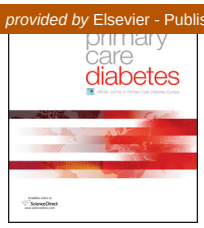
PRIMARY CARE DIABETES XXX (2016) XXX–XXX

Contents lists available at ScienceDirect
Primary Care Diabetes
journal homepage: http://www.elsevier.com/locate/pcd



Original research

Increased healthcare utilization costs following initiation of insulin treatment in type 2 diabetes: A long-term follow-up in clinical practice

Almina Kalkan[a,*], *Johan Bodegard*[a], *Johan Sundström*[b], *Bodil Svennblad*[b], *Carl Johan Östgren*[c], *Peter Nilsson Nilsson*[d], *Gunnar Johansson*[b], *Mattias Ekman*[a]

[a] *AstraZeneca Nordic-Baltic, Södertälje, Sweden*
[b] *Uppsala University, Uppsala, Sweden*
[c] *Linköping University, Linköping, Sweden*
[d] *Lund University, Malmö, Sweden*

ARTICLE INFO

Article history:
Received 7 July 2016
Received in revised form
4 November 2016
Accepted 6 November 2016
Available online xxx

Keywords:
Type 2 diabetes mellitus
Healthcare utilization
Healthcare costs
Observational study

ABSTRACT

Aims: To compare long-term changes in healthcare utilization and costs for type 2 diabetes patients before and after insulin initiation, as well as healthcare costs after insulin versus non-insulin anti-diabetic (NIAD) initiation.

Methods: Patients newly initiated on insulin (n = 2823) were identified in primary health care records from 84 Swedish primary care centers, between 1999 to 2009. First, healthcare costs per patient were evaluated for primary care, hospitalizations and secondary outpatient care, before and up to seven years after insulin initiation. Second, patients prescribed insulin in second line were matched to patients prescribed NIAD in second line, and the healthcare costs of the matched groups were compared.

Results: The total mean annual healthcare cost increased from €1656 per patient 2 years before insulin initiation to €3814 seven years after insulin initiation. The total cumulative mean healthcare cost per patient at year 5 after second-line treatment was €13,823 in the insulin group compared to €9989 in the NIAD group.

Conclusions: Initiation of insulin in type 2 diabetes patients was followed by increased healthcare costs. The increases in costs were larger than those seen in a matched patient population initiated on NIAD treatment in second-line.

* *Corresponding author at*: AstraZeneca Nordic-Baltic, Department of Health Economics, Astraallén, B674, Södertälje SE-151 85, Sweden.
E-mail addresses: almina.kalkan@astrazeneca.com, almina.kalkan@gmail.com (A. Kalkan).

http://dx.doi.org/10.1016/j.pcd.2016.11.002

1. Introduction

The prevalence of drug treated type 2 diabetes mellitus (T2DM) in Sweden is increasing and has recently been reported to be 4.4% [1]. T2DM is a major cause of morbidity and premature mortality, primarily through macrovascular and microvascular complications [1–5]. The disease and its complications increase the use of healthcare services with associated increases in total healthcare costs [6–8].

Glycemic control is a cornerstone in T2DM management to avoid diabetes related complications, where insulin is considered to be an effective HbA1c lowering intervention [9]. In Sweden, with a relatively high use of insulin compared to other European countries, insulin has now surpassed sulphonylurea as the most commonly dispensed drug in second-line add-on to metformin [10,11]. This "treatment ladder" is in line with the Swedish national guidelines, recommending second line insulin when metformin fails, only subsequently followed by other available glucose lowering drugs [12]. International T2DM guidelines however recommend several options as second line treatment, including also more innovative second line treatment options, such as dipeptidyl peptidase (DPP)-4 inhibitors, sodium glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RA) [13,14].

In addition to the benefits on glucose levels, insulin also carries a number of unwanted side effects like weight gain, hypoglycemia, reactions from injections and increased treatment complexity [15–18]. Furthermore, recent studies report associations between insulin and increased risk of cancer, cardiovascular disease and all-cause mortality [18–20]. Thus, despite the low direct cost of insulin treatment, unwanted side effects and treatment complexity of insulin may lead to increased long-term health care costs [21–23]. Despite several studies on health care costs and T2DM [24–30] there are limited data on use of health care resource associated with insulin. Since insulin is widely used in Sweden, a cost analysis might contribute useful evidence to the understanding of the implications for the healthcare system of the insulin use. Recently, one study has reported increased health care costs after insulin initiation, but findings were limited to a highly selected group of patients with no hospitalization data, low representativity and short follow-up [31].

The aim of this study was to compare long-term changes in healthcare utilization and costs before and after insulin initiation in Sweden. In addition, also to compare healthcare costs after insulin versus non-insulin anti-diabetic (NIAD) initiation.

2. Material and methods

2.1. Study sample

Patients diagnosed with type 2 diabetes mellitus (ICD E11) and/or prescription of any blood glucose-lowering drug (ATC A10) were identified at 84 primary-care centers in Sweden between 1 January 1999 to 31 December 2009 (www.clinicaltrials.gov; NCT: 01121315). Effort was made to ensure a representative selection of primary care centers [8]. A total of 58 333 patients could be included, and data linked to the Swedish National Patient-, Prescribed Drug- and Cause of Death registries by using the unique personal identification number, mandatory for all citizens from birth or immigration. Details on study design and the data extraction from primary care records and registers have been described elsewhere [2,4,8,22,32].

2.2. The insulin initiation cohort

This cohort is used to compare long-term changes in healthcare utilization and costs before and after insulin initiation in all patients. The cohort will also be important when assessing the representativity of the smaller matched second line cohort, see below. We identified all patients >30 years of age initiating insulin after having 15 months with no insulin prescription to be included. Patients were excluded if they had no registered visit or contact in the electronic patient record within two years prior to index treatment start. Any gap larger than 15 months between prescriptions was considered as discontinuation. In order to control for other cost driving comorbidities, we excluded all patients with history of CVD and cancer at baseline. Patients with any hospital visit (in hospital stay or outpatient clinic visit) within 90 days prior to insulin initiation were excluded. Patients were followed from two years prior to index date and until discontinuation, death or end of study period from electronic patient records.

2.3. Matched second line cohort

In order to compare healthcare costs after insulin initiation with healthcare costs after initiation of NIADs, we defined two similar groups. We identified patients with metformin monotherapy for at least 2 years and no gaps of more than 15 months between two prescriptions. They were indexed when they either were prescribed second line insulin (Insulin group) or second line non-insulin antidiabetic drug (NIAD group). To reduce the likelihood of rescue insulin treatment, only patients with two prescriptions within 15 months were included. Any gap larger than 15 months between second line prescriptions was considered as discontinuation.

2.4. Patient baseline characteristics

Baseline data were extracted from electronic patient records for the variables of systolic and diastolic blood pressure; total-, low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol; serum triglycerides; HbA1c values; lipid-lowering-, glucose-lowering- and blood pressure-lowering drugs; and estimated glomerular filtration rate (eGFR), age and sex. Data on HbA1c is reported in DCCT.

Disease history at baseline was collected by searching for diagnoses coded with International Classification of Diseases, 9th (ICD-9) and 10th (ICD-10) revision in primary care- and hospital data, defined in an earlier publication [8].

2.5. Healthcare resource use

All patient healthcare resource use (primary care, inpatient care (hospitalizations) and/or secondary outpatient care), both diabetes and non-diabetes related, was considered and

Please cite this article in press as: A. Kalkan, et al., Increased healthcare utilization costs following initiation of insulin treatment in type 2 diabetes: A long-term follow-up in clinical practice, Prim. Care Diab. (2016), http://dx.doi.org/10.1016/j.pcd.2016.11.002

Table 1 – Unit costs applied in the analyses.

Cost item	Unit cost (€)
Primary care	Per contact
GP visit	148
GP home visit	296
GP phone contact/administration work	49
Nurse visit	54
Nurse home visit	108
Nurse phone contact/patient administration	18
Other primary care visit	54
Other primary care home visit	108
Other primary care phone contact/patient administration	18
Laboratory visit	57
Hospitalizations	Per event
Cardiovascular	5336
Gastrointestinal	4853
Urogenital	5067
Cancer	7081
Respiratory	5181
Endocrine	4990
Musculoskeletal	6552
Neurological	5833
Infections	5729
All other causes	3370

€1 = 8.7034 SEK (2012 values).

included. Data on primary care use was extracted from electronic patient records and consisted of visits to physician, nurse, and other primary care professions such as physiotherapist, podiatrist, laboratory tests and administration (e.g., prescription renewal).

Primary care contacts were obtained by item through the primary care medical records. Hospitalizations and secondary outpatient care were extracted from the mandatory, Swedish National Patient Register. Hospitalizations were clustered into 10 diagnosis-related groups based on the main ICD-9 and ICD-10 codes assigned to a hospitalization (cardiovascular, gastrointestinal, urogenital, cancer, respiratory, endocrine, musculoskeletal, neurological, infectious and all others). For secondary outpatient visits the 25 most frequent diagnoses based on the ICD-9 and ICD-10 were identified.

2.6. *Cost assignment*

Annual healthcare costs per patient were evaluated from the healthcare perspective for the resource use in primary care, hospitalizations and secondary outpatient care. In order to estimate costs before and after the initiation of insulin, Swedish unit costs were applied to the healthcare resource use data (Table 1). Unit costs for primary care visits were extracted from cost databases with nationwide average costs per contact. Unit costs for hospitalizations, with the exception of cancer and other causes, were extracted from the cost per patient database from the Swedish Association of Local Authorities and Regions (KPP database). Since no uniform ICD code is available for cancer, unit costs for cancer-related hospitalizations were estimated by applying the mean cost per hospitalization based on diagnosis-related group (DRG) cost weights. Unit costs for hospitalizations that falls into the ICD group of other causes were calculated by deriving the weighted average costs of the fifteen most commonly observed diagnoses in the sample. For secondary outpatient care, unit costs for the 25 most frequent ICD-9 and ICD-10 codes were assessed using the KPP database (Appendix A). For the remaining causes in secondary outpatient care, the average cost for all diagnoses was used. All unit costs are in year 2012 values (average exchange rate: €1 = SEK 8.7034). Since Sweden has had a negligible deflation in the general price level since year 2012, the values from 2012 are assumed to still be relevant (Consumer price index, CPI: 2015 = 1, 2012 = 0.997). Costs of pharmaceuticals and devices of glucose monitoring are excluded from this study because prescription data were not available for the full study period. More details on the cost assessment have been described previously [22].

2.7. *Statistical analysis*

Descriptive statistics on an aggregated level were used to display baseline patient characteristics, resource utilization, and annual costs per patient in the dataset. For continuous variables, the mean is presented. For categorical variables, the number and proportions (percentage) in each category are presented. The per patient mean consumption of primary care, hospitalizations and secondary outpatient care is reported for the full study period and by yearly intervals in order to explore patterns in resource use over time. Annual costs per patient were estimated by applying the unit costs above, and presented in total as well as by healthcare category (primary care, hospitalization and secondary outpatient care).

The insulin and NIAD group patients were matched 1:1 on mean two-year cost before index, HbA1c, age and gender.

For many patients the follow-up was shorter than the maximum observation time of 7 years due to death or censoring at the end of the study period. To account for censoring, the partitioned method of Bang and Tsiatis was used for calculating the mean annual costs for contacts in primary care, hospitalisations and secondary outpatient care [33].

2.8. *Ethical approval*

The study was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr. 2010/077).

3. Results

Of 58,333 T2DM patients; 2823 patients fulfilled the criteria and could thus be included. Patients were most frequently initiated on medium long acting (NPH) followed by mixed medium long-, long acting and short acting insulin. Patients were followed up to 7 years (mean 3.8 years and total number of patient years 10,727). Mean age of patients at initiation of insulin was 61 years and 42% were female. Mean patient HbA1c level was 8.7%. Further baseline characteristics are reported in Table 2.

Please cite this article in press as: A. Kalkan, et al., Increased healthcare utilization costs following initiation of insulin treatment in type 2 diabetes: A long-term follow-up in clinical practice, Prim. Care Diab. (2016), http://dx.doi.org/10.1016/j.pcd.2016.11.002

Table 2 – Baseline characteristics.

	All patients started with insulin	Before matching		Matched patients (1:1)	
		Insulin	NIAD	Insulin	NIAD
Number of patients, N	2823	511	1859	432	432
Age, years,	60.8 (11.1)	59.4 (11.0)	59.3 (11.5)	59.5 (10.1)	59.5 (10.1)
Sex, male, n (%)	1645 (58.3)	279 (54.6)	1028 (55.3)	243 (56.2)	253 (58.6)
Follow up, years	3.8 (2.6)	4.2 (3.1)	3.3 (2.6)	4.0 (3.0)	3.2 (2.6)
Time on metformin monotherapy (days)	n/a	787.7 (752.2)	831.4 (727.6)	795.1 (760.0)	797.9 (696.0)
Insulin type, n (%)					
Short acting	90 (3.2)	15 (3.0)		14 (3.3)	
Medium acting	1558 (55.2)	282 (57.1)		243 (57.9)	
Mixed medium/long acting	620 (22.0)	92 (18.6)		71 (16.9)	
Long acting	554 (19.6)	105 (21.3)		92 (21.9)	
Cardiovascular disease, n (%)	0	0 (0)	0 (0)	0 (0)	0 (0)
Myocardial infarction	0	0 (0)	0 (0)	0 (0)	0 (0)
Stroke	0	0 (0)	0 (0)	0 (0)	0 (0)
Heart failure	0	0 (0)	0 (0)	0 (0)	0 (0)
Atrial fibrillation	0	0 (0)	0 (0)	0 (0)	0 (0)
Other disease, n (%)	0	0 (0)	0 (0)	0 (0)	0 (0)
Cancer	0	0 (0)	0 (0)	0 (0)	0 (0)
Kidney disease	0	0 (0)	0 (0)	0 (0)	0 (0)
Laboratory measurements					
HbA1c, %	8.7 (2.8)	8.8 (2.9)	8.2 (2.6)	8.6 (2.6)	8.6 (2.6)
Glucose, mmol/l	10.5 (3.7)	11.1 (4.1)	9.8 (3.0)	10.9 (3.9)	11.1 (3.2)
BMI, kg/m^2	29.9 (5.5)	31.5 (5.2)	31.9 (5.7)	31.4 (5.0)	32.1 (5.7)
Systolic blood pressure, mmHg	142.9 (18.7)	141.5 (17.5)	142.3 (17.6)	141.6 (17.3)	143.3 (17.3)
Diastolic blood pressure, mmHg	80.6 (9.8)	81.6 (9.2)	81.9 (9.8)	81.5 (9.1)	82.5 (9.8)
Total cholesterol, mmol/l	5.1 (1.1)	5.0 (1.2)	5.2 (1.1)	5.0 (1.2)	5.3 (1.2)
HDL cholesterol, mmol/l	1.3 (0.7)	1.4 (0.8)	1.3 (0.7)	1.4 (0.8)	1.2 (0.5)
LDL cholesterol, mmol/l	2.9 (0.9)	2.9 (0.9)	3.0 (0.9)	2.9 (0.9)	3.1 (0.9)
Triglycerides, mmol/l	2.2 (1.8)	2.2 (1.8)	2.4 (1.6)	2.2 (1.8)	2.4 (1.8)
Creatinine, μmol/l	78.6 (21.6)	74.7 (20.0)	76.3 (19.9)	74.7 (19.4)	76.0 (17.8)
Estimated GFR, ml/min	84.0 (20.3)	87.9 (18.1)	86.8 (19.4)	88.1 (17.9)	87.1 (18.8)
Insulin/add-on treatment initiated, n (%)					
1999	178 (6.3)	21 (4.1)	70 (3.8)	17 (3.9)	21 (4.9)
2000	206 (7.3)	27 (5.3)	100 (5.4)	17 (3.9)	29 (6.7)
2001	206 (7.3)	32 (6.3)	99 (5.3)	24 (5.6)	25 (5.8)
2002	201 (7.1)	36 (7.0)	120 (6.5)	28 (6.5)	26 (6.0)
2003	207 (7.3)	36 (7.0)	171 (9.2)	33 (7.6)	32 (7.4)
2004	237 (8.4)	36 (7.0)	153 (8.2)	34 (7.9)	27 (6.2)
2005	264 (9.4)	40 (7.8)	186 (10.0)	37 (8.6)	46 (10.6)
2006	263 (9.3)	46 (9.0)	204 (11.0)	36 (8.3)	42 (9.7)
2007	323 (11.4)	74 (14.5)	213 (11.5)	58 (13.4)	59 (13.7)
2008	253 (12.5)	76 (14.9)	272 (14.6)	65 (15.0)	59 (13.7)
2009	385 (13.6)	87 (17.0)	272 (14.6)	83 (19.2)	66 (15.3)

All numbers in parenthesis are standard deviation if not stated otherwise. HDL, high density lipoprotein, LDL, low density lipoprotein, GFR, glomerular filtration rate.

3.1. *Healthcare costs of patients initiated on insulin*

The total mean annual healthcare costs increased from €1655 per patient 2 years before insulin initiation to €3814 seven years after insulin initiation (Fig. 1). Almost half of the total increase in mean annual healthcare cost occurred already in year 1, after which the costs continued increasing gradually. Throughout the study period, primary care represents the largest portion of the total healthcare costs (43–59%), closely followed by hospitalisation (31–40%). Primary care costs are especially elevated one year after insulin initiation, while hospitalisation costs increase steadily over time. The costs for secondary care outpatient visits keep a relatively small share (10–16%) of total costs throughout the study period. Mean per patient cumulative healthcare costs were €14,211 at 5 years and €21,334 at 7 years of observation. Primary care had a higher cumulative cost compared with hospital care, €10,001 and €8188 at year 7, respectively.

3.2. *Healthcare costs after second line insulin versus NIAD*

Overall, 511 patients fulfilled the inclusion criteria of having metformin monotherapy for at least 2 years with no gaps of more than 15 months between two prescriptions, and being initiated on second line insulin or NIAD. The unmatched patients who initiated insulin compared to NIAD had slightly higher levels of HbA1c and blood glucose but were similar in

Please cite this article in press as: A. Kalkan, et al., Increased healthcare utilization costs following initiation of insulin treatment in type 2 diabetes: A long-term follow-up in clinical practice, Prim. Care Diab. (2016), http://dx.doi.org/10.1016/j.pcd.2016.11.002

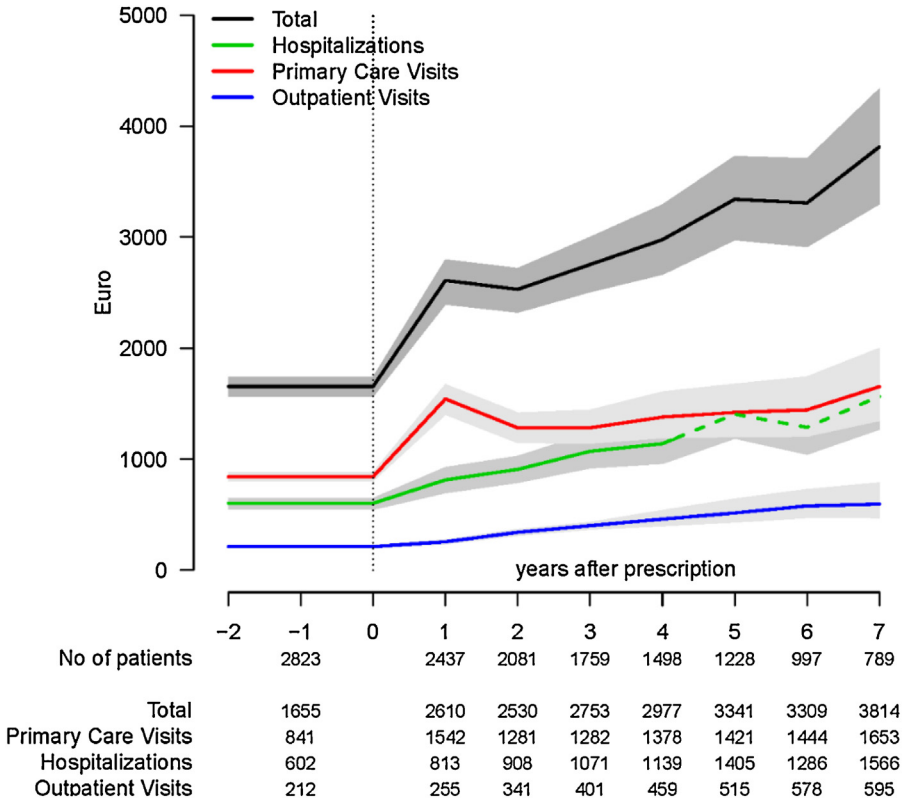


Fig. 1 – Mean annual per patient healthcare costs 2 years prior to insulin start and the years thereafter.

all other respects. The matched groups shared similar characteristics compared to the larger group of all patients initiating insulin, hence the representativity seems to be appropriate.

The total cumulative mean healthcare cost per patient at year 5 after second-line treatment with insulin was €13,823, with hospitalizations as the main cost driver representing 42–51% of total cumulative costs, followed by primary care visits (33–46% of total cost) and outpatient visits (12–16% of total cost). The total cumulative mean healthcare cost per patient at year 5 after second-line treatment with NIAD was €9989, with the same distribution in cost categories as for the insulin group (Fig. 2). Healthcare costs after second line insulin initiation exhibit a 12-fold increase compared to two years before insulin initiation, while the healthcare costs after second line with NIAD exhibit an 8-fold increase. The difference in cumulative healthcare costs between second line insulin and second line NIAD appeared already in year 1 and continued to increase during follow-up (Fig. 3). Hence the increase in healthcare costs associated with insulin initiation is considerably higher that the increase seen after NIAD initiation in second-line.

4. Discussion

Based on data from a large Swedish observational study of T2DM patients, this study demonstrates two important findings; the increased healthcare use and costs after insulin initiation; and significantly higher cumulative costs among patients initiated on second line insulin compared to patients initiated on second line non-insulin anti-diabetics (NIADs).

The insulin initiation resulted in a sharp rise of total healthcare costs within the first year, and was followed by continuously increased total healthcare costs up to 7 years. Mean annual healthcare costs per patient increased 230% over the 7 years. A recent Swedish study has also reported increased healthcare costs 1 year after insulin initiation, although at somewhat different rates than those reported here [31]. In the study by Bexelius et al., the costs increased from €1980 the year before insulin initiation to €3637 already the year after (2012 values, 1€ = 8.7034 SEK). One possible explanation for this discrepancy is that in contrast to Bexelius et al., using data from 100 patients in 1 Swedish county council, this study included geographically dispersed (rural and urban) primary care centers as well as the nationwide Swedish National Patient-, Prescribed Drug- and Cause of Death registries. Another possible explanation for the difference is the stricter inclusion criteria in the present study, excluding patients with known CVD or cancer, or patients who were hospitalized within 90 days prior to insulin initiation, to control for expensive co-morbidities in order to get more accurate estimates of the changes in costs directly linked to insulin initiation.

Baseline characteristics of the unmatched insulin group show that these patients have higher HbA1c and receive slightly earlier add-on treatment than do NIAD patients. This could imply a more progressed disease or later diagnosis setting in the insulin group. A previous study has demonstrated the relationship between costs and HbA1c level, where a 1%-

Please cite this article in press as: A. Kalkan, et al., Increased healthcare utilization costs following initiation of insulin treatment in type 2 diabetes: A long-term follow-up in clinical practice, Prim. Care Diab. (2016), http://dx.doi.org/10.1016/j.pcd.2016.11.002

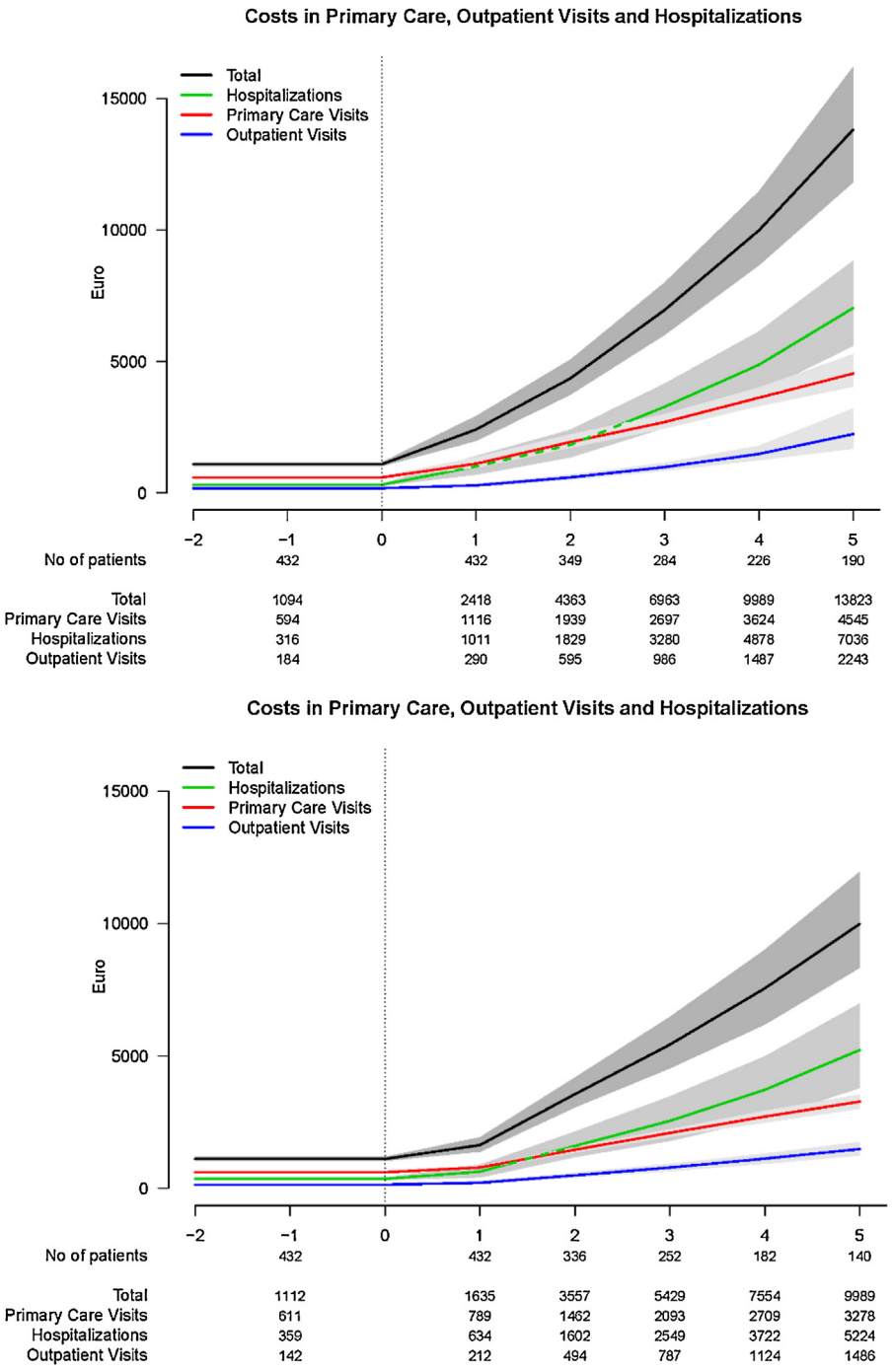


Fig. 2 – Cumulative mean cost per patient prior and after add-on treatment in patients treated with insulin (upper pane) and patients treated with NIAD (lower pane).

point increase in HbA1c led, on average, to a 4.4% increase in diabetes-related medical costs for type 2 diabetes [34]. This relationship could help explain the cost increase over time as the disease progresses. In the present study, on matching the insulin patients in HbA1c and other important variables to patients receiving NIAD-treatment in second line, the insulin initiation was followed by a higher use of healthcare services and a larger increase in total healthcare costs, than non-insulin treatment. To our knowledge, the present study is the first to compare healthcare costs of patients initiated on second line insulin to a matched group of patients initiating second line with another NIAD. The difference in health care costs was visible already after the first year and continued to grow during 5 year observation period. At year 5, insulin patients had incurred €3800 more in cumulative healthcare costs per patient than non-insulin patients. The difference in costs is striking, especially in the view that insulin is put

Please cite this article in press as: A. Kalkan, et al., Increased healthcare utilization costs following initiation of insulin treatment in type 2 diabetes: A long-term follow-up in clinical practice, Prim. Care Diab. (2016), http://dx.doi.org/10.1016/j.pcd.2016.11.002

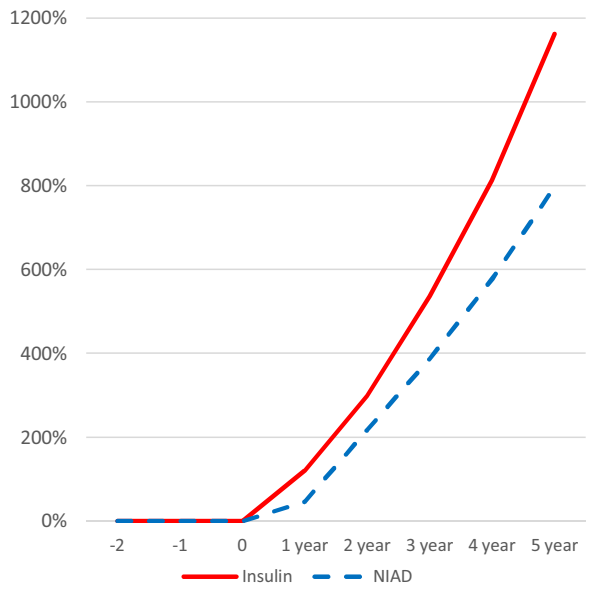


Fig. 3 – Increase in cumulative mean cost per patient year 1–5 versus date of add-on treatment in patients treated with insulin (red full line) and patients treated with NIAD (blue dashed line).(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

forward for its alleged low cost compared to non-insulin treatments [13].

The increase in primary care contacts is of particular interest as it indicates a need for a more intense follow up after insulin initiation. In Sweden, interaction with diabetes teams after insulin initiation is well established and recommended in the national guidelines, which could help explain the increase in primary care costs. In addition, hospitalizations increased substantially in the first year after insulin initiation, compared to patients prescribed non-insulin treatment. The observed difference in hospitalization costs may be mainly related to the adverse effects of insulin, particularly hypoglycemia, that require additional healthcare. Despite the known benefits with early insulin initiation [35–37], it also carries a number of unwanted side effects [11,15–17]. Hypoglycemic responses, such as sympathoadrenergic activation, are suspected to act as a causal pathway between insulin treatment and risk of CVD, mortality, and potential serious cardiac arrhythmias [38].

Furthermore, the increased hospitalization might be linked to weight gain, which is a well-known side-effect of insulin treatment. Several studies have shown that overweight is a major contributor to the increased risk for CV morbidity and mortality in T2DM patients [8,32,39,40]. In addition, treatment induced weight gain has been reported as having a negative effect on adherence to diabetic medications [41]. Consequently, several studies have shown that weight changes in T2DM-patients had effect on healthcare costs due to increased healthcare consumption [42–44]. For instance, every unit gain in BMI was found to be associated with 20% increase in costs among patients who increased their BMI over 12 months (change in BMI >0) [44].

Previous research of healthcare costs for T2DM in Sweden has evaluated costs for 1 year at a time, and often in limited cohorts [24–31]. This study longitudinally follows patients' healthcare use and cost development after initiation of insulin in a large patient cohort (n = 2823). Patients with data 2 years prior to insulin initiation were deliberatively chosen to depict the changes in costs after insulin initiation. By using a large data material from 84 primary care centers from different parts of Sweden, selection bias has been reduced. However, this study also has limitations. One is the relatively small number of patients available for the full 7 year observation period. The representativeness of the cohorts included could be questioned, supporting the importance to compare the larger insulin initiating cohort to the second-line cohort match. The matched cohort was very similar to all patients who were initiated on insulin, and the 5-year cumulative mean healthcare costs were similar in both insulin groups (€13,823 versus €14,211), supporting high internal representativeness. The exclusion of patients who have previous experience of CVD or cancer, or who were hospitalized within 90 days prior to insulin initiation, was also performed to minimize the risk for confounding. Another potential drawback are the included cost items. Healthcare utilization is limited to primary care visits, hospitalizations and secondary outpatient visits, and does not account for other emergency care or outpatient care. However, the main treatment of T2DM in Sweden is provided by the included items, why this study gives a well-covered estimate of the costs that follow insulin initiation.

5. Conclusions

Initiation of insulin in type 2 diabetes patients were followed by increased costs in primary, secondary outpatient and hospital care, larger than those seen in a matched patient population initiated on non-insulin treatment in second-line. To fully analyze the implications of insulin and NIAD treatment, a cost-effectiveness analysis is required.

Conflict of Interest

AK, JB, and ME hold full-time positions at AstraZeneca. JS, BS, CJÖ, PN and GJ have received compensation for their work from AstraZeneca.

Acknowledgement

This study was sponsored by AstraZeneca.

Appendix A.

Item costs used to calculate mean and median costs per individual for outpatient visits. Cost reference: KPP Database.

ICD10	EUR/admission	Year	Comments
	297.58	2013	
E11	190.16	2013	
E10	290.81	2013	
H25	167.52	2013	
Z49	447.76	2013	
Z09	237.84	2013	
E14	295.40	2013	
Z13	134.77	2013	
H40	118.23	2013	
I20	381.46	2013	
C61	383.76	2013	
I48	406.51	2013	
Z01	183.38	2013	
M17	290.23	2013	
I25	312.06	2013	
H35	305.97	2013	
R10	341.71	2013	
Z51	416.85	2013	
Z08	478.89	2013	
L40	277.71	2013	
I70	316.77	2013	
R07	392.95	2013	
M79	410.30	2013	
Z96	250.36	2013	
M05	298.16	2013	
other ICD codes	310.91	2013	mean for all diagnosis

REFERENCES

[1] A. Norhammar, J. Bodegard, T. Nystrom, et al., Incidence, prevalence, and mortality of type 2 diabetes requiring glucose-lowering treatment, and associated risks of cardiovascular complications: a nationwide study in Sweden, 2006–2013, Diabetologia 5 (2016) (Epub ahead of print).

[2] J. Sundstrom, R. Sheikhi, C.J. Ostgren, et al., Blood pressure levels and risk of cardiovascular events and mortality in type-2 diabetes: cohort study of 34 009 primary care patients, J. Hypertens. 31 (8) (2013) 1603–1610.

[3] ADVANCE Collaborative Group, A. Patel, S. MacMahon, J. Chalmers, et al., Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes, N. Engl. J. Med. 358 (24) (2008) 2560–2572.

[4] C.J. Östgren, J. Sundström, B. Svennblad, et al., Associations of HbA1c and educational level with risk of cardiovascular events in 32,871 drug-treated patients with type 2 diabetes: a cohort study in primary care, Diabet. Med. 30 (5) (2013) e170–7.

[5] R. Williams, L. Van Gaal, C. Lucioni, C.-A. Board, Assessing the impact of complications on the costs of type II diabetes, Diabetologia 45 (7) (2002) S13–7.

[6] P.E. Wandell, Quality of life of patients with diabetes mellitus: an overview of research in primary health care in the Nordic countries, Scand. J. Prim. Health Care 23 (2) (2005) 68–74.

[7] P. Kanavos, S. van den Aardweg, W. Schurer, Diabetes Expenditure, Burden of Disease and Management in 5 EU Countries, The London School of Economics and Political Science (LSE), London, UK, 2012.

[8] J. Bodegard, J. Sundstrom, B. Svennblad, et al., Changes in body mass index following newly diagnosed type 2 diabetes and risk of cardiovascular mortality: a cohort study of 8486 primary-care patients, Diabetes Metab. 39 (4) (2013) 306–313.

[9] UK Prospective Diabetes Study (UKPDS) Group, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), Lancet 352 (9131) (1998) 837–853.

[10] J. Bodegård, D. Nathanson, T. Nyström, et al., Second-line treatment with sulphonylurea compared to DPP4 inhibitors demonstrated associations with earlier treatment intensification with insulin, in: Poster at the European Association for the Study of Diabetes (EASD) Annual Meeting, Stockholm, Sweden, 2015, Available from: http://www.easdvirtualmeeting.org/resources/second-line-treatment-with-sulfonylurea-compared-to-dpp4-inhibitors-demonstrated-associations-with-earlier-treatment-intensification-with-insulin-3.

[11] E. Heintjes, J. Overbeek, P. Blin, et al., Type 2 diabetes treatment patterns across Europe [Poster], Value Health 17 (2014) A323–A686, Available from: http://www.harmo.nl/uloads/df/Posters/T2DM%20treatment%20atterns%20across%20Euroe_ISPOR2014_20141030.pdf.

[12] Socialstyrelsen, Nationella riktlinjer för diabetesvård. Stöd för styrning och ledning, National Guidelines for diabetes care in Sweden, Socialstyrelsen Stockholm (2015), 2015-2-3.

[13] S.E. Inzucchi, R.M. Bergenstal, J.B. Buse, et al., Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes, Diabetes Care 38 (2015) 140–149.

[14] National Institute for Health and Care Excellence (NICE), Algorithm for Blood Glucose Lowering Therapy in Adults with Type 2 Diabetes, NICE guideline NG 28, 2015. Available from: https://www.nice.org.uk/guidance/ng28/resources/algorithm-for-blood-glucose-lowering-therapy-in-adults-with-type-2-diabetes-2185604173.

[15] D. Russell-Jones, R. Khan, Insulin-associated weight gain in diabetes—causes, effects and coping strategies, Diabetes Obes. Metab. 9 (6) (2007) 799–812.

[16] B.T. Srinivasan, J. Jarvis, K. Khunti, M.J. Davies, Recent advances in the management of type 2 diabetes mellitus: a review, Postgrad. Med. J. 84 (996) (2008) 524–531.

[17] T.M. Davis, R.M. Clifford, W.A. Davis, Effect of insulin therapy on quality of life in Type 2 diabetes mellitus: the Fremantle Diabetes Study, Diabetes Res. Clin. Pract. 52 (1) (2001) 63–71.

[18] S.E. Holden, S. Jenkins-Jones, C.L. Morgan, et al., Glucose-lowering with exogenous insulin monotherapy in type 2 diabetes: dose association with all-cause mortality, cardiovascular events and cancer, Diabetes Obes. Metab. 17 (4) (2015) 350–362.

[19] R.M. Stoekenbroek, K.L. Rensing, S.J. Bernelot Moens, et al., High daily insulin exposure in patients with type 2 diabetes is associated with increased risk of cardiovascular events, Atherosclerosis 240 (2) (2015) 318–323.

[20] C.L. Roumie, R.A. Greevy, C.G. Grijalva, et al., Association between intensification of metformin treatment with insulin vs sulfonylureas and cardiovascular events and all-cause mortality among patients with diabetes, JAMA 311 (22) (2014) 2288–2296.

[21] American Diabetes Association, Economic costs of diabetes in the U.S. in 2007, Diabetes Care 31 (3) (2008) 596–615.

[22] U. Sabale, J. Bodegard, J. Sundstrom, et al., Healthcare utilization and costs following newly diagnosed type-2

Please cite this article in press as: A. Kalkan, et al., Increased healthcare utilization costs following initiation of insulin treatment in type 2 diabetes: A long-term follow-up in clinical practice, Prim. Care Diab. (2016), http://dx.doi.org/10.1016/j.pcd.2016.11.002

diabetes in Sweden: a follow-up of 38,956 patients in a clinical practice setting, Prim. Care Diabetes 9 (5) (2015) 330–337.
[23] B. Berger, G. Stenstrom, G. Sundkvist, Incidence, prevalence, and mortality of diabetes in a large population: a report from the Skaraborg Diabetes Registry, Diabetes Care 22 (5) (1999) 773–778.
[24] Diabetes National Data US: National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation. National Diabetes Report, 2014. Available from: http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
[25] J.B. Brown, G.A. Nichols, H.S. Glauber, A.W. Bakst, Type 2 diabetes: incremental medical care costs during the first 8 years after diagnosis, Diabetes Care 22 (7) (1999) 1116–1124.
[26] F. Henriksson, C.D. Agardh, C. Berne, et al., Direct medical costs for patients with type 2 diabetes in Sweden, J. Intern. Med. 248 (5) (2000) 387–396.
[27] B. Jonsson, C.A. Board, Revealing the cost of type II diabetes in Europe, Diabetologia 45 (7) (2002) S5–12.
[28] M. Brandle, H. Zhou, B.R. Smith, et al., The direct medical cost of type 2 diabetes, Diabetes Care 26 (8) (2003) 2300–2304.
[29] A. Ringborg, M. Martinell, J. Stålhammar, et al., Resource use and costs of type 2 diabetes in Sweden—estimates from population-based register data, Int. J. Clin. Pract. 62 (5) (2008) 708–716.
[30] K. Bolin, C. Gip, A.C. Mörk, B. Lindgren, Diabetes, healthcare cost and loss of productivity in Sweden 1987 and 2005—a register-based approach, Diabet. Med. 26 (September (9)) (2009) 928–934.
[31] C. Bexelius, J. Lundberg, X. Wang, et al., Annual medical costs of Swedish patients with type 2 diabetes before and after insulin initiation, Diabetes Ther. 4 (December (2)) (2013) 363–374.
[32] I. Grundvold, J. Bodegard, P.M. Nilsson, et al., Body weight and risk of atrial fibrillation in 7,169 patients with newly diagnosed type 2 diabetes; an observational study, Cardiovasc. Diabetol. 14 (2015) 5.
[33] H. Glick, J. Doshi, A. Sonnad, D. Polsky, Analyzing Censored Cost. Economic Evaluatuation in Clinical Trial, Oxford University Press, 2010, pp. 115–131.
[34] M. Aagren, W. Luo, Association between glycemic control and short-term healthcare costs among commercially insured diabetes patients in the United States, J. Med. Econ. 14 (1) (2011) 108–114.
[35] M. Alvarsson, G. Sundkvist, I. Lager, et al., Effects of insulin vs glibenclamide in recently diagnosed patients with type 2 diabetes: a 4-year follow-up, Diabetes Obes. Metab. 10 (5) (2008) 421–429.
[36] L.B. Harrison, B. Adams-Huet, P. Raskin, I. Lingvay, Beta-cell function preservation after 3.5 years of intensive diabetes therapy, Diabetes Care 35 (7) (2012) 1406–1412.
[37] J. Weng, Y. Li, W. Xu, et al., Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial, Lancet 371 (9626) (2008) 1753–1760.
[38] S. Zoungas, A. Patel, J. Chalmers, et al., Severe hypoglycemia and risks of vascular events and death, N. Engl. J. Med. 363 (15) (2010) 1410–1418.
[39] K. Eeg-Olofsson, J. Cederholm, P.M. Nilsson, et al., Risk of cardiovascular disease and mortality in overweight and obese patients with type 2 diabetes: an observational study in 13,087 patients, Diabetologia 52 (January (1)) (2009) 65–73.
[40] J. Klenk, K. Rapp, H. Ulmer, et al., Changes of body mass index in relation to mortality: results of a cohort of 42,099 adults, PLoS One 9 (January (1)) (2014) e84817.
[41] Look AHEAD Research Group, R.R. Wing, Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial, Arch. Intern. Med. 170 (September (17)) (2010) 1566–1575.
[42] J. Mukherjee, C. Sternhufvud, N. Smith, et al., Association between weight change, clinical outcomes, and health care costs in patients with type 2 diabetes, J. Manag. Care Spec. Pharm. 22 (5) (2016) 449–466.
[43] U. Sabale, J. Bodegård, J. Sundström et al. Changes in body mass index over time and their association with healthcare costs among newly-diagnosed type-2 diabetes patients in Sweden, forthcoming.
[44] The ECOBIM Study, T. Dilla, A. Valladares, C. Nicolay, et al., Healthcare costs associated with change in body mass index in patients with type 2 diabetes mellitus in Spain, Appl. Health Econ. Health Policy 10 (6) (2012) 417–430.

Please cite this article in press as: A. Kalkan, et al., Increased healthcare utilization costs following initiation of insulin treatment in type 2 diabetes: A long-term follow-up in clinical practice, Prim. Care Diab. (2016), http://dx.doi.org/10.1016/j.pcd.2016.11.002