reporting of data relating to costs six months before the start of insulin therapy allowed for a discussion about the different utilization of health care resources before and after the start of insulin therapy by comparing observation periods of a similar duration.

Our study results show decreases in HbA_{1c} and plasma glucose levels after six months of insulin therapy as compared to before the start of this therapy. However, the values of these achieved clinical parameters continue to be higher than the levels recommended by international clinical guidelines for the management and control of T2DM[19,20]. Several studies have reported similar results as regards metabolic control despite the significance, emphasized in recent publications, of achieving a good control in order to prevent or delay the occurrence of complications associated with T2DM[21-23].

From a financial perspective, our study shows that the mean direct costs of T2DM treatment in this group of Spanish patients amounted to €639 in the six months prior to insulin therapy in 2006, and increased to €1,110 per patient in the six-month period after the start of insulin therapy. Similar findings were made in a retrospective

Table 4 Total direct costs of diabetes care from the perspective of the Spanish health care system six months before and six months after the start of insulin therapy (mean costs per patient and period).

Mean costs (SD) in €	Total No. = 188 (100%)	
Perspective of the Spanish health care system	Six months before the start of insulin therapy	Six months after the start of insulin therapy
PCP visits and telephone calls	134 (117)	159 (147)
Specialist care for blood glucose monitoring	106 (89)	148 (125)
Oral antidiabetic drugs	162 (164)	87 (119)
Insulin	NA	180 (102)
Blood glucose monitoring	97 (123)	153 (142)
Hospital admission	108 (715)	339 (1,880)
Other diabetes-related treatments	33 (49)	43 (80)
Total direct costs	639 (786)	1,110 (1,966)

SD: standard deviation; PCP: primary care physician; n: number of patients; NA: not applicable.
The sum of mean costs by subcategory may not be the same as total direct costs due to the roundoff effect.

cohort analysis of the costs and utilization of health care services in US patients with T2DM who started insulin therapy between 1997 and 2000[24]. In this study, Rosenblum et al. reported an initial increase (by approximately 10%) in health care costs associated with the start of insulin therapy, followed by a consistent and substantial decrease (by approximately 40%) in total health care costs nine months after insulin therapy was started[24].

In the present study, the start of insulin therapy resulted in a change in the key factors responsible for direct costs, with OADs, medical visits, and hospital admissions (which accounted for 25%, 21%, and 17% of costs respectively) being

Table 5 Clinical results in the study population (n = 188) at the start and after six months of insulin therapy.[a]

Clinical result	Total No. = 188 (100%)	
	At the start of insulin therapy	Six months later
HbA_{1c}, %, mean ± SD (CI)	9.22 ± 1.6 (8.99; 9.45)	7.35 ± 1.1 (7.19; 7.52)
FPG, %, mean ± SD (CI)	12.0 ± 3.6 (11.5; 12.6)	8.1 ± 2.4 (7.8; 8.5)
Weight, kg, mean ± SD (CI)	78.5 ± 16.0 (76.2; 80.8)	79.4 ± 14.7 (77.2; 81.5)
BMI, kg/m^2, mean ± SD (CI)	29.7 ± 5.6 (28.9; 30.5)	30.1 ± 5.3 (29.3; 30.8)
Waist, cm, mean ± SD (CI)	100.3 ± 17.1 (97.8; 102. 8)	100.7 ± 16.6 (97.9; 103.6)
HDL-C, mmol/L, mean ± SD (CI)	1.3 ± 0.4 (1.2; 1.3)	1.3 ± 0.3 (1.2; 1.3)
LDL-C, mmol/L, mean ± SD (CI)	2.8 ± 1.0 (2.7; 3.0)	2.6 ± 0.8 (2.5; 2.7)
Triglycerides, mmol/L, mean ± SD (CI)	1.9 ± 1.1 (1.8; 2.1)	1.7 ± 1.2 (1.5; 1.9)
Total cholesterol, mmol/L, mean ± SD (CI)	4.9 ± 1.1 (4.7; 5.1)	4.5 ± 0.9 (4.4; 4.6)
Creatinine, µmol/L, mean ± SD (CI)	91.0 ± 33.1 (86.1; 95.8)	89.9 ± 31.8 (85.1; 94.6)
Patients with any hypoglycemic episode[b], %	6.4	18.1
Patients attending the hospital for a hypoglycemic episode[b], %		0.5 0.5

SD: standard deviation; FPG: fasting plasma glucose; HbA_{1c}: glycosylated hemoglobin; HDL: high density lipoprotein; BMI: body mass index; LDL: low density lipoprotein; n: number of patients.
[a]The results shown in this table are based on the number of evaluable patients for each criterion.
[b]The percentages for the hypoglycemic episodes are for the three month period before the start of insulin therapy.

replaced by hospital admissions, insulin, and medical visits (accounting for 31%, 16%, and 14% of costs respectively). In the study sample, hospital admissions alone accounted for 31% of direct costs in the six months following the start of insulin therapy, which is consistent with the results reported by Oliva et al.[5] (35%-39% depending on the assumptions made). It should be noted that although the mean cost of hospital admissions during the six-month period was high in our study, very few patients were admitted to hospital after the start of insulin therapy. This increase in hospital admissions may be attributed to hypoglycemic or hyperglycemic events, patient noncompliance, or the occurrence of comorbidities[25,26]. Such hospital admissions may potentially be preventable and treated by adequate diabetes management[26].

In our study, mean costs per patient for insulin, blood glucose monitoring, general medical care, and specialist care were almost equally distributed (approximately 14% each) during the period considered, while the costs of OADs to treat the disease were low in relative terms and represented approximately 7.8% of all direct costs in the group of patients with T2DM in the study sample.

This study has several limitations. First, not all the direct medical resources used after the start of insulin therapy may have been collected. Information about resource utilization during the study was not directly collected from patients, which may have led us to underestimate the direct costs associated with diabetes. Second, since the resource utilization questionnaires provided adequate information for assigning group codes related to diagnoses to hospital stays, the costs of diabetes-related hospitalizations were estimated as prices per day of stay at a unit of endocrinology and intensive care or at the emergency room, as appropriate. Moreover, the cost per visit to a nutritionist appears to have been overestimated. The reason for this may be that visits to nutritionists usually last longer than visits to other specialists such as diabetologists or enodocrinologists. However, this cost has no substantial impact on the study results because only seven and ten patients respectively visited a nutritionist before and in the six months following the start of insulin therapy. Finally, we depended on physician understanding and opinion that the resources were used for diabetes, but no cross validation was made of whether or not the use of such resources was effectively due to diabetes.

Despite these limitations, our study points out the financial and clinical issues of treatment of T2DM after insulin therapy was started in this group of diabetic patients and provides an up-to-date estimate of direct health care costs from the perspective of the Spanish health care system. The advantage of the INSTIGATE study is that it was an observational, noninterventional study based on data from actual clinical practice in the outpatient settings where Spanish patients with T2DM are usually treated, and it provides new information concerning the financial issues and clinical results in T2DM patients who first start insulin therapy. What is truly relevant is that short-term increases in total direct costs after starting insulin therapy in this study led to improved clinical results. Additional improvements in blood glucose control and clinical results may delay T2DM progression, decreasing the risk of the development of diabetes-related complications and reducing the utilization of health care resources and costs associated with T2DM and its lifetime complications[27,28]. The maintenance of HbA_{1c} levels at the standard values suggested by the International Diabetes Federation and the American Diabetes Association may result in significant savings in total health care costs, which become greater the longer the follow-up[29]. Thus, observational studies of T2DM patients on insulin therapy with longer follow-up periods are needed to confirm the potential economic benefit of insulin.

To conclude, the clinical results in this Spanish population of T2DM patients improved after insulin therapy was started. This improvement was associated with an increased utilization of direct health care resources and costs during the first six months of insulin therapy.

Conflict of interest

The INSTIGATE study was funded by Eli Lilly and Company. The following authors are employees of Eli Lilly and Company: M.Costi, H. Smith, J. Reviriego, and T. Dilla. Authors C. Castell and A. Goday declare no conflict of interest.

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