RESEARCH

Outcomes and Treatment Patterns of Adding a Third Agent to 2 OADs in Patients with Type 2 Diabetes

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ABSTRACT

BACKGROUND: Patients with uncontrolled type 2 diabetes mellitus (T2DM), despite therapy with 2 oral antidiabetic drugs (OADs), may add a third OAD or a glucagon-like peptide-1 receptor agonist (GLP-1) or initiate insulin therapy. The transition to insulin has been shown to be delayed in current practice, potentially through clinical inertia—the failure of health care providers to initiate or advance therapy when indicated. Patients and physicians may be resistant to insulin therapy because of beliefs about side effects and limitations to patients' lifestyle, while patients may consider that starting injectable therapy signifies a considerable worsening of their disease and may feel they have "failed" to manage it effectively.

OBJECTIVE: To describe current treatment patterns and outcomes among adult patients with T2DM in the United States who were treated with 2 OADs and added a third antidiabetic drug.

METHODS: This retrospective study followed patients with T2DM who added a third OAD (the "3OAD" cohort), insulin ("+Insulin"), or a GLP-1 ("+GLP-1") between July 2000 and March 2009. Patients were followed for up to 2 years. Baseline characteristics and follow-up outcomes—including blood glucose level (HbA1c), hypoglycemia, and health care costs—were examined. Treatment persistence was assessed to determine how long patients continued with their prescribed medications without discontinuing or switching.

RESULTS: A total of 51,771 patients adding a third agent to their 2OAD regimen were included in this study. Most patients added a third OAD (n = 41,052) over insulin (n = 6,904) or GLP-1 (n = 3,815). At baseline, +Insulin patients were older, with higher comorbidity burden and higher HbA1c. During follow-up, 3OAD patients were more likely to be persistent with their treatment than +Insulin or +GLP-1 patients, but +Insulin patients had the greatest HbA1c reduction from baseline, while continuing with insulin treatment was associated with higher HbA1c reduction. Among 3OAD patients, most of those who switched a third agent initiated insulin, and those who switched early during the follow-up period had greater HbA1c reduction than those who continued with the 3OAD treatment regimen. Average annual health care costs declined in +Insulin patients but increased among 3OAD and +GLP-1 patients. Treatment persistence and HbA1c reduction in +GLP-1 patients were low.

CONCLUSIONS: This study found that in current practice, physicians seem to be reluctant to prescribe injectable agents for patients with uncontrolled T2DM despite combination OAD therapy. Despite higher treatment persistence among patients adding a third OAD, this persistence did not translate into better glycemic control and may not necessarily be a long-term cost-saving solution. These data indicate a need for more evidence-based and patient-centered treatment decisions for patients unable to achieve and maintain glycemic targets on multiple OADs.

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What is already known about this subject

- Treatment guidelines recommend a stepwise approach to manage hyperglycemia in type 2 diabetes mellitus (T2DM). Patients who do not achieve treatment goals advance to more intensive treatment regimens.
- Clinical studies evaluating the efficacy and safety of triple-combination antidiabetic therapy comprising oral or oral plus injectable agents have shown triple therapy to be either superior or comparable to dual therapy.
- Because of the progressive nature of the disease, patients with T2DM will eventually need advanced treatment with insulin to achieve and maintain glycemic control. Studies show prescribers are more reluctant and less likely to advance treatment regimens in patients with inadequate glycemic control.

What this study adds

- The results of this study add to the current data available on the clinical use of triple antidiabetic treatment combinations, including oral and injectable agents in "real-world" patients with T2DM.
- Clinical inertia in current clinical practice was evident, as shown by the treatment advancement choices made by prescribers in this study: 4 out of 5 patients not achieving glycemic control on dual oral therapy were prescribed another oral drug.
- This study demonstrates that triple oral therapy is not necessarily a cost-saving solution in the long term: even though patients on triple oral therapy are more persistent with their regimen compared with patients who were prescribed insulin or a glucagon-like peptide-1 receptor agonist in addition to dual oral therapy, this advanced treatment option did not translate into better glycemic control.

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) publish treatment guidelines that recommend a stepwise approach to management of hyperglycemia in patients with type 2 diabetes mellitus (T2DM). As first-line therapy, patients are counseled concerning lifestyle interventions and prescribed metformin. Patients who fail to meet target glycemic goals require the addition of a second oral antidiabetic drug (OAD) or an injectable agent, such as a glucagon-like peptide-1 receptor agonist (GLP-1) or basal insulin. If glycemic goals are still

not met with 2 agents, patients advance to 3-drug combination therapy, with treatment recommendations suggesting that insulin is likely to be more effective for controlling hyperglycemia than most other options as the third agent, particulary when patients are very hyperglycemic (blood glucose level [HbA1c] at least 9%).[1]

Several clinical studies have evaluated the efficacy and safety of triple-combination therapeutic options[2-6] and have shown that triple therapy is more effective than dual therapy.[2,5] Three studies—2 adding insulin glargine or rosiglitazone[3,4] and 1 adding exenatide or sitagliptin[6]—have shown comparable glycemic control regardless of whether the third agent added was injectable or oral. However, there are still only limited data available,[7,8] and further information is required to confirm the clinical use of these triple therapy combinations.

Clinical inertia has been defined as the failure of health care providers to initiate or advance therapy when indicated.[9] In patients with diabetes, clinical inertia has been used to describe the reluctance to advance treatment regimens when patients experience inadequate glycemic control[10]—specifically patient or physician reluctance to initiate timely insulin therapy.[11,12] Patients are more likely to be receptive to the initiation of insulin if their disease worsens through increased distress, poorer control, and more complications, while among health care providers, clinical inertia has been associated with perceptions regarding the clinical efficacy of insulin.[12] Consequently, the transition to insulin is often delayed,[13,14] leaving patients with sustained hyperglycemia and increased risk of diabetes-related complications.[15-19]

This study assessed 2-year treatment and persistence patterns and glycemic and economic outcomes among U.S. patients with T2DM who added a third type of antidiabetic medication (another OAD, insulin, or GLP-1).

Methods

Data Source

Data were obtained from IMPACT, a managed care database that comprises about 50 U.S. health care plans and contains medical claims, pharmacy claims, eligibility data, and laboratory results for 100 million patients, of whom 73% had pharmacy benefits and 19% had laboratory results, from January 2000 to March 2011.

Patient Inclusion and Exclusion Criteria

Patients diagnosed with T2DM, defined as having ≥ 1 inpatient visit or ≥ 2 physician visits dated at least 30 days apart with primary or secondary diagnosis of *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 250.x0 (diabetes mellitus type 2 or unspecified type not stated as uncontrolled) or 250.x2 (diabetes mellitus type 2 or unspecified type uncontrolled), were eligible for inclusion if they had been treated with 2 OADs (metformin, sulfonylureas, dipeptidyl peptidase [DPP]-4 inhibitors, thiazolidinediones [TZD], meglitinides, or α-glucosidase inhibitors) during the 6-month period before adding a third antidiabetic agent (a third OAD, insulin, or GLP-1). The index date was defined as the time of adding the third antidiabetic agent. Adult patients (aged ≥ 18 years on the index date) who had continuous health plan coverage of both medical and pharmacy benefits for ≥ 6 months before (baseline period) and ≥ 2 years after the index date (follow-up period) were included in the study. Since this study was designed to assess insulin and GLP-1 as injectable therapies, patients who initiated with amylin analog pramlintide as the third agent were excluded because pramlintide is an injectable agent that is used together with mealtime insulin treatment. In addition, those who did not have 2-year follow-up data available were excluded from the analysis.

Patient Cohorts

Patients were assigned to 1 of 3 cohorts, based on the drug class of the third agent added to their 2OAD regimen: patients who added a third OAD were assigned to the "3OAD" cohort; patients who were prescribed insulin (including basal, prandial, or premixed insulins) as the third agent were assigned to the "+Insulin" cohort; and patients who were prescribed GLP-1 as the third agent were assigned to the "+GLP-1" cohort.

Study Outcomes

This study was designed to descriptively examine the distribution of the third agent (additional OAD or insulin or GLP-1) for patients who had 2 years of follow-up. The 2 years of follow-up data were examined quarterly, and results from the fourth quarter of each year of follow-up were used to examine treatment patterns and outcomes. In addition to baseline characteristics, analyses included treatment persistence, clinical outcomes, hypoglycemia, and annual health care costs over 2 years.

Treatment persistence among each of the study groups was assessed through the percentage of patients continuing with, switching, or discontinuing the index treatment: "persisting" was defined as remaining on the index drug treatment until the end of the fourth and eighth quarters of follow-up; "switching" was defined as change of index drug at the end of the fourth quarter of each year of follow-up; and "discontinuation" was defined as no prescriptions filled for any OAD, insulin, or GLP-1 during the fourth quarter of each year of follow-up.

Clinical outcomes included HbA1c value at the end of follow-up and HbA1c reduction from baseline. Baseline HbA1c was defined as the HbA1c value within the baseline period that was closest to the index date; end of follow-up HbA1c was defined as the HbA1c value within a 3-month window from the end of the fourth quarter of each year of follow-up that was closest to the end of the follow-up period.

Hypoglycemia was defined as a health care encounter (outpatient, inpatient, or emergency department [ED] visit) with a primary or secondary ICD-9-CM code for hypoglycemia (ICD-9-CM codes 250.8–diabetes with other specified

TABLE 1 Baseline Characteristics

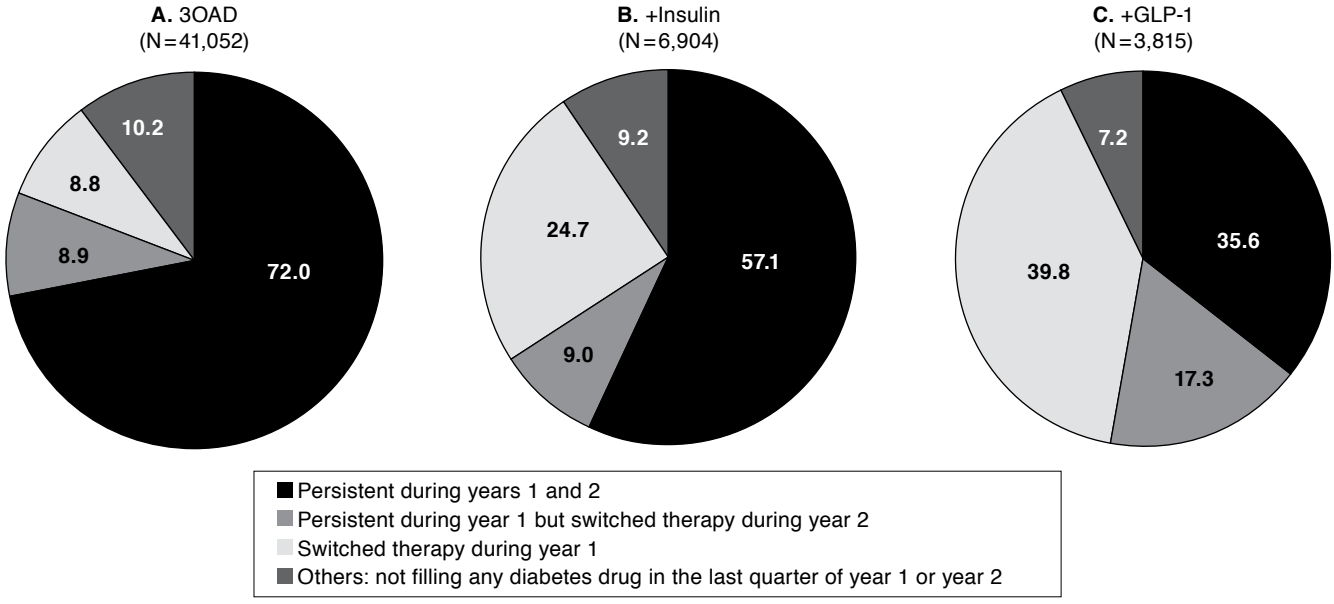
Characteristics	3OAD (N = 41,052)	+Insulin (N = 6,904)	*P* Value 3OAD Compared with +Insulin	+GLP-1 (N = 3,815)	*P* Value 3OAD Compared with +GLP-1
Age in years, mean (SD)	55.9 (9.8)	55.4 (10.7)	0.0004	52.8 (9.2)	<0.0001
Men, n (%)	25,303 (64.6)	3,817 (55.3)	<0.0001	1,825 (47.8)	<0.0001
Baseline HbA1c %, mean (SD) [mmol/mol (SD)]	8.36 (1.6) [68 (17.5)]	9.22 (2.0) [77 (21.9)]	<0.0001	7.80 (1.5) [62 (16.4)]	<0.0001
Patients with HbA1c data available, n (%)	8,992 (21.9)	1,123 (16.3)		802 (21.0)	
≥9%/≥75 mmol/mol, n (%)	2,578 (28.7)	568 (50.6)	<0.0001	167 (20.8)	<0.0001
Geographic region, n (%)					
Northeast	17,249 (42.0)	2,606 (37.7)	<0.0001	999 (26.2)	<0.0001
South	13,843 (33.7)	2,249 (32.6)	0.0622	1,756 (46.0)	<0.0001
Midwest	6,015 (14.7)	1,252 (18.1)	<0.0001	702 (18.4)	<0.0001
West	3,300 (8.0)	650 (9.4)	0.0001	358 (9.4)	0.0037
Unknown	645 (1.6)	147 (2.1)	0.0008	0	<0.0001
Comorbidity, n (%)					
Hypertension	24,765 (60.3)	4,193 (60.7)	0.5224	2,452 (64.3)	<0.0001
Hyperlipidemia	25,070 (61.1)	3,861 (55.9)	<0.0001	2,598 (68.1)	<0.0001
Myocardial infarction	562 (1.4)	240 (3.5)	<0.0001	43 (1.1)	0.2154
Congestive heart failure	1,295 (3.2)	583 (8.4)	<0.0001	88 (2.3)	0.0038
Peripheral vascular disease	1,361 (3.3)	387 (5.6)	<0.0001	107 (2.8)	0.0899
Retinopathy	3,417 (8.3)	694 (10.1)	<0.0001	237 (6.2)	<0.0001
Neuropathy	2,527 (6.2)	795 (11.5)	<0.0001	324 (8.5)	<0.0001
Nephropathy	833 (2.0)	318 (4.6)	<0.0001	123 (3.2)	<0.0001
Mental illness	3,653 (8.9)	922 (13.4)	<0.0001	453 (11.9)	<0.0001
Charlson comorbidity index, mean (SD)	0.35 (0.9)	0.71 (1.4)	<0.0001	0.32 (0.8)	0.0599
Baseline medication, n (%)					
Metformin	34,991 (85.2)	5,840 (84.6)	0.1619	3,459 (90.7)	<0.0001
Sulfonylureas	29,451 (71.7)	5,509 (79.8)	<0.0001	2,335 (61.2)	<0.0001
Dipeptidyl peptidase-4 inhibitors	1,416 (3.4)	209 (3.0)	0.0729	131 (3.4)	0.9600
Thiazolidinediones	14,968 (36.5)	2,042 (29.6)	<0.0001	1,627 (42.6)	<0.0001
Baseline hypoglycemia rates, n (%)					
Any hypoglycemia	658 (1.6)	310 (4.5)	<0.0001	70 (1.8)	0.2779
Any inpatient/ED-related hypoglycemia	201 (0.5)	185 (2.7)	<0.0001	11 (0.3)	0.0829
Baseline all-cause health care utilization, n (%)					
Any hospitalization	2,248 (5.5)	1,351 (19.6)	<0.0001	157 (4.1)	0.0004
Any ED visit	5,160 (12.6)	1,677 (24.3)	<0.0001	541 (14.2)	0.0043
Any endocrinologist visit	3,913 (9.5)	1,084 (15.7)	<0.0001	1,023 (26.8)	<0.0001
Baseline all-cause health care cost, mean $ (SD)					
Total cost	4,728 (8,433)	10,272 (19,106)	<0.0001	5,211 (8,133)	0.0005
Baseline diabetes-related health care cost, mean $ (SD)					
Total cost	1,703 (3,896)	3,715 (9,096)	<0.0001	1,770 (4,087)	0.3317

ED = emergency department; GLP-1 = glucagon-like peptide-1 receptor agonist; HbA1c = blood glucose level; mmol/mol = millimole per mole; OAD = oral antidiabetic drug; SD = standard deviation.

manifestations; 251.0–hypoglycemic coma; 251.1–other specified hypoglycemia; or 251.2–hypoglycemia, unspecified) during the follow-up period.[20] Hypoglycemia was assessed as the prevalence of hypoglycemia-related events, defined as the percentage of patients with at least 1 hypoglycemia-related event during each year of follow-up.

A cost analysis was performed on annualized health care costs during baseline and at the first and second years of follow-up. All-cause and diabetes-related health care costs were calculated at baseline and at the end of follow-up, measured as the standardized allowed payment by the health plan to the provider. The costs were calculated in 2009 and measured in U.S. dollars. Costs were considered diabetes-related if the claim had a primary diagnosis code ICD-9-CM 250.xx or was a pharmacy claim for antidiabetic medication and supplies. Total costs were calculated as aggregates of inpatient, outpatient, ED, and pharmacy prescription costs.

FIGURE 1 Two-Year Treatment Patterns for 2OAD Patients Adding (A) a Third OAD, (B) Insulin, or (C) a GLP-1: Treatment Persistence[a]



[a]*Defined as remaining on the index drug treatment until the end of the fourth and eighth quarters of follow-up, without discontinuation or switching.*
GLP-1 = glucagon-like peptide-1 receptor agonist; OAD=oral antidiabetic drug.

Statistical Analysis

Baseline differences were examined by comparing patients who added insulin or GLP-1 with patients who added the third OAD, with Student t-tests for continuous variables and $\chi 2$ tests for categorical variables. Because of the significant baseline differences between these 3 cohorts, and the descriptive nature of this study, only descriptive statistics and bivariate analyses were conducted to assess treatment patterns and study outcomes. Statistical analyses were conducted using SAS v9.0 software (Cary, NC).

Results

Patient Characteristics

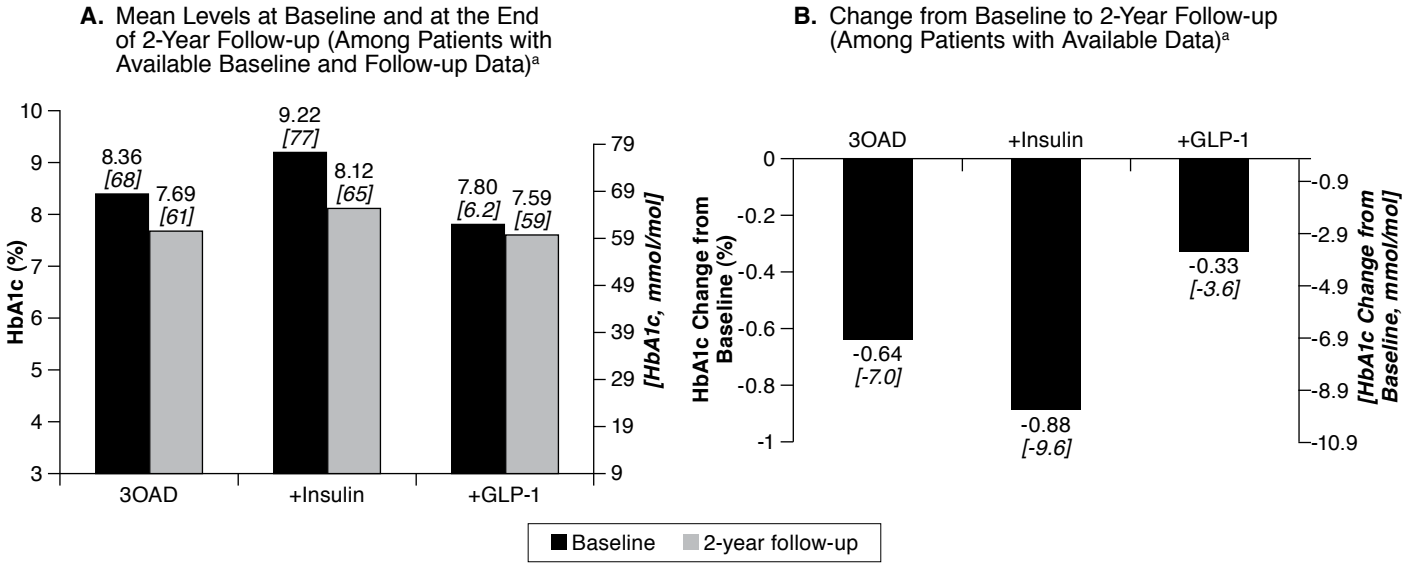
A total of 51,771 patients, with 2-year follow-up data available, were included in the analysis; baseline characteristics of these patients are shown in Table 1. Most patients (41,052 [79.3%]) were prescribed a third OAD to their baseline regimen of 2 OADs; 13.3% of the patients were prescribed insulin; and 7.4% were prescribed GLP-1. Appendix A shows the percentages of patients among the total patient cohort who were prescribed a third agent to their double OAD treatment regimen by drug class, type of OAD, and type of insulin. Only patients adding exenatide were included in the +GLP-1 group because liraglutide was not available until 2010, and patients were required to have 2-year follow-up data available to be included in the study. Prior to 2006, most patients added a TZD; after 2006, the most commonly added OAD was a DPP-4 inhibitor. Among those patients adding insulin, basal analog insulins were the most commonly used.

There were significant differences in baseline demographic and clinical characteristics among the 3 cohorts (Table 1). In general, patients in the +GLP-1 group were significantly younger (mean age 52.8 years compared with 55.4 years in the +Insulin group and 55.9 years in the 3OAD group; $P < 0.001$); more likely to be women (52.2% vs. 44.7% and 35.4%, respectively); and had lower baseline HbA1c levels (7.80% vs. 9.22% and 8.36%, respectively) compared with patients in the other 2 cohorts. In addition, compared with patients in the 3OAD or +GLP-1 groups, patients in the +Insulin group were more likely to be at least 75 years of age and have higher baseline HbA1c levels, more comorbidities, and higher all-cause health care resource utilization (including hospitalization, ED visits, and endocrinologist visits) and costs (Table 1; $P < 0.05$).

Follow-up Treatment Persistence

Treatment persistence data are presented in Figure 1. Among patients in the 3OAD group, 72% remained peristent for 2 years; 9% switched therapy during the first year of treatment; another 9% switched therapy during the second year; and the remaining 10% discontinued therapy (Figure 1A). Most therapy switches were to insulin (71.4%).

FIGURE 2 Baseline and 2-Year Follow-up HbA1c Levels



[a]*N = 4,566 for 3OAD, N = 547 for +Insulin, and N = 376 for +GLP-1.*

GLP-1 = glucagon-like peptide-1 receptor agonist; HbA1c = blood glucose level; mmol/mol = millimole per mole; OAD = oral antidiabetic drug.

Among patients in the +Insulin group, 57% remained persistent for 2 years of follow-up. A quarter of patients switched therapy during the first year; 9% switched therapy during the second year; and an additional 9% discontinued their antidiabetic medication (Figure 1B). Most of the therapy switched in this group was back to OAD only (94.6%).

Of those patients in the +GLP-1 group, only 36% were persistent with therapy for 2 years; 17% were persistent for 1 year but switched therapy during the second year; and 40% switched therapy during the first year of treatment. Treatment was discontinued by 7% of patients (Figure 1C).

HbA1c Reduction from Baseline

Among patients who had HbA1c data available (5,489 [10.6%]) at both baseline and the end of the 2-year follow-up, patients in the +Insulin group had a change in HbA1c from baseline to 2-year follow-up of −0.88% (−9.6 millimole per mole [mmol/mol]). The change in HbA1c from baseline to 2-year follow-up was −0.33% (−3.6 mmol/mol) for patients in the +GLP-1 groups and −0.64% (−9.6 mmol/mol) for patients in the 3OAD group (Figure 2).

Association Between Treatment Persistence and HbA1c Reduction

In patients with HbA1c data available, among those in the 3OAD group (4,566 [83%]), HbA1c change from baseline was significantly greater among patients who switched to insulin or GLP-1 in the first year of treatment (−0.92% [−10.1 mmol/mol]), compared with patients who continued therapy for 2 years (−0.65% [−7.1 mmol/mol]; $P < 0.01$).

In contrast, patients in the +Insulin group (547 [10%]) who continued insulin therapy for 2 years had a significantly greater HbA1c reduction than those who switched therapy during the first year (−0.99% [−10.8 mmol/mol] vs. −0.59% [−6.4 mmol/mol]; $P < 0.05$). Patients in the +GLP-1 group (376 [7%]) had the lowest HbA1c reduction from baseline; while there was a greater HbA1c reduction among patients with 2 years of treatment persistence, the difference did not attain statistical significance (Appendix B).

Hypoglycemia

During the second year of follow-up, patients in the +Insulin group incurred more hypoglycemic events than patients in the +GLP-1 or 3OAD groups. The percentage of patients in the +Insulin group with at least 1 hypoglycemic event increased from 4.5% during the baseline period to 7.0% during the second year of follow-up. The annual hypoglycemia rates increased from 1.6% at baseline to 3.7% in the 3OAD group and from 1.8% to 3.5% in the +GLP-1 group during the second year of follow-up. The incidence of hypoglycemic events that led to hospitalization or an ED visit during the second year of follow-up was higher among patients in the +Insulin group (3.0%) than in the 3OAD (1.4%) and +GLP-1 groups (1.0%), but at a smaller increase from baseline incidence (2.7%, 0.5%, and 0.3%, respectively).

Health Care Costs

The annualized all-cause costs at baseline and after 1 year and 2 years of follow-up are shown in Figure 3A. Among patients in the 3OAD and +GLP-1 groups, all-cause health care costs increased during each follow-up year: in the 3OAD group, costs increased from $9,456 at baseline to $12,085 after 1 year and to $13,100 after 2 years; in the +GLP-1 group costs increased from $10,422 to $14,042 and $15,082, respectively. In contrast, the health care costs decreased for patients in the +Insulin group from $20,544 at baseline to $19,390 after 1 year and to $18,824 after 2 years. The decrease was mainly caused by decreased inpatient costs. Diabetes-related health care costs followed a similar trend to all-cause costs across the 3 patient cohorts (Figure 3B).

Discussion

In our study, most patients added a third OAD (79%) with only 13% adding insulin to their 2OAD regimens. Those patients who did add insulin had the highest baseline HbA1c levels. The ADA/EASD guidelines recommend insulin as a treatment option for patients with high HbA1c (e.g., >8.5% [69 mmol/mol] or >9.0% [75 mmol/mol] or above their individualized target). Higher HbA1c levels at baseline imply that the degree of beta cell loss or insulin resistance has reached a stage where adding a third oral agent, albeit with a complementary mechanism of action, is unlikely to provide sufficient benefit. However, in the current study, patients who added a third OAD also had a relatively high baseline HbA1c of 8.3% (67 mmol/mol). While triple noninsulin therapy has been shown to be of sufficient benefit to certain patient populations, it is unlikely to decrease HbA1c to target levels in patients with HbA1c >8.5 or >9.0% (>69 or >75 mmol/mol), and ADA/AACE guidelines recommend that these patients be considered to start insulin therapy rather than the addition of a third OAD.[1,4] The fact that many patients in this study received a third OAD instead of an insulin also reflects a resistance to prescribe or start taking insulin in current practice.

There were also other significant differences at baseline between patients adding a third OAD, insulin, or GLP-1. These differences suggest that physicians take patient characteristics into consideration when selecting a treatment option that follows the ADA/EASD guideline recommendations of individualizing treatment regimens.[1] For example, the lower HbA1c values among patients adding GLP-1 reflect the recommendations for this therapy as an option when HbA1c is only modestly raised. Patients in the +Insulin group were "sicker" when compared with those in the 3OAD and +GLP-1 groups, with higher baseline HbA1c, higher comorbidity index, and higher health care expenditure. Patients from the +Insulin group were older than those in the other 2 groups, especially compared with patients who added GLP-1. According to the ADA/EASD guidelines, elderly patients who have a shorter life expectancy (and, likely, more comorbidities) should receive a less stringent approach to management of hyperglycemia. The fact that these elderly patients received insulin instead of a third OAD suggests that the clinical inertia to initiating insulin is predominant in younger patients. The observation that sicker patients were more likely to receive insulin may indicate a delay in treatment advancement and suggests the use of insulin as a last resort. Possibly treatment decisions may be influenced by a fear of adverse events, particularly weight gain and hypoglycemia for insulin and also by gastrointestinal discomfort associated with GLP-1 treatment.

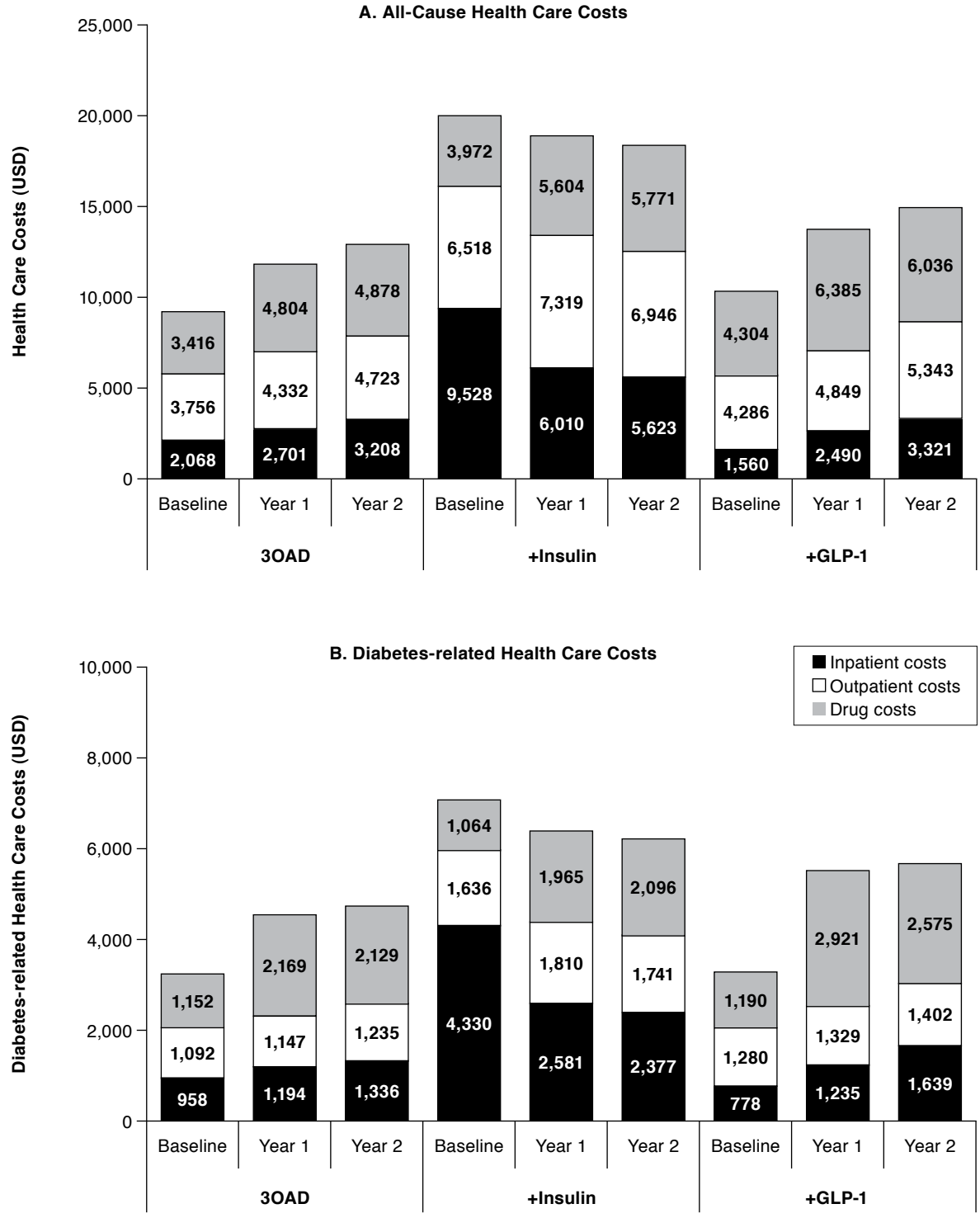
A similar association between patient profile and initiation of either insulin treatment or GLP-1 treatment has been reported in the European multicountry CHOICE study. Patients initiating insulin treatment, as compared with patients initiating GLP-1 treatment, were older (64 vs. 58 years), less obese (body mass index 29.7 vs. 35.3 kilogram per square meter) with a lower waist circumference (40.7 vs. 45.1 inches), had a higher HbA1c value at baseline (9.2 vs. 8.4% [77 vs. 68 mmol/mol]), and a longer duration of disease (10 vs. 8 years), with more microvascular (21.4 vs. 14.7%) and macrovascular (25.8 vs. 18.0%) complications.[21]

Taken together, the significant baseline differences between our study's 3 cohorts suggest that there may be strong drivers in current practice behind prescribing different third antidiabetic agents for patients.

This analysis also shows a link between clinical inertia and outcomes. For example, the highest 2-year persistence rate was observed in the group of patients who added a third OAD, with almost three-quarters of patients continuously taking medication. This result is not surprising, as persistence has been reported to be higher in patients receiving oral therapy compared with injectable therapy.[22] However, the greatest decrease from baseline in HbA1c levels was observed not in the group who continued with their 3OAD regimen, but in those who switched within 1 year. This unexpected result suggests that higher persistence alone does not guarantee better outcomes, and what may be more important is receiving the regimen that provides most effective glycemic control. Patients adding insulin had the greatest decline from baseline in HbA1c over the follow-up period; adding a third OAD instead of insulin compromised the glycemic control in these patients.

Costs also differed between the groups initiating the various third antidiabetic agents. At baseline, patients in the +Insulin group had higher inpatient costs compared with patients in the 3OAD and GLP-1 groups. However, they also had more advanced diabetes at baseline as represented by higher HbA1c and a higher comorbidity burden. Following treatment, both the total health care costs and the diabetes-related health care costs decreased in the +Insulin group but increased compared with baseline in both the 3OAD and GLP-1 groups. The reduction in costs with +Insulin was largely driven by the decrease in inpatient costs. Although patients had worse glycemic control at

FIGURE 3 Health Care Costs at Baseline and After 1- and 2-Year Follow-up[a]



[a]*Baseline costs are annualized from 6-month costs.*

GLP-1 = glucagon-like peptide-1 receptor; OAD = oral antidiabetic drug; USD = U.S. dollars.

baseline, administration of insulin resulted in greater decrease from baseline in HbA1c and lower cost of hospitalization, suggesting that insulin is a cost-saving treatment. Previous studies have also shown that improved glycemic control is associated with cost reductions.[23,24] Therefore, the clinical inertia of using a third OAD instead of insulin increased long-term costs. Further assessment of the comparative effectiveness and return on investment of various interventions has been identified by the Agency for Healthcare Research and Quality as an important step in reducing the problem of clinical inertia.[18] There is also a need for further clarification of the most appropriate treatment course for patients unable to achieve and maintain glycemic targets on multiple OADs, given the availability of other options for advancing treatment of T2DM.

Limitations

The analyses in this study were conducted using health care claims data, which are generated mainly for billing purposes. Therefore, the data are potentially subject to coding errors. In addition, this study was a retrospective analysis and was observational and exploratory in nature. As such, it cannot be used to establish causality of the observed outcomes. As this analysis was conducted to examine descriptively the current practice and associated outcomes, no statistical modeling was conducted to adjust for potentially confounding factors when comparing outcomes. Furthermore, this study only includes patients from a U.S. managed care setting that limits the generalizability to all patients with T2DM. In addition, although we state that there is a GLP-1 cohort, the GLP-1 cohort only received twice-daily exenatide, which may not be reflective of all currently available GLP-1 longer-acting, once-daily/weekly formulations. We reported data on persistence, HbA1c changes from baseline, hypoglycemia, and cost, but other relevant parameters such as body weight should be investigated in future trials.

Conclusions

This study suggests that clinical inertia may be an important barrier in current diabetes practice. In this article, we define "clinical inertia" as a delay of insulin use,[9,10] which was evident as 4 of 5 patients with T2DM added a third OAD after failing 2 OADs. This study suggests that although adding a third OAD to a regimen of 2 OADs may result in higher persistence over 2 years, the addition does not translate into better glycemic control and is not necessarily a cost-saving solution in the long term. The data from this study suggest the need for more evidence-based treatment decision making for patients who are unable to achieve and maintain glycemic targets on multiple OADs. Further research is warranted to evaluate barriers in initiating timely and evidence-based insulin initiation in different age populations.

Authors

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DISCLOSURES

This study was funded by Sanofi U.S., Inc. Levin serves on an advisory panel for Sanofi U.S. Wei and Zhou are employees of Sanofi U.S., and Xie and Baser are employees of STATinMED Research, under contract with Sanofi U.S.

Zhou and Xie researched data, contributed to discussion, and reviewed the manuscript. Levin, Wei, and Baser contributed to discussion, provided clinical insights, and reviewed the manuscript. All authors had full access to all the data in the study. Wei is the guarantor of this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis.

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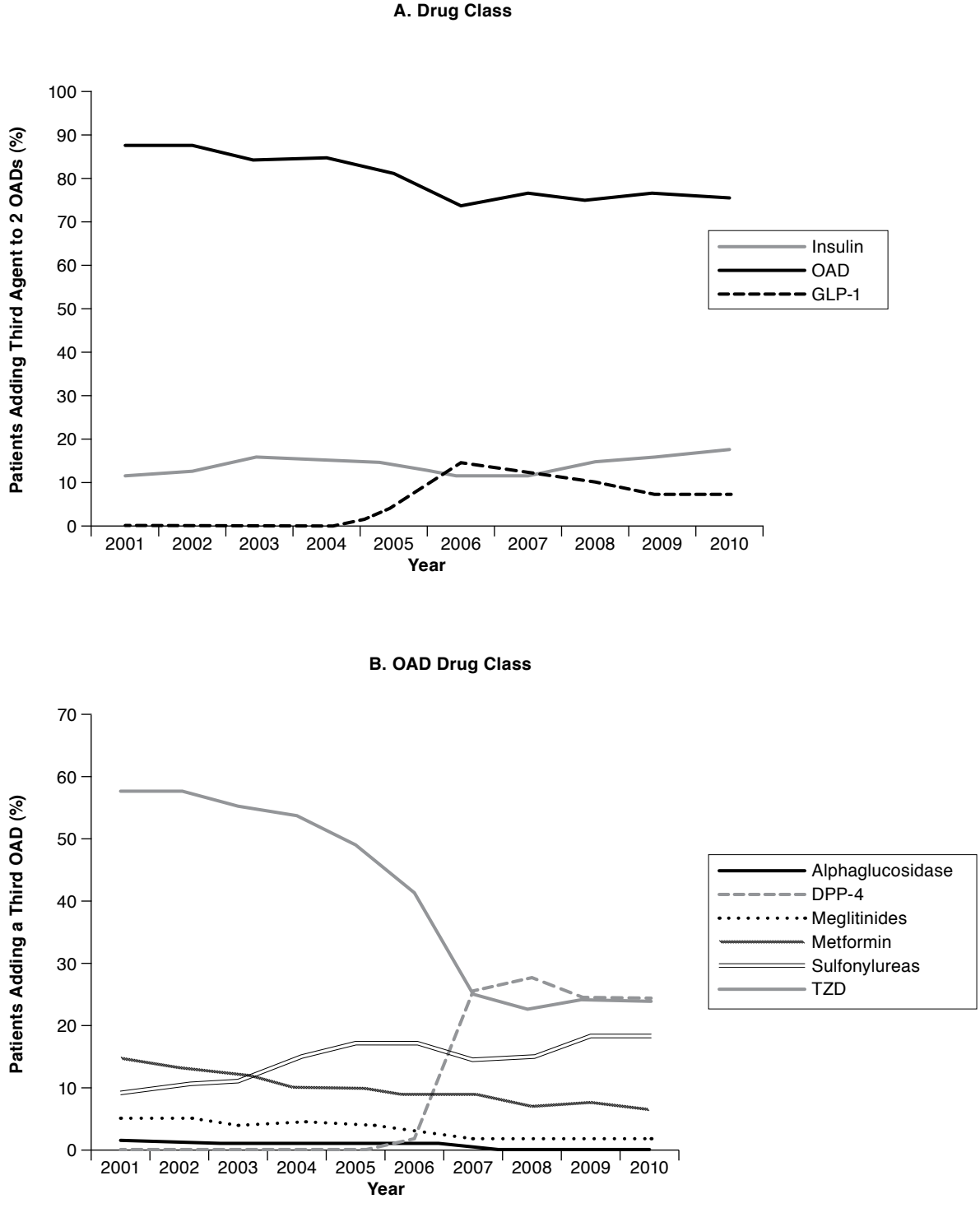
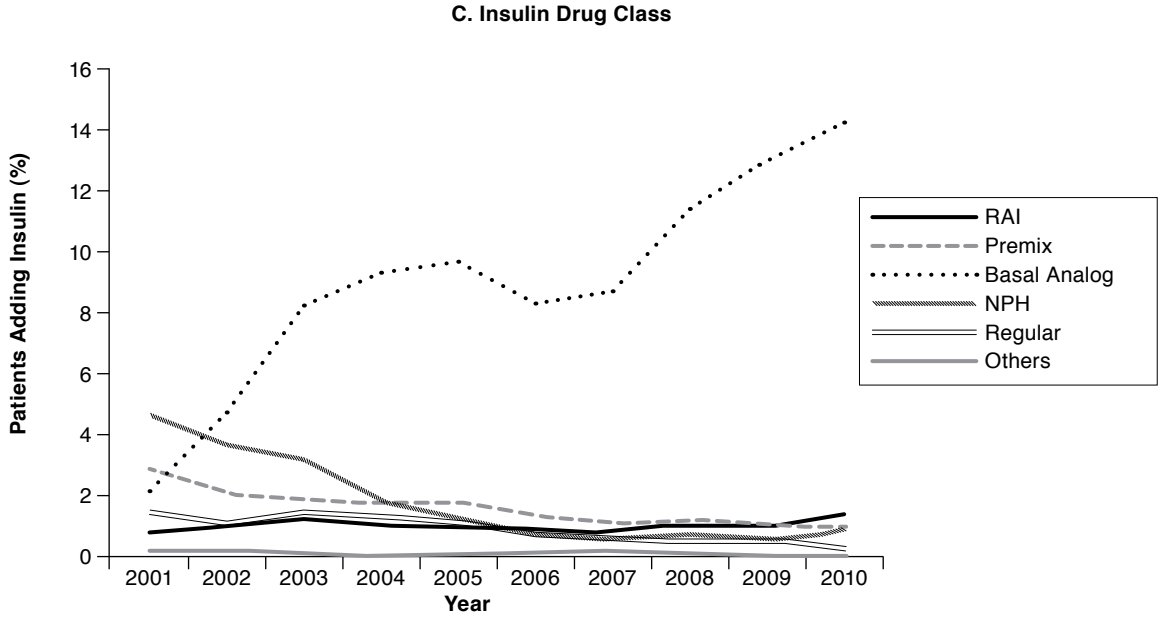
APPENDIX A Percentage of Patients Among Total Cohort Adding a Third Agent to 2OAD Treatment Regimens

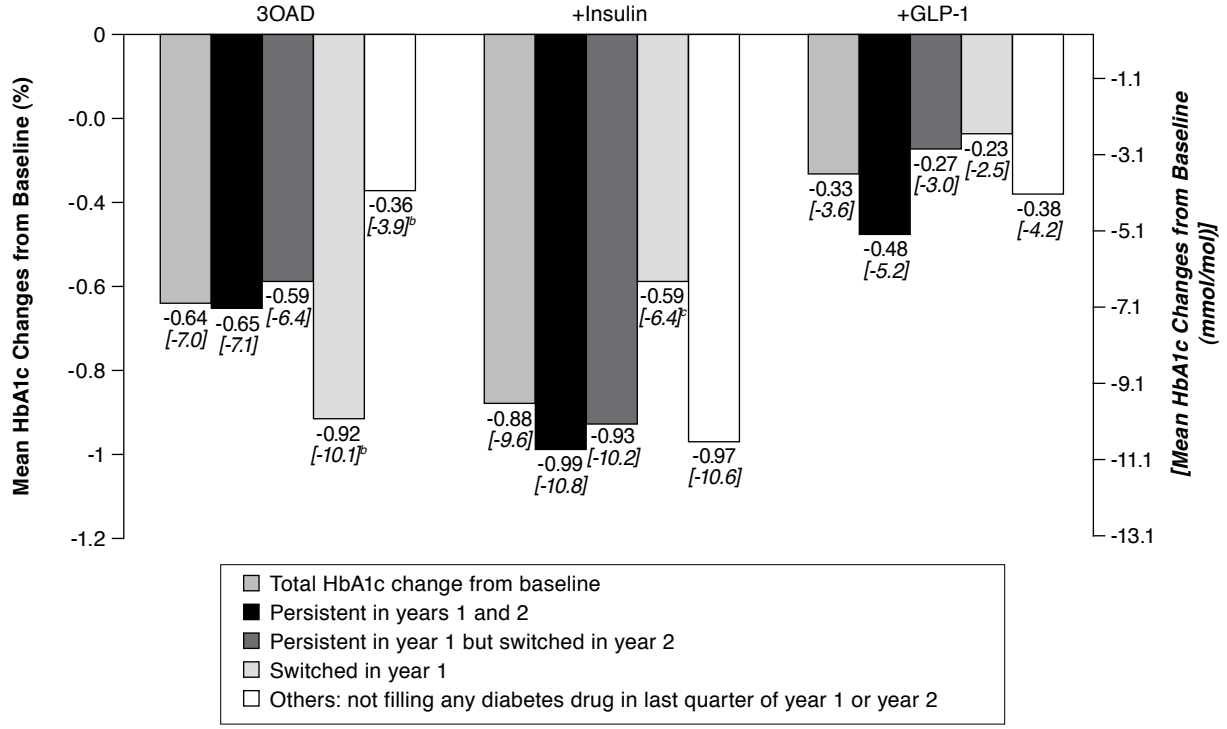


APPENDIX A Percentage of Patients Among Total Cohort Adding a Third Agent to 2OAD Treatment Regimens *(continued)*



DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; NPH = neutral protamine Hagedorn; OAD = oral antidiabetic drug; RAI = rapid-acting insulin; TZD = thiazolidinedione.

APPENDIX B HbA1c Reduction from Baseline Among Patients with 2-Year Follow-up Data Available[a]



[a]N = 4,566 for 3OAD, N = 547 for +Insulin, and N = 376 for +GLP-1. To assess the influence of treatment persistence (defined as continuing with prescribed medications over 1 or 2 years of follow-up, without discontinuing or switching) on HbA1c change from baseline, outcomes are compared for all patients combined as well as stratified by treatment persistence pattern.

[b]P < 0.01; compared with patients persistent in year 1 and year 2.

[c]P < 0.05; compared with patients persistent in year 1 and year 2.

GLP-1 = glucagon-like peptide-1 receptor agonist; HbA1c = blood glucose level; mmol/mol = millimole per mole; OAD = oral antidiabetic drug.