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Medication usage, treatment intensification, and medical cost in patients with type 2 diabetes: a retrospective database study

Machaon Bonafede,[1] Arthi Chandran,[2] Stefan DiMario,[2] Rita Saltiel-Berzin,[3] Drilon Saliu[3]

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[1]Truven Health Analytics, Cambridge, Massachusetts, USA
[2]Health Economics and Outcomes Research, Becton Dickinson, Franklin Lakes, New Jersey, USA
[3]Medical Affairs, Becton Dickinson, Franklin Lakes, New Jersey, USA

Correspondence to
Dr Machaon Bonafede; machaon.bonafede@truvenhealth.com

ABSTRACT

Objective: The goal of this study was to describe medication usage patterns in patients with type 2 diabetes mellitus (T2DM) initiating treatment with non-insulin antidiabetic drugs (NIADs), basal insulin, or prandial/mixed insulin using real-world data.

Research design and methods: A retrospective analysis using the Truven Health MarketScan Research Databases was conducted to identify adults (≥18 years) with T2DM from 2006 to 2012. Patients were categorized into four cohorts based on diabetes treatment. Cohort 1 (n=597 664) consisted of newly diagnosed patients who did not receive any treatment, cohort 2 (n=342 511) included NIAD initiators, cohort 3 (n=99 578) included basal insulin initiators, and cohort 4 (n=62 876) included prandial/mixed insulin initiators. Patients transitioned out of a cohort once they met the criteria for the next one.

Results: Patients in cohort 2 were younger (56.2 years, SD±12.1) than patients in cohorts 1, 3, and 4 (58 years, SD±0.75). Metformin was the most commonly prescribed drug in cohort 2 patients. Basal insulin usage decreased from 71% in year 1 to 47% in year 4, in cohort 3 patients. Approximately one-third of these patients switched to prandial/mixed insulin each year. In cohort 4, the usage of prandial/mixed insulin decreased to 61% by year 4. Use of basal insulin and NIAD remained common in this group. Mean glycosylated hemoglobin (HbA1c) values decreased by ~1% for each of the treatment cohorts following treatment initiation and remained stable during follow-up. All-cause and diabetes-related medical costs were highest for patients in cohorts 3 and 4.

Conclusions: Overall, our findings demonstrate that treatment intensification was low in all study cohorts despite elevated HbA1c levels during preindex and follow-up period.

Key messages

- When glycosylated hemoglobin (HbA1c) is ≥9% and/or when patients remain uncontrolled despite maximally tolerated non-insulin antidiabetic medication, intensification of therapy with the addition of insulin is recommended.
- Patients starting basal or prandial/mixed insulin previously had extensive non-insulin medication despite prolonged elevated HbA1c, suggesting a need for more aggressive treatment intensification.
- These findings may be particularly useful for health plans and providers planning interventions aimed at improving patient glycemic control and health outcomes. Future efforts should focus on facilitating treatment intensification in patients with uncontrolled type 2 diabetes.

person living with T2DM in the USA incurs ~$85 000 in lifetime medical costs to treat the disease and its complications, suggesting that there may be opportunities for savings associated with more appropriate care.[2] Maintaining glycemic control is the primary goal for patients with T2DM, which has been shown to reduce long-term diabetes-related complications, thereby reducing the clinical and economic burden.[3 4]

The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines recommend starting metformin at the time of diagnosis.[5] Additional non-insulin antidiabetic medications, glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin may be added if non-insulin monotherapy at the maximal tolerated dose does not achieve or maintain glycosylated hemoglobin (HbA1c) targets within 3 months.[5] The intensification of diabetes therapies also depends on the individual patient's characteristics, including age, comorbidities, the risk of hypoglycemia, and the provider's and patient's preferences.[6]

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common, chronic, progressive, and costly disease with an annual direct medical cost of $176 billion and indirect cost of $69 billion in the USA.[1] A recent study reported that a

Despite evidence in literature documenting the benefits of good glycemic control, particularly early in the disease trajectory, people with T2DM often do not reach recommended glycemic targets.[3] Findings from previous studies indicate that insulin-naïve and insulin-experienced patients may have mean HbA1c values above the recommended target levels, reflecting the existence of patients with poor glycemic control in routine clinical care.[7–9] Furthermore, evidence from a recent analysis suggests that the reported median time to treatment intensification with insulin is 7 years after the start of the last non-insulin antidiabetic drug (NIAD). Mean HbA1c values >9% (75 mmol/mol) have been reported at the time of insulin initiation, indicating periods of prolonged hyperglycemia which can equate to long-term microvascular and macrovascular damage.[10] The delay in timely treatment intensification has been termed 'clinical inertia' and is gaining prominence in diabetes management.[11] Failure to achieve optimal glycemic control is often associated with an increased risk of developing complications as well as increased healthcare usage and costs.[12]

As inadequate glycemic control may signal the need for treatment modification, it is important to gain an understanding of treatment progression and intensification patterns in patients with T2DM. The goal of this retrospective database analysis was to describe treatment intensification patterns in patients with T2DM initiating therapy with NIAD, basal insulin, or prandial/mixed insulin using real-world data in the USA. As a secondary goal, the study estimated the average direct medical cost associated with diabetes treatment in this patient population.

RESEARCH DESIGN AND METHODS
Study design and data source
A retrospective cohort analysis of patients with T2DM was conducted using the Truven Health MarketScan Research Databases, a large administrative claims database comprising commercially insured patients in the USA. The Truven Health MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits (COB) (Medicare) Databases contain medical and prescription data on ~35 million employees and their dependents, while the Medicare Database contains data of individuals with Medicare supplemental insurance paid for by employers. Detailed cost, use, and outcomes data are available for both databases covering inpatient services, outpatient services, and prescription drug claims. As deidentified data were used in this retrospective database analysis, institutional review board (IRB) approval was not sought.

Study population
Adult patients (≥18 years of age) who were diagnosed with T2DM (International Classification of Diseases,

Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of 250.x0 or 250.x2) from 1 January 2006 to 31 December 2011 (study period), with at least 12 months of continuous enrollment during preindex and postindex period, were included in the study. Index date was defined as the date of the first antidiabetic prescription. Patients with a medical claim for type 1 diabetes (ICD-9-CM diagnosis codes 250.x1 or 250.x3) and gestational diabetes (ICD-9-CM diagnosis code 648.8x) were excluded from the analysis.

Based on the use of T2DM medications during the preindex and index period, patients were categorized into four study cohorts for the purpose of this analysis (table 1). Cohort 1 consisted of patients with T2DM who had not received any treatment in the year prior to or following diagnosis. In cohort 1, index date was defined as the date of T2DM diagnosis. Cohort 2 consisted of patients with T2DM who were newly initiated on NIAD and had not received any antidiabetic medications during the preindex period. Cohort 3 included patients with T2DM who were newly initiated on basal insulin but could have previously used other antidiabetic medication during the preindex period. Likewise, cohort 4 included patients who newly started prandial or mixed insulin but could have previously used other antidiabetic medications during the preindex period. Patients were followed for a minimum of 1 year after the index date up to a maximum of 4 years. Patients were transitioned out of a cohort once they met the criteria for the next cohort. Patients could qualify for more than one cohort depending on the timing of diabetes medication usage.

Demographic characteristics (age, gender, geographic region, and health plan type) were described for the different cohorts on the index date. Clinical variables measured in the preindex period included HbA1c values, macrovascular complications (ie, myocardial infarction, ischemic heart disease, peripheral vascular disease, cerebrovascular disease, and congestive heart failure), and microvascular complications (ie, diabetic neuropathy, diabetic nephropathy, renal disease, and diabetic retinopathy). The presence of other comorbid conditions commonly associated with T2DM, such as obesity, hypertension, hyperlipidemia, and non-alcoholic fatty liver disease, was also evaluated. The Deyo-Charlson comorbidity index score was calculated to measure the severity of comorbid conditions using all of the diagnoses on medical claims from the 12-month preindex period.[13]

Direct medical cost
Total annual direct medical costs and resources associated with emergency department visits, inpatient stays, outpatient visits, and endocrinologist visits were estimated for patients in all cohorts. Mean costs associated with diabetes-related prescriptions and supplies were also calculated for all study cohorts. Direct medical costs were measured for the follow-up period as the amount reimbursed by the healthcare plan and represent total

Table 1 Baseline demographic and clinical characteristics of study cohorts

Demographic and clinical characteristics	Cohort 1 No medication	Cohort 2 NIAD initiators	Cohort 3 Basal insulin initiators	Cohort 4 Prandial/mixed insulin initiators
Number of patients	597 664	342 511	99 578	62 876
Age (mean (SD) (years))	59.1 (13.9)	56.2 (12.1)	57.8 (12.2)	59.1 (13.2)
Gender (%)				
Male	49.0	54.3	54.8	52.7
Female	51.0	45.7	45.2	47.3
Geographic region (%)				
North-East	16.5	12.6	11.0	10.5
North Central	29.9	27.4	29.0	29.4
South	36.2	42.1	39.7	40.7
West	16.9	17.3	19.7	18.8
Unknown	0.6	0.6	0.6	0.6
Insurance plan type (%)				
Comprehensive	19.0	12.8	15.4	17.7
EPO	0.9	1.0	0.9	0.8
HMO	15.6	17.3	20.0	19.1
POS (includes plans w/o capitation)	7.7	9.0	9.1	8.7
PPO	50.0	51.7	47.2	46.6
Unknown/missing	4.0	4.4	3.7	3.8
Other (basic/major medical, CHDP, HDHP)	2.8	3.7	3.6	3.4
Deyo-Charlson comorbidity index (mean (SD))	1.8 (1.5)	1.6 (1.4)	2.3 (1.9)	2.5 (2.1)
Microvascular and macrovascular complications (%)				
Diabetic neuropathy	6.7	7.4	14.8	16.8
Renal disease	9.8	7.4	16.0	19.7
Ischemic heart disease	16.3	12.9	20.2	23.4
Disorders of lipid metabolism	42.3	40.9	40.1	38.7
Hypertension	54.7	52.2	56.3	58.5

CHDP, Child Health and Disability Prevention; EPO, exclusive provider organization; HDHP, high-deductible health plan; HMO, house in multiple occupation; NIAD, non-insulin antidiabetic drug; POS, point of service; PPO, preferred provider organization.

costs from the perspective of a large managed care organization. Patient copayments and deductibles were not included in the total direct medical costs calculations. Costs were expressed in year 2012 US dollars.

Statistical analyses

Continuous variables were reported using mean and SD. Categorical variables were summarized using percentages. Data used for this study were obtained from administrative health insurance claims database and did not include any individually identifiable data. All statistical analyses were performed using SAS software V.9.2 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Demographic and clinical characteristics

A total of 597 664 patients with T2DM in cohort 1, 342 511 in cohort 2, 99 578 in cohort 3, and 62 876 in cohort 4 met the study inclusion and exclusion criteria (table 1). Patients in cohort 2 were younger (56.2 years, SD±12.1) than patients in cohorts 1, 3, and 4 (average of 58 years, SD±0.75). More than half of the patients in cohorts 2, 3, and 4 were males, while 51% of the initially untreated patients in cohort 1 were females (table 1). Hypertension, lipid disorders, ischemic heart disease, and renal disease were the more commonly occurring comorbid conditions in each cohort. As reported in table 2, average HbA1c value for cohort 1 remained consistent at 6.2% (44 mmol/mol) over the follow-up period. For patients in cohort 2, mean HbA1C was highest in the preindex period (8.0% (64 mmol/mol)) but decreased at year 1 after initiation of non-insulin therapy (7.1% (54 mmol/mol)) and remained consistent over the follow-up period; likewise, the proportion of patients with HbA1c>7.0% (53 mmol/mol) decreased from 62.2% preindex to 51.7% postindex. For patients in cohorts 3 and 4, mean HbA1C values were highest during the preindex period (9.2% (77 mmol/mol) and 8.9% (74 mmol/mol), respectively). The percentage of patients with HbA1c>7.0% (53 mmol/mol) decreased from 89.7% and 83.8% preindex to 83.4% and 80.0% postindex for cohorts 3 and 4, respectively. Overall, HbA1c values decreased by ~1% in the year following treatment initiation and remained stable during the study follow-up period. However, it was observed

Table 2 HbA1c values for study cohorts from preindex to year 4

Cohorts	Preindex	Year 1	Year 2	Year 3	Year 4
Cohort 1 (%)	6.4	6.2	6.2	6.2	6.2
% >7.0	11.3	7.9	20.2	23.9	26.5
Cohort 2 (%)	8.0	7.1	7.1	7.2	7.3
% >7.0	59.1	49.7	41.8	45.0	47.7
Cohort 3 (%)	9.2	8.1	8.1	8.1	8.2
% >7.0	88.9	82.7	74.0	82.0	74.1
Cohort 4 (%)	8.9	8.0	8.0	8.1	8.0
% >7.0	82.6	78.8	70.3	69.4	73.0

HbA1c, glycosylated hemoglobin.

that despite treatment with antidiabetic medications, average HbA1c values did not decrease below 7.0% (53 mmol/mol) during the study follow-up period for patients in cohorts 2–4.

Medication usage

As the average HbA1c value of patients with T2DM in cohort 1 was 6.2% (44 mmol/mol), treatment initiation for up to 4 years postdiagnosis was low with roughly 9%, 15%, and 19% receiving medications by years 2, 3, and 4, respectively. Patients initiating treatment in this cohort were mainly prescribed oral antidiabetic medications which included biguanides (metformin), sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, and GLP-1 agonists. The majority (72%) of the patients in cohort 2 initiated treatment with metformin. From year 1 to year 4, however, its usage decreased from 77% to 54%.Other commonly prescribed treatments for this cohort included sulfonylureas (15%), combination products (8%), thiazolidinediones (6%), DPP-4 inhibitors

(3%), and GLP-1 agonists (1%). A gradual increase in the use of incretin agents, such as GLP-1 agonists (3–4%) and DPP-4 inhibitors (7–10%), was observed during the follow-up period. As expected, the overall transition from non-insulin medications to insulin therapy was low (∼1%/year) for patients in this group (table 3).

Patients in cohort 3 primarily initiated treatment with insulin glargine (69%) followed by insulin detemir (21%) and NPH human insulin isophane suspensions (10%). However, there was a decrease in usage of basal insulin. For example, insulin glargine usage decreased from 71% in year 1 to 47% in year 4. Treatment with non-insulin medications remained common during the preindex and follow-up period (table 3). Between 33% and 38% of patients were transitioned to prandial/mixed insulin each year following basal insulin initiation. For patients in cohort 4, there was a decrease in usage of mealtime and mixed insulin from year 1 to year 4. For example, usage of insulin as part in year 1, 37.5%,

Table 3 Concomitant medication usage among NIAD initiators, basal insulin initiators, and prandial/mixed insulin initiators

	Preindex	Year 1	Year 2	Year 3	Year 4
NIAD initiators					
Metformin (%)	–	77.0	58.4	55.4	53.6
DPP-4 inhibitors (%)	–	6.9	7.3	8.5	9.5
GLP-1 agonists (%)	–	2.9	3.0	3.3	3.7
Sulfonylureas (%)	–	23.7	21.1	23.1	25.2
TZDs (%)	–	9.5	7.7	8.2	8.9
Fixed-dose combinations (%)	–	11.5	10.2	10.8	11.3
Basal insulin initiators					
Metformin (%)	55.4	52.1	48.7	47.5	46.2
DPP-4 inhibitors (%)	15.8	12.4	10.9	10.3	9.7
GLP-1 agonists (%)	12.0	8.6	8.8	8.9	8.7
Sulfonylureas (%)	52.1	41.4	35.1	33.8	32.6
TZDs (%)	29.6	18.8	15.0	14.2	13.5
Fixed-dose combinations (%)	17.5	13.7	12.0	11.2	10.4
Prandial/mixed insulin initiators					
Metformin (%)	49.1	44.1	41.2	40.3	39.0
DPP-4 inhibitors (%)	11.7	8.1	7.7	7.6	7.5
GLP-1 agonists (%)	10.4	6.1	6.8	6.9	6.8
Sulfonylureas (%)	46.7	29.9	24.8	23.8	23.6
TZDs (%)	24.7	14.1	11.1	10.3	10.0
Fixed-dose combinations (%)	14.0	8.9	8.0	7.5	7.3

DPP, dipeptidyl peptidase; GLP, glucagon-like peptide; NIAD, non-insulin antidiabetic drug; TZD, thiazolidinedione.

Table 4 Resource usage for study cohorts from year 1 to year 4

Cohorts All cause	Inpatient admissions (%)		Outpatient visits (%)		Endocrinologist visits (%)		Emergency department visits (%)	
	Year 1	Follow-up (average)	Year 1	Follow-up (average)	Year 1	Follow-up (average)	Year 1	Follow-up (average)
Cohort 1	16.9	12.2	99.9	96.1	3.6	2.6	1.1	0.6
Cohort 2	11.0	10.7	99.1	97.0	5.5	4.8	2.3	2.4
Cohort 3	18.8	16.3	99.3	97.8	15.7	13.5	4.1	4.7
Cohort 4	23.8	19.5	99.2	97.7	19.1	15.3	4.8	5.0
Diabetes related								
Cohort 1	0.2	0.1	95.4	42.8	2.1	0.9	1.1	0.6
Cohort 2	0.3	0.2	94.0	84.6	4.7	3.9	2.3	2.4
Cohort 3	0.9	0.8	95.7	90.7	15.1	12.9	4.1	4.7
Cohort 4	1.2	1.1	94.4	89.4	18.4	14.6	4.8	5.0

dropped to 20.3% at year 4. Similarly, there was a 12% decrease in the number of patients who used insulin lispro from year 1 to year 4. Furthermore, it was noted that 69% of patients in cohort 4 who were using basal insulin in year 1 decreased during follow-up to 54% at year 4. The decrease and drop-off in medication use noted above is a significant finding of the study. Overall, the majority of patients in cohorts 3 and 4 were extensively treated with non-insulin medications prior to initiation of basal or prandial/mixed insulin, indicating that early adoption of treatment intensification with insulin was limited despite elevated HbA1c in both groups.

Direct medical costs
Health resource usage for all four study cohorts is reported in table 4, while mean direct 'all-cause' and 'diabetes-related' medical costs are reported in table 5. Patients in cohorts 3 and 4 had higher endocrinologist visits and inpatient admissions than patients in cohort 2. This could be attributed to the fact that patients in cohorts 3 and 4 spent long periods of time in poor glycemic control before insulin initiation. Early treatment intensification may have reduced the number of inpatient admissions and endocrinologist visits in these cohorts. All-cause medical expenditure for patients in cohort 2 was $8591 in the first year versus $15 339 and $20 350 for patients in cohorts 3 and 4, respectively. Mean all-cause medical expenditure increased across study cohorts but remained relatively stable within each cohort, over time. Similarly, diabetes-related mean total costs were lower for cohort 2 ($1333) compared with cohort 3 ($2276) and cohort 4 ($2779). However, these costs remained relatively stable over time within each cohort after initially declining at the end of year 1. As expected, diabetes-related mean pharmacy cost increased from cohort 2 to cohort 4 but remained relatively stable within cohorts. For patients in cohort 2, mean diabetes-related pharmacy expenditure remained stable over the follow-up period, starting at $314 in the first year and averaging $272 in years 2–4.

Mean total pharmacy costs for patients in cohort 3 increased modestly from $2346 in year 1 to $2710 in year 4. Similarly, for patients in cohort 4, mean pharmacy costs increased modestly from $2484 in year 1 to $2762 in year 4.

DISCUSSION
The importance of early glucose control and its impact on patient prognosis cannot be overemphasized. Failure to intensify treatment is a common barrier in optimizing diabetes care.[14 15] Findings from our study demonstrate clinical inertia seen in the real-world setting. For example, patients in cohorts 3 and 4 received extensive therapy with NIAD despite having mean HbA1c levels during the preindex period of 9.2% (77 mmol/mol) and 8.9% (74 mmol/mol), respectively, for whom intensification with insulin therapy would be beneficial. It is likely that these patients endured prolonged periods of poor glycemic control which may, in the long term, negatively impact health outcomes and contribute to increased medical costs. Furthermore, the use of multiple NIADs was common and remained consistent over time among most patients receiving treatment with basal and prandial insulin. Instead of insulin intensification, there was a decrease in the use of basal and prandial insulin over the follow-up period for patients in cohorts 3 and 4.

The choice of second-line agents used to intensify treatment after metformin monotherapy included sulfonylureas, thiazolidinediones, GLP-1 agonists, and DPP-4 inhibitors. These trends are consistent with recently published data about the overall use of antidiabetic drugs.[16 17] While metformin is regarded as the first-line agent in the treatment of T2DM, there is no consensus supporting the use of one second-line agent over another.[18 19] Consistent with previous studies, we found that while sulfonylureas continue to be the most common choice for second-line therapy, their use decreased over time, while the use of other agents such as GLP-1 agonists and DPP-4 inhibitors increased.[20–22] We also noticed a decline in the use of thiazolidinediones which have

Table 5 Direct medical costs for study cohorts from year 1 to year 4

Cohorts	All-cause medical expenditure (US$)		Diabetes-related medical expenditure (US$)		Diabetes-related prescription expenditure (US$)	
	Year 1	Follow-up (average)*	Year 1	Follow-up (average)*	Year 1	Follow-up (average)*
Cohort 1	11 997	8780	934	360	–	–
Cohort 2	8591	8005	1333	1095	314	272
Cohort 3	15 339	12 391	2276	1937	2346	2591
Cohort 4	20 350	14 999	2779	2186	2484	2704

*Follow-up costs were averaged from year 2 to year 4 for all study cohorts.

become progressively unpopular since the controversial reports published on rosiglitazone.[23 24]

Adherence is an important factor in diabetes treatment, especially when considering real-world insulin therapy. Non-adherence to insulin therapy is associated with worse glycemic control[25] and increased risk of diabetes-related microvascular complications.[26] Non-adherence to insulin therapy was found to be significantly and independently associated with two aspects of injection burden: having to plan daily activities around insulin injections and injections interfering with activities of daily life.[27] Most patients and physicians delay starting insulin therapy for several reasons, all of which contribute to clinical inertia: fear of increased risk of hypoglycemia and weight gain, higher costs, the 'bad reputation' that insulin therapy is a sign of disease progression, fear of dependency on the medication, needle anxiety, and other beliefs.[28] Fear of hypoglycemia is a concern in patients prescribed insulin with T2DM. Inappropriate or aggressive titration can lead to hypoglycemia and this is one reason patients may skip doses, omit insulin, or stop therapy altogether.[29 30] End-stage renal disease (ESRD) is a relative contradiction for patients on insulin and often, dialysis patients will require every other day or every 2-day basal injections due to the protein not being filtered through the dialysis machine.[31] Once on insulin therapy, many factors could have potentially impacted the significant decrease in insulin use observed in our study, including financial burden due to high cost of medications, polypharmacy, tolerance issues, inconvenience, and persistence issues among insulin users. Future efforts to effectively manage T2DM need to focus on developing and implementing strategies to overcome potential barriers to insulin therapy with support from healthcare providers including physicians, nurses, and pharmacists. This can include designing educational tools for patient self-management as well as creating ongoing collaborative relationships between patients and allied health professionals that facilitate timely monitoring of clinical outcomes. These strategies should focus on decreasing the barrier to insulin initiation and include ways to have patients continue long-term insulin therapy once they have made the transition. Patient support and follow-up cannot be overlooked as they are crucial to successful diabetes management.

As reported in previous studies, inadequate glycemic control is associated with long-term adverse clinical and economic consequences.[32] A German study reported that the total average cost of diabetes care for 6 months post insulin initiation rose from €579 to €961, which included the cost of blood glucose monitoring and specialist care in addition to insulin itself.[33] These costs were greater in patients with higher HbA1c values and body mass index, highlighting the importance of good glycemic control using early treatment intensification and lifestyle modification strategies. Similarly, results from our study report that average all-cause and diabetes-related medical costs were higher for patients in cohorts 3 and 4. These two cohorts included patients on insulin who were further along in the course of their disease. Some cost drivers within these groups include increased visits to endocrinologists, due to a more complex insulin regimen, as well as increased hospitalizations due to either disease progression or adverse effects of insulin, notably severe hypoglycemia. Timely initiation of insulin therapy in this group can be beneficial in maintaining optimal glycemic control and therefore assist in reducing long-term complications and costs associated with uncontrolled T2DM.[34–36]

The results of our study should be interpreted keeping in mind potential limitations that are inherent to claims data. These include absence of certain information in the databases which may be relevant to the treatment and management of T2DM such as body weight, body mass index, adherence to lifestyle modifications, and health behavior information. The definition of T2DM is limited to the occurrence of specific diagnosis codes in the database making it dependent on the accuracy of claims coding. Administrative claims data include paid claims only and cannot identify a member's use of sample medications or therapies for which the member paid solely out of pocket. Alternatively, a claim for a medication does not necessarily mean the member actually took the medication. Furthermore, there may be members who elect not to fill their prescriptions for a variety of reasons (eg, out-of-pocket cost of the medication, inability to return to the pharmacy). However, neither member nor physician behavior was evaluated in the present analysis. Future studies are warranted to further elucidate these factors. Similarly, free generic medications, specifically

metformin, may not have been captured in this study, resulting in a potential underestimation. The study did not account for the impact of comorbid conditions and other risk factors on treatment patterns. When assessing treatment intensification, we were not able to evaluate how adherence, side effects, cost, or contraindications impacted results. Also, the study did not look into reasons or predictors of various treatment patterns that were observed. Our study provided a conservative estimate of direct medical costs associated with the treatment of patients with a diagnosis code of T2DM. Indirect costs, including costs associated with lost productivity, were not estimated. Results from this study apply to a population of commercially insured patients and their dependents, limiting generalizability to other patient populations. Last, as this was an observational study, no causal inferences can be made from these data.

In conclusion, our analysis provides an understanding of treatment intensification patterns observed in a real-world setting and supports findings from other studies that have demonstrated delays in escalating treatment intensity in patients with poor glycemic control despite recommendations set forth in the guidelines. These findings may be particularly useful for health plans and providers planning interventions aimed at improving glycemic control and health outcomes. Findings from other studies suggest that early insulization may be more cost-effective than prescribing multiple non-insulin therapies. However, there is a level of uncertainty as to when insulin should be initiated in patients exhibiting poor glycemic control in routine clinical practice and how to identify patients who are more likely to benefit from early insulization. A variety of patient-related factors such as adherence to treatment, occurrence of drug-related side effects, medication contraindication (eg, worsening of kidney function), and cost of medications along with provider-related factors have been found to delay initiation of early treatment intensification when warranted and therefore negatively impact clinical outcomes.[11 15 37–39] Various approaches have been proposed to help overcome clinical inertia, such as implementing a patient-centered approach, promoting patient self-management, and providing education for physicians and patients with diabetes.[39] Future efforts should be aimed at developing and assessing interventions which facilitate treatment intensification in patients with uncontrolled T2DM.

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