INTRODUCTION

The recommended approach to the management of type 2 diabetes (T2D) for newly diagnosed patients involves the administration of oral antidiabetes drugs (OADs) combined with exercise and dietary adjustments. \(^1,^2\) Current treatment guidelines issued by the American Diabetes Association (ADA) recommend individualized glycated haemoglobin A\(_{1c}\) (A1C) targets based on age, disease severity, the presence of comorbidities and other individual patient factors. \(^2\)

Guidelines suggest that patients who do not achieve their target A1C levels within 3 months of initiating monotherapy and lifestyle changes may benefit from the addition of basal insulin (BI) therapy. \(^1,^2\)
If glycaemic control is still not achieved, ADA guidelines recommend intensification of treatment by the addition of a prandial insulin or a glucagon-like peptide-1 receptor agonist (GLP-1 RA), or switching to a premixed insulin. The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) guidelines also recommend intensifying with a prandial insulin, a GLP-1 RA, a sodium glucose cotransporter 2 (SGLT-2) inhibitor or a dipeptidyl peptidase-4 (DPP-4) inhibitor if target A1C levels are not reached with BI therapy. However, despite the presence of clear treatment guidelines, approximately 50% of patients with T2D in the United States do not achieve optimal glycaemic control. Delayed treatment adjustment or failure to intensify therapy when appropriate (described as “clinical inertia”) is often associated with poor clinical outcomes among these patients. Clinical inertia has also been suggested to contribute to poor outcomes in patients with T2D and results in higher healthcare utilization and associated costs.

Factors known to drive clinical inertia involve both patients and physicians. At the patient level, erroneous perceptions and fears about insulin therapy, poor adherence to treatment and the need for training and education, as well as the presence of comorbidities and risk of hypoglycaemia (particularly in the elderly), play a role in delaying intervention when glycaemic control is suboptimal. Physician-related factors include lack of evidence for best practices, limited experience or time for the treatment of patients and the complexity of the currently available regimens. The evaluation of the real-world consequences of clinical inertia in patients with T2D who are poorly controlled with OADs or BI may provide important information that can be used to improve treatment decision-making.

This retrospective analysis of a large US insurance database was conducted to determine the clinical outcomes of treatment intensification (TI) vs no treatment intensification (NTI) in patients with T2D who are inadequately controlled on dual OAD therapy or BI therapy.

2 | MATERIALS AND METHODS

2.1 | Study design and eligibility criteria

Administrative claims data for commercial and Medicare Advantage patients from the Optum™ Research Database were used, with a study period from 1 January 2009 to 31 August 2015. The database includes medical and pharmacy claims data for approximately 13 million commercially insured individuals annually across the United States. Additionally, data for 8 million Medicare Advantage patients with medical and pharmacy coverage are available in the database.

Eligible patients were adults ≥18 years of age, who have a diagnosis of T2D and uncontrolled glycaemia after ≥6 months of dual OAD therapy or BI use (Figure 1). The index date was defined as the date of the first qualifying A1C measurement showing poor glycaemic control (A1C ≥7%) following dual OAD or BI therapy.

For the analysis, patients were divided into cohorts based on evidence of TI ≤6 months after the index date. For patients on dual OADs, intensification consisted of the addition of a SGLT-2 inhibitor, DPP-4 inhibitor or a third OAD (other than SGLT-2 inhibitors, DPP-4 inhibitors, or pre-index agents); or addition of switching to a GLP-1 RA, an insulin (premixed, basal and/or bolus) or a combination of these. For patients on BI, intensification consisted of an increase in BI dose (±10% relative to the last pre-index dose, calculated as the daily average consumption using quantity supplied and days between claims, as recorded in the pharmacy claims database); or addition of a SGLT-2 inhibitor, GLP-1 RA, or bolus insulin; or addition of switching to premixed insulin or multiple medications.

The pre-intensification period was defined as the 6 months prior to the intensification date, and the follow-up period was defined as the 12 months following the intensification date (Figure 1). Patients were required to be continuously enrolled in the health plan for both the pre-intensification period and the follow-up period. The control group comprised patients who did not undergo treatment intensification (NTI) ≤6 months after the index date, and an intensification date was randomly assigned to these patients based on the observed distribution of intensification dates in the TI cohort.

2.2 | Clinical outcomes

Patient characteristics at baseline including age, gender, geographic region, health insurance plan type, index A1C, pre-intensification anti-diabetes medication use, pre-intensification Diabetes Complications Severity Index (DCSI), pre-intensification comorbidities and pre-intensification healthcare resource utilization were described for the different cohorts. A1C levels and hypoglycaemia events were assessed during the 12-month postintensification follow-up period.
The A1C measurement closest to the end of this period was used for patients with an A1C result obtained at least 90 days after intensification, and the change from index A1C to postintensification A1C was calculated.

Hypoglycaemia events were identified by the presence of ICD-9-CM diagnosis codes 251.0, 251.1, 251.2 and 270.3 for hypoglycaemia, or an ICD-9-CM code for 250.8x without any claims with codes for 259.8, 272.7, 681.xx/682.xx/689.9x, 701.1-707.9, 709.3, or 730.0-730.2/731.8 on the same date as the claim for 250.8x.14 Visits for hypoglycaemia in any setting were captured, and hypoglycaemia events recorded during visits to an inpatient/emergency department were considered to be severe.

2.3 | Healthcare resource utilization and costs

Pre-intensification healthcare resource utilization included inpatient hospitalizations, emergency department visits and ambulatory visits. Healthcare costs were measured in the pre-intensification period and were calculated as the sum of health plan-paid and patient-paid amounts. Diabetes-related healthcare utilization and costs were identified as services from medical claims with a primary or secondary diagnosis of diabetes (ICD-9-CM: 250.xx); pharmacy costs were calculated from pharmacy claims for oral or injectable diabetes medications. Data on prescription fills were obtained from outpatient pharmacy settings.

2.4 | Statistical analyses

Bivariate comparisons were made between the TI and NTI groups, and ordinary least squares models and logistic regression were used to adjust for confounders in A1C change and hypoglycaemia, respectively.

Key covariates in the final models included study cohort, age, gender, health plan region, pre-intensification comorbidity, pre-intensification diabetes-related medication use, pre-intensification diabetes-related healthcare resource utilization, pre-intensification diabetes-related costs, pre-intensification hypoglycaemia and index A1C level.

3 | RESULTS

3.1 | Patient demographic characteristics

Of the 28 123 adult patients with T2D inadequately controlled with dual OAD therapy who were eligible for inclusion in the study, 3990 (14.2%) patients underwent TI within 6 months of evidence of poor glycaemic control: 1611 (40.4%) added a DPP-4 inhibitor; 88 (2.2%) added a SGLT-2 inhibitor; 1145 (28.7%) added a third OAD; 535 (13.4%) switched to or added insulin; 519 (13.0%) switched to or added a GLP-1 RA; 92 (2.3%) received multiple agents (Figure 2). The remaining 24 133 (85.8%) patients did not undergo intensification within 6 months of evidence of poor glycaemic control.

Of the 16 140 adult patients with T2D inadequately controlled with BI therapy who were eligible for inclusion in the study, 10 425 (64.6%) patients underwent TI within 6 months of evidence of poor glycaemic control: 52 (0.5%) added a SGLT-2 inhibitor; 179 (1.7%) added or switched to premixed insulin; 233 (2.2%) added a GLP-1 RA; 1085 (10.4%) added bolus insulin; 8707 (83.5%) increased BI dose; 169 (1.6%) intensified with multiple medications (Figure 2). The remaining 5715 (35.4%) patients did not undergo intensification within 6 months of evidence of poor glycaemic control.

Patient baseline demographic and clinical characteristics are shown in Table 1. Patients with T2D who received intensification were younger, had higher mean A1C values, were more likely to be on a commercial health insurance plan, were more likely to receive particular pre-intensification OADs, were more likely to have T2D with complications and had higher pre-intensification diabetes-related costs during the baseline period.

3.2 | Glycaemic control

Patients in the OAD cohort who underwent TI had a greater adjusted mean reduction in A1C levels at follow-up compared with patients in the NTI group (−0.59% vs −0.25%; P < .001) (Figure 3A).

Patients in the BI cohort who underwent TI had a greater mean reduction in A1C levels at follow-up compared with patients in the NTI group (−0.30% vs −0.16%; P < .001) (Figure 3B).

3.3 | Hypoglycaemia events

The proportions of patients in the OAD cohort with reported overall and severe hypoglycaemia events were higher in the TI group than the NTI group (4.9% vs 3.2%, P < .001; 1.4% vs 0.9%, P = .005, respectively). In the adjusted analysis, the odds of hypoglycaemia were 68% higher in the TI group vs the NTI group (odds ratio [OR] 1.68, 95% confidence interval [CI] 1.41-2.01; P < .001) (Table 2).

The proportions of patients in the BI cohort with reported overall and severe hypoglycaemia events were higher in the TI group than in the NTI group (6.9% vs 5.8%, P = .004; 2.6% vs 2.0%, P = .031, respectively). In the adjusted analyses, the odds of hypoglycaemia were 23% higher in the TI group vs the NTI group (OR 1.23, 95% CI 1.07-1.41; P = .004) (Table 2).

4 | DISCUSSION

Our study shows that most patients in a managed-care setting in the United States who were receiving 2 OADs, and about a third of the patients who were receiving BI, did not have their treatment intensified within 6 months of an A1C measurement of ≥7%, despite evidence of poor glycaemic control and the availability of multiple other antihyperglycaemia agents. It is not clear why patients receiving treatment with OADs were less likely to receive timely intensification compared with patients on BI. It could be speculated that for patients already receiving insulin, taking the step to increase insulin...
Evidence of claims for 2 classes of OADs and no evidence of claims for intensification therapies (DPP-4/SGLT-2 inhibitors or injectable therapies) in the 6-mo pre-index period N = 49,793

Evidence of ≥2 claims for BI in the 6-mo period prior to the index date (≥1 refill in ≥90 d prior to the index date) and ≥1 BI refill on or following the index date and no evidence of claims for bolus insulin or premixed insulin, GLP-1 RA, SGLT-2 inhibitor or pramlintide in the 6-mo pre-index period N = 26,078

Continuous enrollment in the 6-mo pre-index period and ≥12 mo following the index date N = 30,327

Continuous enrollment in the 6-mo pre-index period and ≥12 mo following the index date N = 17,416

Evidence of treatment intensification ≤6 mo after the index date n = 4393

No evidence of treatment intensification ≤6 mo after the index date n = 25,934

Evidence of treatment intensification ≤6 mo after the index date n = 11,197

No evidence of treatment intensification ≤6 mo after the index date n = 6,219

Patients who underwent treatment intensification and remained enrolled in the health plan for 12 mo after the intensification date n = 33980

Patients who did not undergo treatment intensification and remained enrolled in the health plan for 12 mo after a randomly selected date n = 24,133

Patients who underwent treatment intensification and remained enrolled in the health plan for 12 mo after the intensification date n = 10,425

Patients who did not undergo treatment intensification and remained enrolled in the health plan for 12 mo after a randomly selected date n = 5,715

OAD cohort

BI cohort

FIGURE 2  Study population attrition for the OAD and the BI cohorts. A1C, glycated haemoglobin A1c; BI, basal insulin; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; OAD, oral antidiabetes drug; SGLT-2, sodium glucose cotransporter 2; T2D, type 2 diabetes

dose, or to add bolus insulin, presents less of a barrier for both patients and physicians than taking the step to initiate a first injectable therapy for patients treated with only OADs. Additionally, patients who are already on insulin are likely to be treated by an endocrinologist, whereas patients on OADs are more likely to be treated by a primary care physician, who may have less expertise in the treatment of T2D than an endocrinologist and may be less aggressive in treatment intensification. It should be noted, however, that details of treating physicians were not available for this study and were not included in the analysis.

The high rate of clinical inertia in our study is in agreement with results obtained in another insurance claims analysis in the United States. Among more than 11,500 patients with A1C levels ≥8% after 3 months of treatment with metformin ± other OADs, 52% did not have their regimen adjusted within 12 months of evidence of poor glycaemic control. Additionally, a population-based analysis of patients treated with BI in Denmark showed that only 43.7% had undergone treatment intensification after a median of 11 months.

The most frequent intensification strategies for patients uncontrolled on dual OAD therapy in our study were the addition of a third OAD (DPP-4 inhibitor or another agent other than SGLT-2 and DPP-4 inhibitors), whereas most patients who were receiving BI pre-study increased their daily doses of BI, with a small proportion adding bolus insulin, an SGLT-2 inhibitor, or a GLP-1 RA. Similar results were obtained in other real-world studies in the United States. In a retrospective analysis of an insurance claims database, most patients uncontrolled on dual OAD therapy received a prescription for a third OAD (79.3%) compared with insulin (13.3%) or a GLP-1 RA (7.4%), possibly reflecting the convenience of oral agents. A more recent study reported insulin (32.4%), DPP-4 inhibitors (22.1%) and thiazolidinediones (21.2%) as the most frequently prescribed drugs among patients with A1C levels uncontrolled after 3 months of treatment with metformin plus another OAD. In a study of older patients receiving BI, approximately 64% had their doses increased, while only
Many patients with T2D are overweight or obese, which are independent risk factors for cardiovascular disease.22 Unfortunately, many antidiabetes treatments aimed at maintaining and improving glucose control are associated with weight gain. A number of studies have implicated BI use as a potential cause of weight gain in people with T2D.23,24

**TABLE 1** Baseline demographic and clinical characteristics of eligible patients on dual OADs (N = 28 123) or BI (N = 16 140)

|                        | OAD cohort | BI cohort |
|------------------------|------------|-----------|
|                        | TI (n = 3990) | NTI (n = 24 133) | TI (n = 10 425) | NTI (n = 5715) |
| **Age, mean (SD), y**  | 58.3 (11.3)* | 61.3 (11.8) | 61.1 (11.3)* | 62.2 (11.4) |
| **Male, n (%)**        | 2355 (59.0)** | 13 808 (57.2) | 5573 (53.5) | 3045 (53.3) |
| **Geographic region, n (%)** |           |            |              |              |
| Northeast              | 484 (12.1)** | 3219 (13.3) | 1146 (11.0)** | 709 (12.4) |
| Midwest                | 513 (12.9) | 3249 (13.5) | 1620 (15.5) | 893 (15.6) |
| South                  | 2526 (63.3) | 15 021 (62.2) | 6275 (60.2) | 3423 (59.9) |
| West                   | 467 (11.7) | 2641 (10.9) | 1383 (13.3)** | 690 (12.1) |
| **Other**              | 0 (0.0) | 3 (0.0) | 1 (0.0) | 0 (0.0) |
| **Health insurance plan, n (%)** |           |            |              |              |
| Commercial             | 2715 (68.1)* | 14 121 (58.5) | 6020 (57.8)* | 3050 (53.4) |
| Medicare advantage     | 1275 (32.0)* | 10 012 (41.5) | 4405 (42.3)* | 2665 (46.6) |
| **DCSI, mean (SD)**    | 0.81 (1.30) | 0.82 (1.28) | 1.34 (1.68) | 1.36 (1.68) |
| **Index A1C, mean (SD), %** | 8.8 (1.6)* | 8.0 (1.2) | 8.9 (1.7)* | 8.6 (1.6) |
| **Pre-intensification OADs, n (%)** |           |            |              |              |
| Metformin              | 3665 (91.9)* | 22 516 (93.3) | 6266 (60.1)* | 3637 (63.6) |
| Sulfonylureas          | 3228 (80.9)* | 20 324 (84.2) | 4555 (42.7)* | 2621 (45.9) |
| Thiazolidinediones     | 878 (22.0)* | 4190 (17.4) | 1328 (12.7)** | 795 (13.9) |
| Meglitinides           | 48 (1.2) | 217 (0.9) | 252 (2.4) | 155 (2.7) |
| DPP-4 inhibitors       | N/A | N/A | 2057 (19.7) | 1173 (20.5) |
| Alpha-glucosidase inhibitors | 19 (0.5)** | 57 (0.2) | 51 (0.5) | 40 (0.7) |
| Ergot derivatives      | 6 (0.2)** | 14 (0.1) | 9 (0.1) | 8 (0.1) |
| **Pre-intensification comorbidities, n (%)** |           |            |              |              |
| Hypertension           | 3070 (76.9) | 18 773 (77.8) | 8424 (80.8) | 4643 (81.2) |
| Disorders of lipid metabolism | 3127 (78.4) | 18 808 (77.9) | 8109 (77.8)** | 4557 (79.7) |
| Diabetes with complications | 2243 (56.2)* | 11 794 (48.9) | 6804 (65.3) | 3716 (65.0) |
| Diseases of the heart  | 998 (25.0)* | 6627 (27.5) | 3599 (34.5) | 1938 (33.9) |
| Eye disorders          | 940 (23.6)* | 6350 (26.3) | 3066 (29.4) | 1751 (30.6) |
| Other connective tissue diseaseb | 782 (19.6) | 4785 (19.8) | 2722 (26.1)** | 1387 (24.3) |
| **Pre-intensification diabetes-related resource utilization, n (%)** |           |            |              |              |
| Ambulatory visit       | 3748 (93.9) | 22 818 (94.6) | 9928 (95.2)* | 5526 (96.7) |
| ED visit               | 328 (8.2) | 1833 (7.6) | 1228 (11.8)** | 610 (10.7) |
| Hospitalization        | 216 (5.5) | 1162 (4.8) | 858 (8.2) | 431 (7.5) |
| **Pre-intensification diabetes-related costs, mean (SD), $** |           |            |              |              |
| Medical + pharmacy     | 2340 (8130)** | 1954 (6788) | 4230 (10 794)** | 3829 (8085) |

A1C, glycated haemoglobin A1C; BI, basal insulin; DCSI, Diabetes Complications Severity Index; DPP-4, dipeptidyl peptidase-4; ED, emergency department; N/A, not available; NTI, no treatment intensification; OAD, oral antidiabetes drug; SD, standard deviation; TI, treatment intensification. P values refer to intensification ≤6 mo after the index date vs no intensification.

aPre-intensification comorbidities were based on the comorbidity categories designated by the Agency for Healthcare Research and Quality and is based on ICD-9-CM codes.15

bExcludes gout, arthritis, spondylosis, osteoporosis, fractures and lupus.

*P ≤ .001.

**P < .05.

25% initiated treatment with rapid-acting insulin, with fewer than 10% of the patients adding a GLP-1 RA or another injectable agent.17

Many patients with T2D are overweight or obese, which are independent risk factors for cardiovascular disease.22 Unfortunately,
targets, where addition of a GLP-1 RA was associated with significant weight loss and a lower risk of hypoglycaemia, as well as equivalent or slightly better glycaemic control than the addition of prandial insulin. Nevertheless, the use of GLP-1 RAs in the intensification strategies observed in our study appears to be low. Furthermore, administration of GLP-1 RA requires fewer injections and is associated with a lower rate of hospitalization and lower all-cause healthcare costs than rapid-acting insulin. Nonetheless, approximately 10% of the patients in the BI cohort had their regimens intensified with bolus insulin and only about 2% received a prescription for a GLP-1 RA. Our study thus shows that clinical practice is not completely aligned with current treatment guidelines and data from clinical trials, most likely reflecting slow adaptation to an increasing body of evidence.

As expected, TI within 6 months of the first elevated measure of A1C was associated with better glycaemic control vs NTI in both cohorts, but was associated with a higher rate of hypoglycaemia, primarily driven by basal-bolus insulin and BI dose increases.

This study is subject to a number of possible limitations. Possible confounders, which may affect treatment intensification decisions including the nature of the prescribing physician and the site of the prescribing physician, were not investigated. Prescription data were obtained from outpatient pharmacy settings, prescription fills were not provided in inpatient settings. Outcomes analyses based on claims databases are naturally associated with selection bias and reduced generalizability to the general diabetes population. Data interpretation may be affected by diagnosis-coding errors and the absence of confirmation of the diagnoses captured in the database. Information on use of weekly or daily GLP-1 RA was not captured. BI dose was estimated based on quantities supplied and days between pharmacy refills, according to pharmacy claims data, but the actual dosing schedule and dose administered are unknown. Additionally, it is possible that some patients who were still undergoing titration of their BI were classified as receiving treatment intensification.

Further baseline A1C levels and higher insulin dose requirements have been shown to be independently associated with greater weight gain. Weight reduction is an important element of T2D management, as weight gain may contribute to patient frustration, which can have a negative impact on therapy persistence and adherence. The selection of antidiabetes agents that not only improve glucose control but reduce or have a neutral effect on weight, with beneficial effects on lipids, are ideal options for managing patients with T2D.

Several reports have demonstrated the effectiveness of including a GLP-1 RA in the BI regimens of patients who do not achieve

**FIGURE 3** Adjusted change in A1C from index date to 12 mo after TI in patients with T2D with TI (A) following dual OAD therapy vs NTI (N = 17,334) and (B) following BI therapy vs NTI (N = 9,937). A1C, glycated haemoglobin A1c; BI, basal insulin; NTI, no treatment intensification; T2D, type 2 diabetes; TI, treatment intensification.

| TABLE 2 Hypoglycaemia rates and adjusted hypoglycaemia odds ratio for patients with T2D undergoing TI vs NTI |
|---------------------------------------------------------------|---------------|----------------|----------------|----------------|----------------|
|                                                               | OAD cohort     |                |                | BI cohort       |                |
|                                                               | TI (n = 3990)  | NTI (n = 24,133) | P value | TI (n = 10,425) | NTI (n = 5,715) | P value |
| Overall hypoglycaemia, %                                     | 4.9            | 3.2            | <.001         | 6.9            | 5.8            | .004   |
| Severe hypoglycaemia, %                                      | 1.4            | 0.9            | .005          | 2.6            | 2.0            | .031   |
| Hypoglycaemia, OR (95% CI)                                   | 1.68 (1.41-2.01) |               | <.001         | 1.23 (1.07-1.41) |               | .004   |

BI, basal insulin; CI, confidence interval; OAD, oral antidiabetes drug; OR, odds ratio; NTI, no treatment intensification; T2D, type 2 diabetes; TI, treatment intensification.
were no limitations on medication changes that may have taken place after the random intensification date. Data on duration of disease, adherence to treatment and discontinuation rates were not collected. Also, data on fasting plasma glucose or postprandial glucose were not available, making it difficult to judge if the appropriate agent was selected for a particular glycaemic defect. A1C results are available for a subset of patients in the Optum Research Database, and only patients with sufficient A1C measures were retained for analysis. Due to the nature of claims data our study is likely to underreport hypoglycaemia, as only clinically significant events resulting in contact with a healthcare professional would be captured in data based on the ICD-9-CM/ICD-10-CM codes, moreover, the definition of severe hypoglycaemia used differed from that generally used in clinical trials which also capture data on events which required assistance. The decision to proceed to TI was based on an A1C goal of 7.0%, which may not have been recommended for all patients in this study according to the current ADA treatment guidelines.

In conclusion, the main goal of treatment of T2D is to control hyperglycaemia in order to prevent or delay disease progression, and a stepwise approach is commonly used to counteract continued suboptimal glycaemic control despite therapy. However, intensification may involve a higher risk of hypoglycaemia, which may affect compliance. In this study, we analysed A1C reductions and the incidence of hypoglycaemia in patients intensifying treatment after therapy with OADs or BI in real-world clinical practice. The addition of a DPP-4 inhibitor or a new OAD, and BI dose increases, was the most common intensification strategies for patients receiving dual OAD therapy or BI, respectively. Despite treatment intensification not being initiated as frequently as one would expect in patients with suboptimal glycaemic measurements, our data show that it resulted in improved A1C levels, albeit accompanied by an increase in the number of hypoglycaemia events. Our study provides insights into the practice of treatment intensification in the real world; it highlights a need for new and/or improved antidiabetes agents that effectively manage glycaemia while reducing hypoglycaemia risk, as well as the need to address policy challenges that contribute to clinical inertia among healthcare professionals.

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CONFLICT OF INTEREST

Buysman and Blauer-Peterson are employees of Optum US, Inc., under contract with Sanofi US, Inc. Miller-Wilson is an employee and stock/shareholder of Sanofi US, Inc. Fan was an employee of Sanofi US, Inc. at the time the study was conducted.

AUTHOR CONTRIBUTIONS

E.B. and C.B.-P contributed to designing the study and acquiring the data. L.-A.M.-W. and T.F contributed to designing the study. All authors contributed to the data analysis and interpretation and critically reviewed the manuscript.

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REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes – 2017. Diabetes Care. 2017;40(Suppl. 1):S1–S135.
2. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38:140–149.
3. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2017 executive summary. Endocr Pract. 2017;23:207–238.
4. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988–2010. Diabetes Care. 2013;36:2271–2279.
5. Triplitt C. Improving treatment success rates for type 2 diabetes: recommendations for a changing environment. Am J Manag Care. 2010;16(7 Suppl.):S195–S200.
6. Hsu WC. Consequences of delaying progression to optimal therapy in patients with type 2 diabetes not achieving glycemic goals. South Med J. 2009;102:67–76.
7. Dunn JD. Diabetes pharmacy management: balancing safety, cost, and outcomes. Am J Manag Care. 2010;16(7 Suppl.):S201–S206.
8. Zieman DC, Miller CD, Rhee MK, et al. Clinical inertia contributes to poor diabetes control in a primary care setting. Diabetes Educ. 2005;31:564–571.
9. Kurt T, Snoek FJ. Barriers to insulin initiation and intensification and how to overcome them. Int J Clin Pract. 2009;63(4 Suppl.):6–10.
10. Zafar A, Stone MA, Davies MJ, Khunti K. Acknowledging and allocating responsibility for clinical inertia in the management of type 2 diabetes in primary care: a qualitative study. Diabet Med. 2015;32:407–413.
11. Optum. Real world health care experiences from over 150 million unique individuals since 1993. https://www.optum.com/content/dam/optum/resources/productSheets/5302_Data_Assets_Chart_Sheet_ISPOR.pdf. Accessed February 20, 2018.
12. Young BA, Lin E, Von Korff M, et al. Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. Am J Manag Care. 2008;14:15–23.
13. Chang HY, Weiner JP, Richards TM, Bleich SN, Segal JB. Validating the adapted Diabetes Complications Severity Index in claims data. Am J Manag Care. 2012;18:721–726.
14. Ginde AA, Blanch PG, Lieberman RM, Camargo CA. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycaemia visits. BMC Endocr Disord. 2008;8:4.
15. Agency for Healthcare Research and Quality. Clinical Classifications Software (CCS) for ICD-9-CM (software). https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp. Accessed February 20, 2018.
16. Fu AZ, Sheehan JJ. Treatment intensification for patients with type 2 diabetes and poor glycaemic control. Diabetes Obes Metab. 2016;18:892-898.

17. Hopson SD, Ye F, Mudumby P, Fan T, Dufour R, Renda AM. Factors associated with nonintensification of insulin therapy among patients with type 2 diabetes. Diabetes. 2017;66(Suppl 1):A449.

18. Khunti K, Nikolajsen A, Thorsted BL, et al. Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. Diabetes Obes Metab. 2016;18:401-409.

19. Blak BT, Smith HT, Hard M, Curtis BH, Ivanyi T. Optimization of insulin therapy in patients with type 2 diabetes mellitus: beyond basal insulin. Diabet Med. 2012;29:e13-e20.

20. Thomsen RW, Baggesen LM, Sagaard M, et al. Effectiveness of intensification therapies in Danes with type 2 diabetes who use basal insulin: a population-based study. Diabet Med. 2017;34:213-222.

21. Levin PA, Wei W, Zhou S, Xie L, Baser O. Outcomes and treatment patterns of adding a third agent to 2 OADs in patients with type 2 diabetes. J Manag Care Spec Pharm. 2014;20:501-512.

22. Fox CS, Pencina MJ, Wilson PW, et al. Lifetime risk of cardiovascular disease among individuals with and without diabetes stratified by obesity status in the Framingham heart study. Diabetes Care. 2008;31:1582-1584.

23. Larger E. Weight gain and insulin treatment. Diabetes Metab. 2005;31(4 Pt 2):4551-4556.

24. Pontiroli AE, Miele L, Morabito A. Increase of body weight during the first year of intensive insulin treatment in type 2 diabetes: systematic review and meta-analysis. Diabetes Obes Metab. 2011;13:1008-1019.

25. Shaefer CF, Reid TS, Dailey G, et al. Weight change in patients with type 2 diabetes starting basal insulin therapy: correlates and impact on outcomes. Postgrad Med. 2014;126:93-105.

26. Balkau B, Home PD, Vincent M, Marre M, Freemantle N. Factors associated with weight gain in people with type 2 diabetes starting on insulin. Diabetes Care. 2014;37:2108-2113.

27. Leslie WS, Hankey CR, Lean ME. Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review. QJM. 2007;100:395-404.

28. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet. 2014;384:2228-2234.

29. Charbonnel B, Bertolini M, Tinahones FJ, Domingo MP, Davies M. Liixisenatide plus basal insulin in patients with type 2 diabetes mellitus: a meta-analysis. J Diabetes Complications. 2014;28:880-886.

30. Dalal MR, Xie L, Baser O, DiGenio A. Adding rapid-acting insulin or GLP-1 receptor agonist to basal insulin: outcomes in a community setting. Endocr Pract. 2015;21:68-76.

31. Wysham CH, Lin J, Kuritzky L. Safety and efficacy of a glucagon-like peptide-1 receptor agonist added to basal insulin therapy versus basal insulin with or without a rapid-acting insulin in patients with type 2 diabetes: results of a meta-analysis. Postgrad Med. 2017;129:436-445.

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