Clinical and Economic Outcomes Associated With the Timing of Initiation of Basal Insulin in Patients With Type 2 Diabetes Mellitus Previously Treated With Oral Antidiabetes Drugs

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ABSTRACT

Purpose: In patients with type 2 diabetes mellitus (T2DM) not achieving glycemic targets using oral antidiabetes drugs (OADs), studies suggest that timely insulin initiation has clinical benefits. Insulin initiation at the early versus late stage of disease progression has not been explored in detail. This retrospective database analysis investigated clinical and economic outcomes associated with the timing of insulin initiation in patients with T2DM treated with ≥1 OAD in a real-world US setting.

Methods: This study linked data from the Truven Health MarketScan® Commercial database, Medicare Supplemental database, and Quintiles Electronic Medical Records database. A total of 1830 patients with T2DM were included. Patients were grouped according to their OAD use before basal insulin initiation (1, 2, or ≥3 OADs) as a proxy for the timing of insulin initiation. Clinical and economic outcomes were evaluated over 1 year of follow-up.

Findings: During follow-up the 1 OAD group, compared with the 2 and ≥3 OADs groups, had a greater reduction in glycosylated hemoglobin A_{1c} (−1.7% vs −1.0% vs −0.9%, respectively; $P < 0.0001$), greater achievement of glycemic target (38.2% vs 26.7% vs 19.6%, respectively; $P < 0.0001$), and a lower incidence of hypoglycemia (2.7% vs 6.6% vs 5.0%, respectively; $P = 0.0002$), with no difference in total health care costs ($21,167 vs $21,060 vs $20,133, respectively).

Implications: This study shows that early insulin initiation (represented by the 1 OAD group) may be clinically beneficial to patients with T2DM not controlled with OADs, without adding to costs. This supports the call for timely initiation of individualized insulin therapy in this population.

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Key words: early insulinization, economic outcomes, insulin initiation, type 2 diabetes.

INTRODUCTION

After diagnosis of type 2 diabetes mellitus (T2DM), lifestyle changes and oral antidiabetes drugs (OADs) are recommended.[1] If blood glucose targets are not achieved with first-line therapy after approximately 3 months, guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) advocate the addition of another OAD or insulin to the treatment regimen.[1] Importantly, the treatment regimen should be tailored to each patient's needs. However, because of the progressive nature of diabetes, most patients will eventually need insulin therapy to maintain or achieve glycemic targets (generally glycosylated hemoglobin A_{1c} [A1C] <7.0%).[1,2]

Several clinical studies suggest that timely initiation of insulin therapy is beneficial for patients with diabetes.[3–5] However, the differences between initiating insulin when a patient is unable to control hyperglycemia on an OAD or at a later stage of a patient's disease progression when taking multiple OADs have not been examined fully. This is important because many patients with T2DM with inadequate glycemic control using OADs endure

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a prolonged glycemic burden before they begin insulin therapy.[6,7] Clinical inertia, the failure to intensify treatment despite a patient not meeting glycemic targets, may be a contributing factor.[8,9] Both patients and physicians are responsible for clinical inertia: concerns about hypoglycemia, weight gain, and injectable agents contribute to resistance to the initiation of insulin therapy.[10] However, the association between the timing of insulin initiation and health care outcomes in real-world settings, including the economic impact, remains to be explored.

This analysis assessed the clinical and economic outcomes associated with the timing of basal insulin initiation in US patients with T2DM previously treated with ≥1 OAD.

METHODS

Study Design and Patients

This was a retrospective database analysis of combined data from 3 databases: 2 Truven Health MarketScan databases (Claims and Encounters [Commercial] and Medicare Supplemental and Coordination of Benefits [Medicare]) and the linked Quintiles Electronic Medical Records (EMR) database. These 3 sources provided data for patients insured commercially or through Medicare and information from their EMR. The MarketScan Commercial database contains the health care experience of ~39.5 million employees and their dependents, covered under a variety of fee-for-service and managed-care health plans. The MarketScan Medicare database contains the health care experience of ~3.4 million retirees with Medicare supplemental insurance paid for by employers. Both the MarketScan Commercial and Medicare databases provide detailed cost, use, and outcomes data for health care services performed in the inpatient and outpatient settings. The Quintiles EMR database contains ambulatory clinical data from >9000 providers and covers >13.5 million unique patient lives.

A hybrid deterministic-probabilistic approach was used to link a subset of patients in the MarketScan databases to the Quintiles EMR database at the patient level. The deterministic match required an exact match on several variables from both sources, including the 3-digit ZIP code of residence, sex, and month and year of birth. The probabilistic match involved finding exact matches for ≥3 physician visits. Physician visits were selected as the attribute for matching due to likely agreement between medical records and claims data. In total, 1,348,279 patients were included in the linked MarketScan and Quintiles database.

Patients included in the study were 18 years of age or older and received a diagnosis of T2DM between July 1, 2004 and December 31, 2011. Eligible patients were defined as having had ≥1 inpatient visit or ≥2 non-inpatient visits (≥30 days apart) with a primary or secondary diagnosis of T2DM (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnosis code 250.x0 or 250.x2).[11] Patients initiated on a basal insulin (neutral protamine Hagedorn [NPH] insulin, insulin glargine, or insulin detemir) between July 1, 2004 and December 31, 2010 (index date) and who were also receiving ≥1 class of OADs (metformin, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, meglitinides, dipeptidyl peptidase-4 inhibitors) at baseline were included. Patients were required to have had continuous health care coverage for 6 months before (baseline) and 12 months after (follow-up) initiation of insulin. Baseline A1C values and weight measurements were available for all patients.

Patients were excluded from the study if they had filled any prescription claims for insulin during the baseline period other than rapid-acting insulin claims within 15 days before insulin initiation, which could be initiated in addition to basal insulin as part of a basal bolus insulin treatment regimen.

The study population was stratified by the number of baseline OADs (1, 2, or ≥3) as a proxy for the timing of insulin initiation relative to diabetes disease progression. This was based on previous[12] and current[1] ADA guidelines on pharmacological therapy for hyperglycemia in T2DM in which the recommendation is to start with OAD monotherapy (metformin or a sulfonylurea), and insulin may be added to either an OAD or subsequently to a combination of OADs.

Baseline Measures

Patient demographic and clinical variables comprised sex, age, weight, body mass index (BMI), duration of diabetes, comorbidities, Deyo-modified Charlson Comorbidity Index,[13] hypoglycemic events, and A1C values for the 6-month baseline period or 15 days after the index date. If there were multiple measurements during the baseline period, the value from the test closest to the index date was used.

Health care resource utilization was described by place of service (outpatient office visits, emergency department [ED] visits, and inpatient admissions) for the 6-month baseline. Diabetes-related health care resource utilization included claims with a primary or secondary diagnosis of diabetes (ICD-9-CM diagnosis code 250.xx). Health care costs were computed as total paid amounts of adjudicated claims during the 6-month baseline and were annualized for comparability. Diabetes-related health care costs included costs from medical claims with a primary or secondary diagnosis of diabetes (ICD-9-CM diagnosis code 250.xx), antidiabetes medications, and glucose meters and test strips. All costs were adjusted to 2011 US dollars using the medical care component of the US consumer price index.[14]

Endpoint Measures

Clinical outcomes were evaluated over 1 year of follow-up. They included A1C reduction from baseline and the proportion of patients achieving A1C $<7.0\%$, and changes in body weight and BMI; values reported within 3 months of the end of the 12-month follow-up period were included; if there were multiple measurements the value from the test closest to the end of follow-up was used. Hypoglycemia in the follow-up period was also reported; hypoglycemia was defined as a health care encounter with a primary or secondary diagnosis of hypoglycemia (ICD-9-CM diagnosis codes 251.0, hypoglycemic coma; 251.1, other specified hypoglycemia; or 251.2, hypoglycemia, unspecified)[15] and other relevant codes using an algorithm developed by Ginde et al.[16] The setting of a hypoglycemic event (outpatient office, inpatient admissions, or ED) was used as a proxy for its severity. Treatment persistence was defined as a patient remaining on study drugs during the follow-up period without discontinuation or switching after study drug initiation.[17] Study medication was considered discontinued if the prescription was not refilled within the expected time of medication coverage (the 90th percentile of the time, stratified by the metric quantity supplied, between first and second fills in patients with ≥ 1 refill).[17] Patients who restarted their initial medication after a period without it during follow-up were considered nonpersistent.

Health care resource utilization was described by place of service (outpatient office, ED, inpatient admission) during the 1-year follow-up. Diabetes-related health care resource utilization included claims with a primary or secondary diagnosis of diabetes (ICD-9-CM diagnosis code: 250.xx). Health care costs were computed as total amounts of adjudicated claims during the 1-year follow-up. Diabetes-related health care costs included costs from medical claims with a primary or secondary diagnosis of diabetes (ICD-9-CM diagnosis code: 250.xx), antidiabetes medications, and glucose meters and test strips.

Statistical Analysis

Confounding factors are an issue in nearly all observational research in which patients are not randomly assigned to treatment cohorts, and, therefore, certain patient characteristics may be associated with both exposure and outcome. Such issues were addressed using the inverse probability-of-treatment weighting method,[18–21] which adjusts for differences in baseline characteristics between study cohorts, rendering groups more comparable. A multinomial logistic regression model was used to predict the propensity of timing of insulin initiation (after 1, 2, or ≥ 3 OADs) given the demographic and clinical characteristics of the patient; the variables included in this model were age group, sex, region, urbanicity, index year, index insulin type (basal or basal plus short acting), baseline high-density cholesterol, provider specialty (specialist, primary care, unknown), duration of diabetes, baseline hypoglycemia, baseline obesity, baseline depression, baseline cerebrovascular disease, baseline diabetes-related outpatient office visit, and baseline diabetes-related other outpatient services. The inverse of the propensity was applied as the probability weight to outcome measures to produce weighted results. Baseline results are presented unweighted, whereas outcomes were weighted using the inverse probability-of-treatment weighting method.

Global tests (χ^2 tests for categorical variables and ANOVA for continuous variables) were used to determine statistically significant differences between the patient groups for unweighted baseline characteristics and weighted study outcomes. Pairwise statistical comparisons between the 1, 2, and ≥ 3 OADs groups were conducted using χ^2 tests for categorical variables and t tests for continuous variables in unweighted and weighted results.

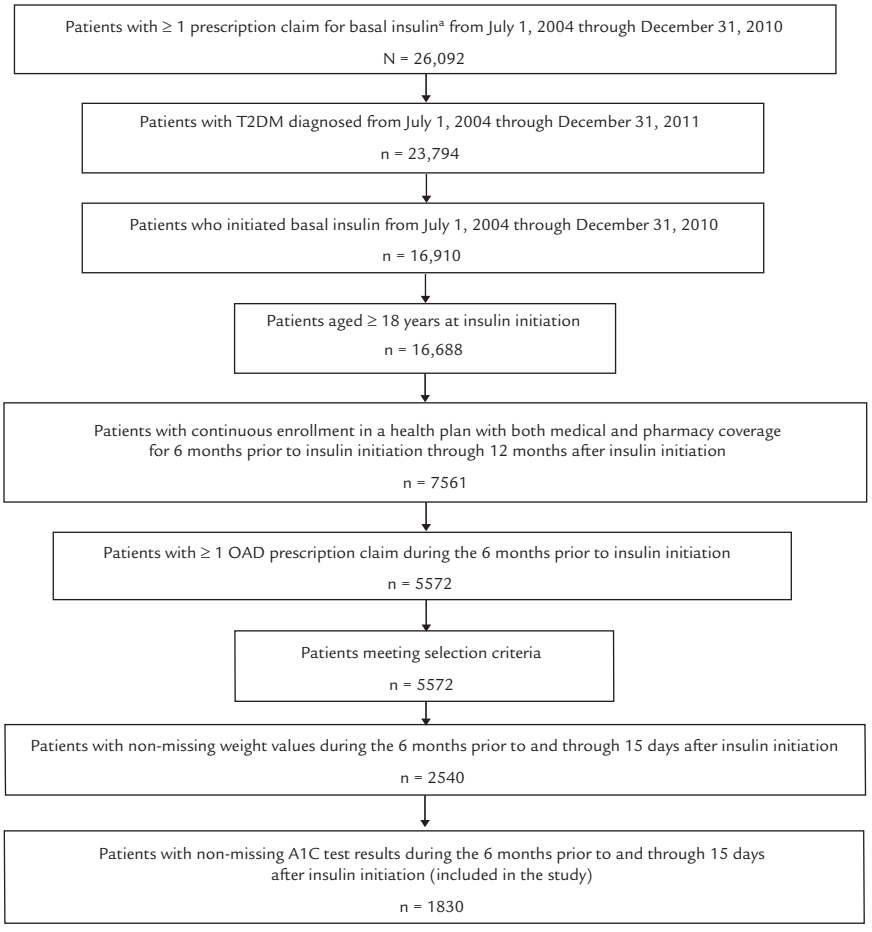

Figure 1. Data attrition. *Insulin glargine, insulin detemir, or NPH insulin. A1C = glycosylated hemoglobin A_{1c}; EMR = electronic medical record; OAD = oral antidiabetes drug; T2DM = type 2 diabetes mellitus.

RESULTS

Baseline Patient Characteristics

A total of 1830 eligible patients were included in the analysis; patient attrition details are shown in Figure 1. Of the included patients, 24.6% used 1 OAD at baseline, 40.3% used 2 OADs, and 35.1% used ≥3 OADs (Table I). In the 1 OAD group, 46.0% of the patients were previously treated with metformin and 34.4% with a sulfonylurea. In the 2 OADs group, the most commonly used OADs were metformin (80.9%), sulfonylureas (74.4%), and thiazolidinediones (24.0%). In the ≥3 OADs group, the most commonly used OADs were metformin (95.6%), sulfonylureas (93.1%), thiazolidinediones (71.3%), and dipeptidyl peptidase-4 inhibitors (46.3%).

The mean age was 57 years, 47% were female, the mean A1C was 9.2%, the mean weight was 99.5 kg with a mean BMI of 34.5 kg/m^2, and 3% of patients had experienced ≥1 hypoglycemic event. Table I shows the baseline clinical and demographic data for the patients grouped by number of OADs at baseline. In these unweighted data, there were significant differences between the 2 OADs and ≥3 OADs groups compared with the 1 OAD group for sex ($P = 0.008$) and duration of diabetes at insulin initiation ($P = 0.002$).

Health Care Resource Utilization Outcomes (Baseline)

At baseline, patients in the 1 OAD group had significantly higher all-cause inpatient admissions

Table I. Baseline characteristics (all data are unweighted).

	1 OAD (n = 450)	2 OADs (n = 738)	≥3 OADs (n = 642)	P*
Age, y, mean (SD)	56.7 (13.9)	57.4 (12.1)	57.4 (11.4)	0.550
Female, no. (%)	234 (52.0)	347 (47.0)	273 (42.5)	0.008
Weight, kg, mean (SD)	99.2 (26.3)	98.8 (23.2)	100.4 (22.6)	0.480
BMI, kg/m^2, mean (SD)	34.7 (8.9)	34.4 (7.4)	34.3 (7.1)	0.746
A1C, %, mean (SD)	9.3 (2.3)	9.2 (2.0)	9.1 (1.8)	0.146
Duration of diabetes at insulin initiation, no. (%)				
<1 years	118 (26.2)	113 (15.3)	117 (18.2)	0.002
1–2 years	7 (1.6)	14 (1.9)	10 (1.6)	
3–4 years	3 (0.7)	8 (1.1)	7 (1.1)	
≥5 years	4 (0.9)	10 (1.4)	12 (1.9)	
Unknown	318 (70.7)	593 (80.4)	496 (77.3)	
OADs, no. (%)				
Sulfonylureas	155 (34.4)	549 (74.4)	598 (93.1)	<0.001
Metformin	207 (46.0)	597 (80.9)	614 (95.6)	<0.001
Thiazolidinediones	46 (10.2)	177 (24.0)	458 (71.3)	<0.001
α-Glucosidase inhibitors	1 (0.2)	3 (0.4)	22 (3.4)	<0.001
Meglitinides	9 (2.0)	32 (4.3)	48 (7.5)	0.001
Dipeptidyl peptidase-4 inhibitors	32 (7.1)	118 (16.0)	297 (46.3)	<0.001
Deyo-CCI score,[13] mean (SD)	1.9 (1.7)	1.8 (1.7)	1.7 (1.5)	0.051
Comorbid conditions, no. (%)				
Retinopathy	11 (2.4)	35 (4.7)	28 (4.4)	0.131
Nephropathy	0	6 (0.8)	4 (0.6)	0.173
Neuropathy	51 (11.3)	62 (8.4)	61 (9.5)	0.247
Hypertension	205 (45.6)	332 (45.0)	269 (41.9)	0.391
Dyslipidemia	137 (30.4)	223 (30.2)	226 (35.2)	0.100
Depression	22 (4.9)	39 (5.3)	36 (5.6)	0.873
Hypoglycemia, no. (%)				
≥1 Hypoglycemic event	12 (2.7)	25 (3.4)	18 (2.8)	0.728
All-cause health care utilization, no. (%)				
≥1 Inpatient admission	95 (21.1)	133 (18.0)	89 (13.9)	0.006
≥1 ED visit	125 (27.8)	155 (21.0)	119 (18.5)	0.001
≥1 Endocrinologist visit	63 (14.0)	89 (12.1)	106 (16.5)	0.060
Diabetes-related health care utilization, no. (%)				
≥1 Inpatient admission	57 (12.7)	93 (12.6)	65 (10.1)	0.284
≥1 ED visit	27 (6.0)	45 (6.1)	38 (5.9)	0.990

A1C = glycosylated hemoglobin A_{1c}; BMI = body mass index; CCI = Charlson Comorbidity Index; ED = emergency department; OAD = oral antidiabetes drug.
*A χ^2 test was used for categorical variables and ANCOVA was used for continuous variables.

(21.1%; $P = 0.006$) and ED visits (27.8%; $P = 0.001$) than those in the 2 and ≥3 OADs groups (2 OADs: 18.0% and 21.0%, respectively; and ≥3 OADs: 13.9% and 18.5%, respectively) (Table I). There were no significant differences between the groups for diabetes-related health care utilization at baseline (Table I).

Health Care Costs (Annualized Baseline)

Total all-cause health care costs differed between the groups at baseline, with higher costs for the group treated with 2 OADs than the ≥3 OADs group ($23,998 vs $19,517, respectively; $P = 0.048$), but there was no significant difference between the 1 OAD and 2 or ≥3 OADs groups (Figure 2A). Non-office outpatient costs ($6088 vs $4019, respectively; $P = 0.008$) and outpatient office costs ($1173 vs $1044, respectively; $P = 0.012$) were higher for the 1 OAD group versus the ≥3 OADs group. Prescription charges were higher for the ≥3 OADs group ($5535) than for the 1 OAD group ($3363; $P < 0.0001$) and the 2 OADs group ($3859; $P < 0.0001$). There were no other significant differences between the groups.

There were no differences in total diabetes-related health care costs between the groups at baseline (Figure 2B). However, prescription costs were higher at baseline for the ≥3 OADs group ($2330) compared with the 1 OAD ($400) and 2 OADs ($909) groups ($P < 0.0001$ for both). Baseline outpatient office costs were also higher for the ≥3 OADs group ($473) versus the 1 OAD ($395) and 2 OADs ($413) groups ($P = 0.0007$ and $P = 0.003$, respectively). There were no other differences between the groups.

Clinical Outcomes and Treatment Persistence (1-Year Follow-Up)

Weighted results show that, at follow-up, compared with the 2 OADs and ≥3 OADs groups, the 1 OAD group had a significantly greater reduction in A1C, a higher proportion of patients achieving A1C <7.0%, and fewer patients experiencing ≥1 hypoglycemic event (Table II).

Treatment persistence was significantly lower in the 1 OAD group than in the other 2 groups (51.8% vs 58.0% for the 2 OADs group [$P = 0.004$] and 68.7% for the ≥3 OADs group [$P < 0.001$]). There was no significant difference in the duration of persistence between the groups.

Stratified by baseline BMI, the greatest reductions in A1C were among patients in the 1 OAD group when baseline BMI was ≤30 kg/m^2 or 31 to 35 kg/m^2 ($P < 0.01$) (Figure 3). Among patients who were severely obese at baseline (BMI >35 kg/m^2), there were no significant differences in A1C outcome at follow-up between treatment groups. The weight-adjusted daily average consumption of insulin per 100 lb of bodyweight did not differ in the BMI ≤30 kg/m^2 strata (15, 14, and 15 U for the 1, 2, and ≥3 OADs groups, respectively) or in the BMI 31 to 35 kg/m^2 strata (12, 13, and 13 U, respectively); in the BMI >35 kg/m^2 strata, it was significantly lower in the 1 OAD group (11 U) compared with the ≥3 OADs group (14 U) ($P = 0.0036$), but not the 2 OADs group (12 U). No significant differences were observed for change in weight (+1.2 kg vs +1.6 kg vs +1.0 kg) or BMI (+0.5 kg/m^2 vs +0.6 kg/m^2 vs +0.4 kg/m^2) between the 1 OAD, 2 OADs, and ≥3 OADs groups, respectively.

Health Care Resource Utilization Outcomes (1-Year Follow-Up)

Weighted results show that, during follow-up, a significantly higher proportion of patients in the 1 OAD group had all-cause inpatient admissions (26.1%) compared with the 2 OADs (20.0%; $P < 0.001$) and ≥3 OADs (13.0%; $P < 0.0001$) groups. The proportion of patients with all-cause ED visits was similar across the 3 groups (26.2%, 27.7%, and 24.1%, respectively). A significantly lower proportion of patients in the 1 OAD group had diabetes-related outpatient office visits (87.9%) compared with the 2 OADs group (94.1%) and the ≥3 OADs group (93.4%) ($P < 0.0001$ for both). A significantly higher proportion of patients in the ≥3 OADs group (95.5%) compared with patients in the 1 OAD group (91.1%; $P = 0.0001$) and 2 OADs group (92.7%; $P = 0.0072$) had ≥1 diabetes supply claim.

Health Care Costs (1-Year Follow-Up)

Weighted results show that during follow-up, there were no differences in medical costs between the OAD groups. Prescription costs were higher in the ≥3 OADs group ($6754) compared with the 1 OAD ($4838) and 2 OADs ($5715) groups ($P < 0.0001$ and $P = 0.0072$, respectively) (Figure 2A).

At follow-up, the overall diabetes-related health care costs were similar, but with higher prescription costs for the ≥3 OADs group ($3121) compared with the 1 OAD ($1759) and 2 OADs ($2090) groups

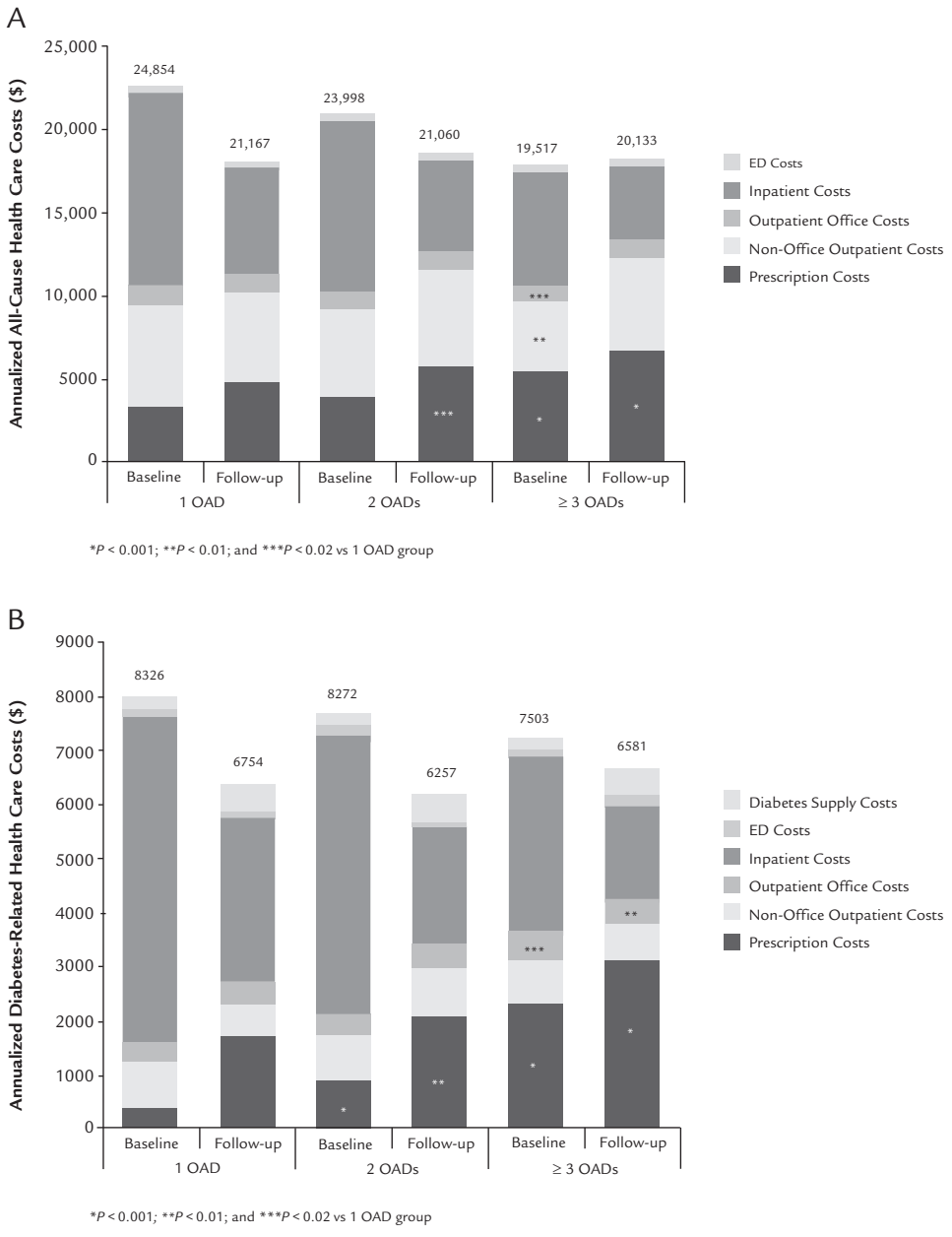

Figure 2. Total all-cause (A) and diabetes-related (B) health care costs per patient at baseline and at 1-year follow-up. Numbers represent total health care costs. Presented baseline data are annualized and unweighted, whereas presented follow-up data are weighted. No statistical comparisons were done on the trend in costs from baseline to follow-up. ED = emergency department; OAD = oral antidiabetes drug.

($P < 0.0001$ for both) (Figure 2B). Outpatient office visit costs were also higher in the ≥3 OADs group compared with the 1 OAD group ($483 vs $385; $P = 0.0015$).

DISCUSSION

In this real-world observational study, initiating basal insulin therapy in patients previously treated with 1 OAD resulted in greater A1C reductions and a lower

Table II. Clinical outcomes at 1-year follow-up (all data are weighted).

	1 OAD (n = 450)	2 OADs (n = 738)	≥3 OADs (n = 642)	Global test, P*	1 OAD vs 2 OADs, P†	1 OAD vs ≥3 OADs, P†	2 OADs vs ≥3 OADs, P†
No. of patients with valid A1C 12 months after insulin initiation	322	527	484				
Change in A1C from baseline, %, mean (SD)	−1.7 (5.1)	−1.0 (3.0)	−0.9 (3.2)	<0.0001	0.0006	0.0002	0.6185
Patients achieving A1C <7.0%, no. (%)‡	124 (38.2)	141 (26.7)	96 (19.6)	<0.0001	<0.0001	<0.0001	0.0020
Hypoglycemia, no. (%)‡							
Total hypoglycemia	12 (2.7)	49 (6.6)	32 (5.0)	0.0002	<0.0001	0.0065	0.1210
Outpatient office visit hypoglycemia	6 (1.3)	22 (3.0)	8 (1.3)	0.005	0.0102	0.8728	0.0069
Inpatient/ED hypoglycemia	4 (0.9)	14 (1.9)	23 (3.7)	0.0001	0.0518	<0.0001	0.0143

A1C = glycosylated hemoglobin A_{1c}; ED = emergency department; OAD = oral antidiabetes drug.
*A χ^2 test was used for categorical variables and ANCOVA was used for continuous variables.
†A t test was used to compare between groups for continuous variables and a χ^2 test was used for categorical variables.
‡Weighting of the data means that the percentages do not calculate exactly.

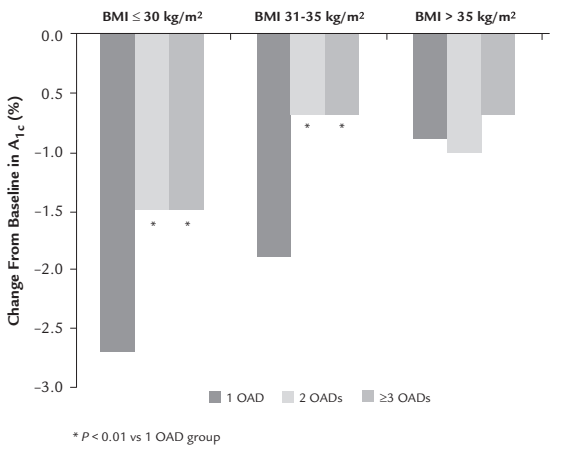

Figure 3. Change in glycosylated hemoglobin A_{1c} from baseline to 1-year follow-up stratified by baseline BMI. A_{1c} = glycosylated hemoglobin A_{1c}; BMI = body mass index; OAD = oral antidiabetes drug.

risk of hypoglycemia than adding insulin to treatment with ≥2 OADs. The greater use of sulfonylureas and thiazolidinediones in the 2 and ≥3 OADs groups indicates that, in this study, those who did not intensify treatment with insulin, intensified it with sulfonylureas and thiazolidinediones as the disease progressed. Risks of hypoglycemia and weight gain are the main disadvantages associated with the use of all insulins,[1] and concerns about these issues are one of the key barriers to insulin initiation.[10] Of note, therefore, were the comparatively lower rates of hypoglycemia among patients previously treated with 1 OAD than with ≥2 OADs. Lower hypoglycemia in the 1 OAD group after insulin initiation could be related to the shorter duration of diabetes in this group, resulting in patients less prone to hypoglycemia[22] or possibly with less hypoglycemia unawareness because of better glucose counterregulation and less autonomic neuropathy.[23] However, baseline neuropathy and nephropathy were not significantly different between the groups, suggesting that this was not the case in this population. Alternatively, the 2 and ≥3 OADs groups had a greater sulfonylurea use at baseline. This may partly explain the higher incidence of hypoglycemia because sulfonylurea use has been linked with hypoglycemia.[1,24] The difficulty in titrating sulfonylurea

dose may explain lower hypoglycemia in the 1 OAD group (where sulfonylurea use is less common) as providers can respond to the threat of hypoglycemia by reducing insulin by a few units, whereas sulfonylurea dosing does not have such flexibility because of fewer dose choices.

After initiation of insulin treatment, patients in the 1 OAD group were more likely to achieve A1C <7.0% with no increase in hypoglycemic events. Conversely, in the 2 and ≥3 OADs groups, a lower proportion of patients achieved A1C <7.0%, yet hypoglycemic events nearly doubled. This suggests that early insulin initiation could reduce unnecessary initiation of sulfonylureas and the higher resultant rate of hypoglycemic events, as seen in those patients on multiple OAD regimens who then add insulin.

The clinical benefits associated with early initiation of insulin were achieved despite the 1 OAD group having the lowest treatment persistence rate. The 1-year persistence rates (ranging from 52% to 69%) compare favorably with other analyses of basal insulin initiation after OAD treatment in real-world US settings, which range between 44% and 80%.[25–29]

According to ADA and EASD guidelines, patient-centered approaches to T2DM treatment should consider age, weight, and comorbidities.[1] As ~80% of patients with T2DM are overweight or obese, key outcomes were stratified by baseline BMI. In severely obese patients (BMI >35 kg/m^2), efficacy was not improved by the early addition of insulin. Those with 1 OAD had lower daily average consumption than those in the ≥3 OADs group. Although greater insulin resistance among more obese patients may be the cause of this finding, obese and leaner patients have been shown to have similar islet dysfunction.[30] More research is required to clarify the underlying reason for this finding.[31–33] Together with our results, these data highlight the need for more personalized approaches to the treatment of patients with T2DM, incorporating factors such as weight and their effect on treatment outcomes.

Although we compared early or late initiation of insulin (using the number of OADs as a proxy for the timing of initiation relative to disease progression), a recent 10-year systematic review comparing insulin initiation with continuation of OAD therapy found earlier initiation of insulin therapy was associated with greater reductions in A1C levels from baseline.[5] The authors proposed a "paradigm shift" in clinical practice toward early initiation of insulin in patients with T2DM. Indeed, the feasibility of initiating insulin and OAD therapy at diagnosis of T2DM was assessed in a small-scale study (n = 58).[34] Patients treated with first-line insulin-based therapy showed no greater weight gain or hypoglycemia and no decreased compliance, treatment satisfaction, or quality of life compared with patients treated with conventional 3 OAD therapy.

Some studies have explored the economic benefits of insulin initiation in patients with T2DM[25,26,29,32,35–38]; however, to our knowledge there are no studies directly addressing the economic outcomes of early versus late initiation of insulin. In this study, we show that, at baseline, there was a trend toward the 1 OAD and 2 OADs groups having higher costs compared with the ≥3 OADs group, except for prescription costs, which were higher for the ≥3 OADs group. After adding insulin to the treatment, there was no overall difference between the groups except for higher prescription costs and outpatient visit costs for the ≥3 OADs group. Although a significantly greater proportion of patients in the 1 OAD group had an all-cause hospital admission compared with the 2 and ≥3 OADs groups, there was no significant difference between the associated inpatient and the overall all-cause health care costs. Therefore, our data suggest that early insulin initiation has no impact on overall costs.

A recently published study sought to investigate health care expenditure stratified by timing of insulin initiation in older adults in a real-world setting.[39] This study, which also showed that early insulin initiation was associated with significantly greater reduction in A1C ($P < 0.001$), suggested no significant differences in hypoglycemia events or health care costs associated with insulin initiation time. This study did not differentiate types of basal insulin or control for the time from diagnosis to when insulin was initiated or consider covariates such as obesity. Here, we demonstrate that the degree of benefit associated with initiating insulin varied according to individual patient characteristics, including BMI and previous OAD regimen as well as time of initiation. A patient-centered approach to treatment, as advocated in the joint ADA/EASD guidelines,[1] is supported by these data.

As this study is based on real-world data from large national US claims databases combined with EMR

data, it has richer information than EMR or claims data alone. However, as this was a retrospective, observational study, the data may be subject to selection bias and confounding and do not establish causality of the treatment on observed outcomes. Also, as the analyses were conducted using health care claims data generated mainly for billing purposes, they were potentially subject to coding errors. The time between baseline and final measures may not have been equal for all patients due to the time windows used to define baseline A1C and final A1C. Persistence with therapy was estimated through pharmacy claims data, which reflected prescriptions filled that were not necessarily taken or consumed. The analyses were based on data from a commercially and Medicare-insured US population and limited to those who had merged claims and EMR data, so they may not be representative or generalizable to other patients. Timing of insulin initiation and the clinical rationale behind the therapy choices may not be accurately reflected in the study because information on the duration of diabetes was available only in a subset of patients and the number of OADs served as a proxy for the timing of insulin initiation relative to disease progression. This study included patients who initiated basal insulin between July 2004 and December 2010. In more recent years, however, the pattern of antidiabetes drug use has changed, with less use of sulfonylureas and thiazolidinediones and a greater use of newer therapies.[40] As such, this study may not be reflective of patients receiving newer therapies.

CONCLUSIONS

Earlier initiation of basal insulin therapy in patients with T2DM previously treated with 1 OAD resulted in better clinical outcomes than adding insulin to OAD treatment later in the course of therapy, with no increase in overall costs. In this setting, the intensification of treatment with insulin as opposed to sulfonylureas and thiazolidinediones could represent a clinical advantage for patients. The early insulin use group has the lowest utilization of sulfonylureas and lowest incidence of hypoglycemia at follow-up. Non-severely obese patients appear to particularly benefit from earlier initiation of basal insulin therapy.

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P. Levin, S. Zhou, W. Wei and J. Gill were involved in the study concept and design. E. Durden and A. M. Farr conducted the data collection. P. Levin, S. Zhou, E. Durden, A. M. Farr, W. Wei and J. Gill were all involved in the data analysis and interpretation. S. Zhou and W. Wei participated in drafting the manuscript and P. Levin, E. Durden, A. M. Farr, and J. Gill critically revised the manuscript at each stage. P. Levin, S. Zhou, E. Durden, A. M. Farr, W. Wei and J. Gill all provided final approval of this manuscript.

CONFLICTS OF INTEREST

P. Levin reports working on the advisory panel for Sanofi US, Inc. and Novo Nordisk; working as consultant for Novo Nordisk, Eli Lilly and Company, and Sanofi US, Inc.; receiving research support from Eli Lilly and Company, Sanofi US, Inc., Novo Nordisk, Amylin Pharmaceuticals, and Boehringer Ingelheim Pharmaceuticals; and participating in speakers bureaus for Eli Lilly and Company, Novo Nordisk, Amylin Pharmaceuticals, and Boehringer Ingelheim Pharmaceuticals. S. Zhou, J. Gill, and W. Wei, are employees of Sanofi US, Inc. E. Durden and A. M. Farr are employees of Truven Health Analytics, which receives funding from Sanofi US, Inc.

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