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Early Discontinuation and Related Treatment Costs After Initiation of Basal Insulin in Type 2 Diabetes Patients: A German Primary Care Database Analysis

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Abstract

Aims: The aim was to compare early discontinuation and related treatment costs in type 2 diabetes in primary care after initiation of insulin glargine or human basal insulin (NPH). **Methods:** Overall, 2765 glargine and 1554 NPH patients from 1072 general practices were analyzed (Disease Analyser). Early discontinuation was defined as switching to a different basal insulin or another insulin treatment regimen within 90 days after first basal insulin prescription (index date, ID). Treatment costs were assessed 365 days prior and post ID in both groups. Propensity score matching and linear regression was used to adjust cost differences (post vs prior ID: discontinued vs continued patients) for age, sex, diabetes duration, antidiabetic comedication, diabetologist care, disease management program participation, costs before ID, and Charlson Comorbidity Index. **Results:** Within 3 months after ID, 13% of glargine patients switched to other insulin treatment regimens (NPH: 18%; $P < .05$). After propensity score matching, adjusted cost differences in 146 discontinued versus 1342 continued glargine patients were calculated (NPH: 146 vs 1342). Diabetes-related prescription costs were lower among persistent glargine patients compared to persistent NPH patients (EUR–49 [19]; $P = .0109$). Mean cost difference for diabetes-related prescriptions was lower among those who persisted on glargine compared to those who switched to other treatment regimens (EUR–74 [42], $P = .0780$). **Conclusions:** Treatment persistence within 3 months after basal insulin initiation was significantly higher under insulin glargine compared to NPH. Diabetes-related prescription costs were significantly lower among patients who adhered to insulin glargine compared to persistent NPH patients.

Keywords

type 2 diabetes, early discontinuation, treatment costs, basal insulin, primary care

If glycemic control cannot be maintained by oral antidiabetic drugs alone, type 2 diabetes patients often start a basal-supported oral therapy (BOT).[1] Either intermediate-acting human insulin (neutral protamine Hagedorn [NPH]) or long-acting insulin analogues such as glargine may be used in combination with oral drugs.[1] Nevertheless, a relevant proportion of type 2 diabetes patients have difficulties in managing the insulin initiation accurately, which often results in early discontinuation from BOT.[2] Few studies have examined the persistence of type 2 diabetes patients on BOT in a real -world setting.[3-7] There is evidence from German studies that BOT initiation with insulin glargine may be associated with a higher persistence compared to initiation with NPH insulin.[5-6]

Little information is available about the impact of basal insulin changes on associated health care costs in real-world primary care settings. In a US study, significantly higher diabetes drug and diabetes supply costs were found in patients who switched from insulin glargine to insulin detemir compared to those who continued on insulin glargine.[3] In another US study, the total overall health care costs were similar for insulin glargine and NPH insulin patients, as were the total diabetes-related health care costs.[4] In German studies, lower treatment costs were found under insulin glargine compared to insulin detemir[7] and human insulin[8] based on longer persistence. A database study from the US indicated that early

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Table 1. Baseline Characteristics of Primary Care Patients With Onset of Glargine or NPH Insulin Therapy (BOT) After Propensity Score Matching.

Variable	Glargine	NPH	*P* value
N	1488	1488	
Age (years)	56.1 (11.8)	59.1 (11.9)	<.0001
Diabetes duration (years)	6.4 (4.1)	5.5 (3.7)	<.0001
Males (%)	53.2	53.7	.7970
Region (western Germany) (%)	70.9	78.8	<.0001
Diabetologist care (%)	15.9	16.2	.8417
Disease management program (%)	70.4	69.4	.5490
Number of different oral antidiabetic drugs (baseline)	1.4 (0.6)	1.4 (0.6)	.4486
Last HbA1c (%) (baseline)	8.8 (1.6)	8.5 (1.6)	<.0001
Charlson Comorbidity Index	2.1 (1.5)	2.0 (1.4)	.4960

Patients were propensity score matched (variables in the table excluding HbA1c, disease management program, and region). Data are means (SD) or proportions (%).

discontinuation of insulin (basal or premixed insulin) in type 2 diabetes was related to approximately 10% higher acute health care costs compared to patients who did continue their insulin therapy.[9] However, the costs related to early discontinuation from BOT (insulin glargine vs NPH) have not yet been assessed. Therefore, the objective of this study is to describe the cost consequences of early discontinuation from initial basal insulin treatment (glargine, NPH insulin) in type 2 diabetes patients under real-world conditions in Germany.

Methods

The Disease Analyser database (IMS HEALTH) assembles drug prescriptions, diagnoses, and basic medical and demographic data directly obtained from the computer system of general practitioners.[10] The analyzed database period was January 2008 to March 2014 (1072 general and internal medicine practices). Patients with type 2 diabetes, who had a basal insulin (glargine, NPH insulin) initiated, whichever came first (index date), were identified. The practice visit records were used to determine 12-month prior and 12-month post index follow-up, respectively.

Direct costs were analyzed from the perspective of the statutory health insurance (payer perspective). The following cost components were included: insulin (any type), oral and injectable antidiabetic agents (eg, metformin, sulphonylureas, DPP-4 inhibitors, GLP-1 agonists), consumables (test strips, needles, lancets), medication to treat symptomatic and severe hypoglycemia (glucagon i.m., glucose i.v.), and diabetes-related medical services (eg, visit costs based on documented frequency and complexity, therapeutic remedies and aids, diabetes education and training, diagnostic procedures such as blood glucose or HbA1c-measurements). Medication and consumables costs were estimated by official pharmacy price (Lauer Taxe[11]) minus legally defined rebates from pharmaceutical companies according to section 130a German Social Security Code, Part V (SGB V). Medical services were calculated based on the official fee scale for physicians' outpatient services (EBM).[12] Under this directive, general consultation and care services were billed as a lump sum. Single services were billed by multiplying the quantity of points times the publicly available value per point of EUR0.035. Costs for hospital stays and referrals to specialists (eg, ophthalmologist, nephrologist) were not available in the database.

Annual cost differences were defined as the difference in average costs of patients during 1 year after ID minus 1 year before ID. The primary outcome was the annual cost difference (post vs prior ID) calculated both for patients who discontinued and those who persisted to their initial BOT. Potential confounders considered were age, sex, diabetes duration, antidiabetic comedication, baseline HbA1c, diabetologist care, and participation in a disease management program, in addition to baseline costs. The Charlson Comorbidity Index (CCI) was used to adjust for baseline characteristics in concomitant diseases.[13]

Descriptive statistics were given and group differences were assessed using linear or logistic regression models. Propensity score matching was used to adjust for age, sex, diabetes duration, antidiabetic comedication, diabetologist care, and CCI between the insulin groups.

Two-sided tests were used and a P value of $<.05$ was considered as statistically significant. All analyses were carried out following the German good practice recommendations of secondary data analysis[14] using SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

The baseline characteristics of type 2 diabetes patients initiating BOT with either insulin glargine or human basal insulin (NPH) are shown in Table 1. In the NPH cohort, patients were slightly older than in the glargine group, whereas average diabetes duration was approximately 1 year longer in

Table 2. Baseline Characteristics of Primary Care Patients With Early Discontinuation or Persistence (≤90 days) of Glargine or NPH Basal Insulin Therapy (BOT).

Variables	Glargine discontinuation	Glargine persistence	NPH discontinuation	NPH persistence	*P* value[a]
N	146	1342	146	1342	
Age (years)	60.5 (12.2)	55.8 (11.6)	60.7 (12.8)	59.0 (11.8)	<.0001
Diabetes duration (years)	5.8 (3.8)	6.5 (4.0)	5.9 (3.1)	5.5 (3.7)	<.0001
Males (%)	52.1	53.4	49.3	54.1	.7045
Region (western Germany) (%)	78.8	70.0	77.4	79.0	<.0001
Diabetologist care (%)	10.3	16.5	8.9	17.0	.0165
Disease management program (%)	62.3	71.2	60.3	70.3	.0086
Number of different oral antidiabetic drugs (baseline)	1.4 (0.5)	1.4 (0.6)	2.0 (1.2)	1.4 (0.6)	.8393
Last HbA1c (%) (baseline)	8.8 (1.6)	8.8 (1.6)	8.5 (1.7)	8.5 (1.6)	<.0001
Charlson Comorbidity Index	2.1 (1.4)	2.1 (1.5)	2.0 (1.2)	2.0 (1.3)	.9098

Data are means (SD) or proportions (%).
[a]*P* values for group differences (linear or logistic regression model).

Table 3. Mean Annual Costs (EUR) of Primary Care Patients With at Least 1-Year Persistence (Glargin Versus NPH).

Variable	Glargin costs prior ID	Glargin costs post ID	NPH costs prior ID	NPH costs post ID	Cost difference (glargin vs NPH)
N	1342	1342	1342	1342	
Total treatment costs	764 (499)	1166 (596)	686 (444)	1160 (645)	−48 (22); *P* = .0288[a]
Diabetes-related prescription costs	506 (443)	907 (553)	451 (393)	908 (566)	−49 (19); *P* = .0109
Insulin, oral/injectable antidiabetics	447 (414)	676 (444)	380 (351)	647 (430)	—
Consumables	59 (110)	232 (253)	72 (145)	261 (293)	—
Treatment of hypoglycemia (glucagon i.m., glucose i.v.)	0.0 (0.0)	0.0 (0.9)	0.0 (0.9)	0.1 (2.3)	—
Other medical services	258 (251)	259 (212)	235 (212)	252 (235)	+7 (8); *P* = .3782

Data are means (SD). Patients with and without discontinuation were propensity score matched for age, sex, diabetes duration, diabetologist care, disease management program participation, and Charlson Comorbidity Index; cost differences were further adjusted for baseline costs and HbA1c. ID, index date of starting basal insulin therapy. Cost difference (last column): positive values represent savings; negative values are excess expenditure.
[a]*P* values: difference (glargin versus NPH) of costs differences (post/prior ID).

glargine patients (both $P < .001$). The mean HbA1c (%) value before insulin initiation was higher in glargine than in NPH patients ($P < .001$), whereas no differences were observed for diabetologist care, disease management program participation, and the number of different oral antidiabetic drugs before insulinization (Table 1). Finally, NPH patients were more frequently treated in practices in western Germany.

Within the first 90 days after initiation of BOT, 13% of patients who started on insulin glargine discontinued their treatment (NPH: 18%; $P < .05$). Fewer than half of the discontinued glargine patients (43%) switched to a different basal insulin or another insulin treatment regimen (NPH: 54%). The other discontinued patients changed to GLP-1 receptor agonists (glargine: 3.8%, NPH: 4.9%) or returned to oral antidiabetic therapy (glargine: 53.2%, NPH: 41.1%).

The baseline characteristics of those patients who switched from their initial basal insulin to a different basal insulin or to another insulin treatment regimen (eg, conventional therapy [CT] with premixed insulin or prandial therapy (SIT) with short acting insulin) are shown in Table 2. Patients who discontinued on NPH-insulin were slightly older, were less often in diabetologist care, and were less frequently enrolled in disease management programs (Table 2). No significant differences were found for gender distribution, the number of oral antidiabetic drugs, or the occurrence of comorbidities (CCI).

After propensity score matching and adjusting for further confounders (baseline HbA1c, region of practice, disease management program participation, and baseline costs), annual direct medical costs of patients who discontinued and adhered to their initial basal insulin were compared for both groups and between both groups (Tables 3-5).

Comparison between the 2 basal insulin groups (glargine vs NPH) showed significant savings for total annual treatment costs (EUR–48 [22]; $P = .0288$) and diabetes-related prescription costs (EUR–49 [19]; $P = .0109$) among persistent glargine patients compared to persistent NPH patients (post vs prior ID), whereas no relevant cost difference was

Table 4. Mean Annual Costs (EUR) of Primary Care Patients (Discontinuation Versus Persistence) in the Glargine Group.

Variable	Discontinuation costs prior ID	Costs post ID	Persistence costs prior ID	Costs post ID	Cost difference (post vs prior ID): discontinuation vs persistence
N	146	146	1342	1342	
Total treatment costs	702 (472)	1199 (580)	764 (499)	1166 (596)	−67 (47); $P = .1535$[a]
Diabetes-related prescription costs	431 (414)	924 (556)	506 (443)	907 (553)	−74 (42); $P = .0780$
Insulin, oral, and injectable antidiabetics	386 (394)	662 (478)	447 (414)	676 (444)	—
Consumables	45 (78)	262 (255)	59 (110)	232 (253)	—
Treatment of hypoglycemia (glucagon i.m., glucose i.v.)	0.0 (0.0)	0.2 (2.7)	0.0 (0.0)	0.0 (0.9)	—
Other medical services	271 (254)	276 (247)	258 (251)	259 (212)	+4 (18); $P = .8264$

Data are means (SD). Patients with and without discontinuation were propensity score matched for age, sex, diabetes duration, diabetologist care, disease management program participation, and Charlson Comorbidity Index; cost differences were further adjusted for baseline costs and HbA1c. ID, index date of starting insulin glargine therapy. Cost difference (last column): positive values represent savings; negative values are excess expenditure.
[a]*P* values: difference (discontinuation vs persistence) of cost differences (post/prior ID).

Table 5. Mean Annual Costs (EUR) of Primary Care Patients (Discontinuation Versus Persistence) in the NPH Group.

Variables	NPH discontinuation costs prior ID	NPH costs post ID	NPH persistence costs prior ID	NPH costs post ID	Cost difference (post vs prior ID): discontinuation vs persistence
N	146	146	1342	1342	
Total treatment costs	724 (460)	1158 (638)	686 (444)	1160 (645)	21 (52); $P = .6781$[a]
Diabetes-related prescription costs	455 (395)	890 (588)	451 (393)	908 (566)	−14 (44); $P = .7570$
Insulin, oral/injectable antidiabetics	403 (376)	627 (469)	380 (351)	647 (430)	—
Consumables	52 (93)	263 (276)	72 (145)	261 (293)	—
Treatment of hypoglycemia (glucagon i.m., glucose i.v.)	0.0 (0.0)	0.2 (2.7)	0.0 (0.9)	0.1 (2.3)	—
Other medical services	269 (219)	268 (303)	235 (212)	252 (235)	−4 (20); $P = .8658$

Data are means (SD). Patients with and without discontinuation were propensity score matched for age, sex, diabetes duration, diabetologist care, disease management program participation, and Charlson Comorbidity Index; cost differences were further adjusted for baseline costs and HbA1c. ID, index date of starting NPH basal insulin therapy. Cost difference (last column): positive values represent savings; negative values are excess expenditure.
[a]*P* values: difference (discontinuation vs persistence) of costs differences (post/prior ID).

observed for medical services (EUR+7 [8]; $P = .3782$) between these 2 groups (Table 3).

Annual cost differences (post vs prior ID) for diabetes-related prescriptions (drugs and consumables) were also lower for those patients who persisted on glargine compared to those who switched to other insulins (EUR–74 [42]; $P = .0780$) (Table 4). Annual cost differences for total treatment costs (diabetes-related prescriptions and other medical services) were also lower for those who persisted on glargine (EUR–67 [47]; $P = .1535$) (Table 4). No relevant cost difference was observed for other medical services provided by the general practitioners (EUR+4 [18]; $P = .8264$) (Table 4). In the NPH cohort, there were no relevant cost differences in any of the cost components after adjusting for potential confounders between patients who discontinued their NPH therapy and those who continued (Table 5).

In a subgroup analysis, the last recorded HbA1c values were analyzed in the 4 patient groups. In glargine users, those who discontinued had significantly higher HbA1c values than those who continued with the basal insulin (mean [SD]: n = 105, 8.5 [1.3]% vs n = 1683 8.0 [1.3]%; $P = .0001$). A similar result was found for NPH basal insulin users (discontinuation: n = 103 8.2 [1.4%]; continuation: n = 942, 7.9 [1.2]%; $P = .0005$).

Discussion

This real-world study shows that adherence to BOT with insulin glargine resulted in significant lower total annual treatment and diabetes-related prescription costs than adherence to BOT with NPH insulin. In addition, adherence to BOT with insulin glargine right from the start was also associated with relevant

savings regarding total annual treatment costs and diabetes-related prescription costs in type 2 patients compared to switching to a different basal insulin or another insulin treatment regimen directional favoring insulin glargine. In line with our data, a recent study showed that switching 2 basal insulin analogues resulted in significantly greater acute care costs.[3] Thus, our results support the medical concept to prolong persistence on BOT with long-acting insulin glargine, provided that sufficient glycemic control is given.

The present real-world data indicate a challenging proportion of patients who discontinued their basal insulin within the first 3 months. Whereas 18% of all patients in the NPH group stopped their BOT prematurely, 13% of all patients in the glargine group withdrew from this treatment regimen. Numerous head-to-head trials of insulin glargine versus NPH insulin and several meta-analyses[15,16] demonstrated a tendency of better glycemic control in favor of glargine as well as less hypoglycemia, especially during the night, which might partly explain the above findings. In addition, once versus twice daily insulin administration, flexible injection times, and a ready to use formulation[17] probably result in a greater treatment satisfaction and improved quality of life[18] and might also contribute to the difference in discontinuation frequency.

Almost half of the patients who discontinued their BOT early with either insulin glargine or human insulin (NPH) returned to some kind of oral antidiabetic therapy. Recently, short-term intensive insulin therapy was reported to achieve long-term glycemic control in patients with newly diagnosed type 2 diabetes.[19-21] Injection related anxiety,[22] fear of hypoglycemia,[23] and weight gain[24] might have also played a role for the return to solely oral antidiabetic therapy. Further studies are needed to analyze the underlying reasons.

The other half of patients who discontinued their basal insulin (BOT) early switched to different insulin treatment regimens. Although BOT was shown to be superior compared with conventional (CT) and prandial insulin therapy (SIT) in head to head trials,[25-27] these alternative treatment options are important for specific diabetes populations. In particular, in blind patients or patients with mental or movement disorders, a switch to conventional insulin therapy (CT) with twice daily premixed insulin may be more suitable and convenient. Other patients (eg, sporty patients or shift workers) might benefit from a more flexible prandial insulin therapy (SIT) with short acting insulin injections to 1 or more meals.

Interestingly, total treatment costs and diabetes-related prescription costs were lower among persistent glargine than NPH patients. It is conceivable that the lower injection frequencies of glargine compared to NPH insulin observed in a recent real-world study may contribute to this cost difference.[28] This is in line with pharmacoeconomic studies performed under German real-world conditions.[29,30]

The unadjusted mean total annual treatment costs for diabetes observed in the present study are in line with recent descriptive health economic studies in Germany.[31,32] Based on nationwide data from a large statutory health insurance (AOK PLUS), annual absolute costs were estimated for different subgroups of type 2 diabetes patients stratified by glycemic and blood pressure control and comorbidity.[31] A direct comparison with the present study, which included patients with newly onset insulin treatment, is not possible. However, in a comparable risk group (HbA1c 7-9%; systolic blood pressure >130 mm Hg, CCI <6), the mean annual absolute costs for antidiabetic medication and consumables amounted to EUR773 and annual absolute costs for outpatient treatment amounted to EUR242,[31] which are in the same range as in the present study. These costs are lower compared to previous studies in Germany. For instance a study based on health insurance data reported average annual treatment costs of diabetes type 2 patients of EUR5958, including diabetes-related excess costs of EUR2608.[2,32] Diabetes-related excess costs in this study were derived from a matched-pairs cost comparison with non-diabetic patients.[32] Instead, we used a bottom-up approach by selecting specific items related to diabetes resource use.

Several limitations of the present study should be mentioned. First, no valid information on diabetes type and prescribed daily doses was available in the database. Furthermore, no valid information regarding onset of diabetes was provided. Also assessment of comorbidities relied on ICD codes by primary care physicians only. Finally, it would be important to analyze the underlying reasons for early discontinuation of basal insulin therapy. Unfortunately, important aspects like compliance of the patient and views of the physicians are not covered in the database. Furthermore, clinical outcomes like HbA1c, BMI and hypoglycemia are only recorded in a subgroup of the patients in the primary care database. We have analyzed the last HbA1c values for those who discontinued and those persisted with the basal insulin therapy. As expected, mean HbA1c values of patients who stopped basal insulin (both glargine and NPH insulin) were significantly higher than those among persistent users. Thus, inadequate glycemic control is 1 factor that influenced change in basal insulin therapy.

In conclusion, persistence to basal insulin glargine was associated with significant lower annual treatment and diabetes-related prescription costs compared to patients who adhered to NPH-insulin. Moreover persistence of basal insulin glargine right from the start in type 2 diabetes was associated with relevant lower annual treatment and diabetes-related prescription costs for diabetes-related prescriptions compared to switching to different basal insulins or other insulin treatment regimens. Further studies are needed to explore the underlying reasons for early basal insulin discontinuation to improve persistence and further reduce treatment costs in type 2 diabetes patients after insulin initiation.

Abbreviations

BOT, basal supported oral therapy; CCI, Charlson Comorbidity Index; CT, conventional therapy; DPP-4, dipeptidylpeptidase 4; GLP-1, glucagon-like peptid 1; ICD, International Classification of

Diseases; ID, index date; NPH, neutral protamine Hagedorn; SD, standard deviation; SIT, supplementary insulin therapy

Declaration of Conflicting Interests

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References

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centred approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2012;55:1577-1596.
2. Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care*. 2004;27:1218-1224.
3. Wei W, Zhou S, Miao R, et al. Much ado about nothing? A real-world study of patients with type 2 diabetes switching Basal insulin analogues. *Adv Ther*. 2014;31:539-560.
4. Wang L, Wei W, Miao R, Xie L, Baser O. Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: a comparative retrospective database study. *BMJ Open*. 2013;3(4).
5. Quinzler R, Ude M, Franzmann A, et al. Treatment duration (persistence) of basal insulin supported oral therapy (BOT) in type-2 diabetic patients: comparison of insulin glargine with NPH insulin. *Int J Clin Pharmacol Ther*. 2012;50:24-32.
6. Pfohl W, Dippel FW, Kostev K, Maltz A, Kotowa W. Higher persistence with basal supported oral therapy (BOT) with insulin glargine compared to NPH insulin therapy combined with oral antidiabetics [in German]. *Diabetologie*. 2009;4:166-171.
7. Pfohl W, Dippel FW, Kostev K, Fuchs S, Kotowa W. Basal supported oral therapy with insulin glargine results in longer persistence and lower costs compared with insulin detemir in type 2 diabetics in Germany. *Health Outcome Res Med*. 2011;2:e39-e50.
8. Pfohl W, Dippel FW, Kostev K, Kotowa W. Modelling of long-term treatment costs in insulin dependent type 2 diabetics due to initiation of insulin therapy: a comparison between insulin glargine and NPH-insulin [in German]. *Gesundh ökon Qual Manag*. 2011;16:182-188.
9. Ascher-Svanum H, Lage MJ, Perez-Nieves M, et al. Early discontinuation and restart of insulin in the treatment of type 2 diabetes mellitus. *Diabetes Ther*. 2014;5:225-242.
10. Becher H, Kostev K, Schröder-Bernhardi D. Validity and representativeness of the "Disease Analyser" patient database for use in pharmacoepidemiological and pharmacoeconomic studies. *Int J Clin Pharmacol Ther*. 2009;47:617-626.
11. Lauer-Fischer GmbH. Große Deutsche Spezialitäten—Taxe. Lauer Taxe® mit Apotheken Ein-und Verkaufspreisen [Official German pharmacy sales prices]. Available at: http://www2.lauer-fischer.de/produkte/lauer-taxe/lauer-taxe/. Accessed August 28, 2014.
12. Kassenärztliche Bundesvereinigung (KBV) [National Association of Statutory Health Insurance-accredited Physicians]. Einheitlicher Bewertungsmaßstab (EBM). Available at: http://applications.kbv.de/ebm/EBMGesamt.htm. Accessed August 28, 2014.
13. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43:1130-1139.
14. Swart E. Good practice of secondary data analysis, first revision. *Gesundheitswesen*. 2008;70:54-60.
15. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycaemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care*. 2005;28:950-955.
16. Mullins P, Sharplin P, Yki Yarvinnen H, Riddle MC, Haring HU. Negative binomial meta-regression analysis of combined glycosylated haemoglobin and hypoglycaemia outcomes across eleven phase III and IV studies of insulin glargine compared with neutral protamin Hagedorn insulin in type 1 and type 2 diabetes mellitus. *Clin Ther*. 2007;29:1607-1619.
17. Jehle PM, Micheler C, Jehle DR, Breitig D, Boehm BO. Inadequate suspension of neutral protamine Hagendorn (NPH) insulin in pens. *Lancet*. 1999;354:1604-1607.
18. Hagenmeyer EG, Schädlich PK, Koster AD, Dippel FW, Häussler B. Quality of life and treatment satisfaction in patients being treated with long acting insulin analogues: systematic review [in German]. *Dtsch Med Wochenschr*. 2009;134:565-570.
19. Hu Y, Li L, Xu Y, et al. Short-term intensive therapy in newly diagnosed type 2 diabetes partially restores both insulin sensitivity and ß-Cell function in subjects with long-term remission. *Diabetes Care*. 2011;34:1848-1853.
20. Xu Wen, Li Y, Deng W, Hao YT, Weng JP. Remission of hyperglycaemia following intensive insulin therapy in newly diagnosed type 2 diabetic patients: a long-term follow-up study. *Chin Med J*. 2009;122:2554-2559.
21. Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multi-centre randomised parallel-group trial. *Lancet*. 2008;371:1753-1760.
22. Zambanini A, Newson RB, Maisey M, Feher MD. Injection related anxiety in insulin treated diabetes. *Diabetes Res Clin Pract*. 1999;46:239-246.
23. Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycaemia in diabetes: implications for diabetes management and patient education. *Patient Educ Couns*. 2007;68:10-15.
24. Balkau B, Home PD, Vincent M, Marre M, Freemantle N. Factors associated with weight gain in people with type 2 diabetes starting on insulin. *Diabetes Care*. 2014;37:2108-2113.
25. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki Jarvinnen H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin therapy for type 2 diabetes. *Diabetes Care*. 2005;28:254-259.
26. Bretzel RG, Nuber U, Landgraf W, Owens DR, Bradley C, Linn T. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. *Lancet*. 2008;371:1073-1084.

27. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med*. 2007;357:1716-1730.
28. Rathmann W, Dippel FW, Kostev K. Different injection frequencies of basal insulins in type 2 diabetes patients under real-life conditions: a retrospective database analysis. *J Diabetes Sci Technol*. 2013;7:1354-1358.
29. Schöffski O, Breitscheidel L, Benter U, et al. Resource utilisation and costs in patients with type 2 diabetes mellitus treated with insulin glargine or conventional basal insulin under real-world conditions in Germany: LIVE-SPP study. *J Med Econ*. 2008;11:695-712.
30. Anderten H, Dippel FW, Schneider T. Cost comparison between treatment regimens in diabetes mellitus based on long-acting insulins in Germany. *Perfusion*. 2013;26:148-153.
31. Wilke T, Groth A, Fuchs A, et al. Real life treatment of diabetes mellitus type 2 patients: an analysis based on a large sample of 449,368 German patients. *Diabetes Res Clin Pract*. 2014;17:A260. http://dx.doi.org/10.1016/j.diabres.2014.08.002.
32. Köster I, Huppertz E, Hauner H, Schubert I. Costs of diabetes mellitus (CoDiM) in Germany, direct per-capita costs of managing hyperglycaemia and diabetes complications in 2010 compared to 2001 [published online ahead of print June 11, 2014]. *Exp Clin Endocrinol Diabetes*.