Early hypoglycaemia and adherence after basal insulin initiation in a nationally representative sample of Medicare beneficiaries with type 2 diabetes

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Abstract
Aims: To estimate risk factors associated with early hypoglycaemia and its impact on adherence to and persistence with therapy in Medicare Part D beneficiaries with type 2 diabetes who are initiating basal insulin (BI).

Materials and methods: This retrospective analysis used a 5% sample of Medicare files from 2007–2013, identifying beneficiaries with type 2 diabetes initiating BI from 1 January 2008 to 31 December 2012. Early hypoglycaemia was defined as ≥1 hypoglycaemic event ≤6 months postindex. Outcomes included medication adherence and persistence over 12- and 36-month follow-up. Multivariable logistic and Cox regression analyses were conducted to examine factors associated with early hypoglycaemia and BI adherence/persistence.

Results: Of the 14,466 included patients, 1,315 (9.1%) experienced hypoglycaemia ≤6 months after initiating BI. Factors associated with early hypoglycaemia were female sex (odds ratio [OR] 1.16 [95% confidence interval [CI] 1.02–1.32]), receipt of a low-income subsidy under Medicare Part D (OR 1.20 [95% CI 1.01–1.43]), high diabetes complication score index (OR 1.08 [95% CI 1.01–1.15]), and hypoglycaemia during the baseline period (OR 4.24 [95% CI 3.63–4.96]). At 12 months, patients with baseline hypoglycaemia were less likely to be adherent to their insulin therapy (OR 0.81 [95% CI 0.70–0.93]) and more likely to discontinue (OR 1.33 [95% CI 1.07–1.66]) compared to patients without hypoglycaemia. Results were similar at 36 months.

Conclusions: Within 6 months of BI initiation, almost 1 in 10 Medicare Part D beneficiaries experienced hypoglycaemia. Early hypoglycaemia was associated with decreased adherence to BI treatment over 12- and 36-month follow-up.

KEYWORDS
adherence, hypoglycaemia, Medicare, type 2 diabetes
The number of people with type 2 diabetes continues to grow. Recent estimates suggest that close to 400 million people worldwide and approximately 29 million people in the USA have type 2 diabetes, including an estimated 25% of US adults aged ≥65 years, or approximately 12 million people. Elderly Americans comprise only 13% of the US population but represent >40% of prevalent cases of diabetes. In 2013, 26.9% of fee-for-service Medicare beneficiaries carried a diagnosis of diabetes, representing the fourth most common chronic condition among individuals covered by Medicare. Additionally, diabetes has substantial co-morbidity with the two most common chronic conditions, hypertension and hyperlipidaemia.

Current national guidelines recognize the long-term consequences of uncontrolled hyperglycaemia in type 2 diabetes patients; however, many patients with type 2 diabetes who could benefit from improved glycaemic control are not prescribed basal insulin (BI) despite having uncontrolled blood glucose levels. Population-based data suggest that delays of ≥7 years in necessary intensification of insulin treatment are common, with patients often having excessive hyperglycaemia (HbA1c > 9.0% [>75 mmol/mol]) during that time. This delay contributes to cardiovascular complications and mortality in patients with type 2 diabetes. Reasons for the delay in insulin initiation include reluctance of clinicians and patients because of insulin-associated weight gain, hypoglycaemia, a misunderstanding of insulin's efficacy, and patient objections to injected therapy. Multiple surveys have reported fear of hypoglycaemia as a leading reason for the delay of insulin initiation among both patients and clinicians. In an international survey, 75.5% of physicians said that hypoglycaemia is a key reason why they delay or avoid initiation of insulin. Among patients with type 2 diabetes who initiate BI, only about 30% achieve their individual glycaemic target, primarily because of a fear of hypoglycaemia limits proper titration. Additionally, patients who are concerned about hypoglycaemia are more likely to discontinue their insulin therapy. Furthermore, patients who do initiate insulin may experience early hypoglycaemia (ie within 6 months of initiation), which may lead to poor insulin adherence and a higher risk of hospitalization, especially in older and disabled patients. Older patients make up the majority of patients with type 2 diabetes and are at a higher risk of hypoglycaemia because of a number of factors, including age-related changes in renal and hepatic metabolism, co-morbid illness, and polypharmacy. Even mild cognitive dysfunction might increase the risk of experiencing severe hypoglycaemia. Many of the symptoms of hypoglycaemia, including dizziness, confusion, weakness, impaired vision and rapid heartbeat, are particularly concerning for elderly individuals, adding to an already increased risk of falls, frailty, depressive symptoms, cognitive impairment, and other complications in this population.

The American Diabetes Association makes specific mention of the importance of avoiding hypoglycaemia among older patients with type 2 diabetes because of its detrimental effects on cognition and other health outcomes. To improve outcomes for patients with type 2 diabetes, an understanding of factors associated with early hypoglycaemia among elderly and disabled patients initiating BI and its effect on adherence to BI treatment is an important first step. However, limited data exist on these issues in the Medicare-insured population. This study aimed to address this gap in the literature, using a nationally representative sample of Medicare beneficiaries to (a) examine the incidence and risk factors associated with early hypoglycaemia events in Medicare beneficiaries with type 2 diabetes who are newly initiating BI, and (b) examine the association between early hypoglycaemia and BI treatment adherence and persistence.

### 2 | MATERIALS AND METHODS

#### 2.1 | Data source

Data on Medicare beneficiaries with type 2 diabetes [International Statistical Classification of Diseases and Related Health Problems (ICD)-9-CM code 250.x0 or 250.x2] were extracted from the 2007–2013 Chronic Conditions Data Warehouse (CCW) 5% Medicare files available from the Centers for Medicare and Medicaid Services (CMS). These files included Part A and Part B medical claims for inpatient care, skilled nursing facility care, home health services, outpatient services, durable medical equipment, and hospice services as well as Part D prescription claims files for outpatient prescription drug events for a 5% random sample of Medicare beneficiaries. These files were linked to personal summary files that contained patient demographics and eligibility information, as well as Part D plan characteristics files and formulary files.

#### 2.2 | Study design and sample

This was a retrospective cohort study design. For both study aims, inclusion criteria included patients with type 2 diabetes newly initiating BI during the identification period from 1 January 2008 to 31 December 2012 (the index date was the date that BI was initiated), continuous Medicare fee-for-service medical (Parts A and B) and prescription drug (Part D) coverage during the baseline period (12 months before index date) and follow-up period (12 months after index date for the 1-year follow-up sample, 36 months after index date for the 3-year follow-up sample), ≥1 inpatient or ≥2 outpatient claims for type 2 diabetes, and ≥1 oral antidiabetes drug or a glucagon-like peptide-1 receptor agonist claims at baseline. Exclusion criteria included a type 1 diabetes diagnosis and ≥1 claim for BI during the baseline period. Additionally, patients with a ≥90-day continuous gap on BI treatment starting within the 6-month postindex period were excluded from the sample used for the second study aim of examining the association between early hypoglycaemia and BI treatment persistence (Figure S1).

#### 2.3 | Outcomes

The first outcome of interest was ‘early’ hypoglycaemia, defined as the occurrence of hypoglycaemia within 6 months of initiating BI therapy (insulin glargine, insulin detemir, or insulin NPH). Hypoglycaemia was identified by a claims-based algorithm (ICD-9 codes: 251.0, 251.1, 251.2, or 962.3) as a primary or secondary diagnosis of the
inpatient and outpatient claims. A claim for ICD-9 code 250.8 in the absence of other concurrent contributing diagnoses (ICD-9 code: 259.8, 272.7, 681.XX, 682.XX, 686.9X, 707.1–707.9, 709.3, 730.0–730.2, or 731.8) was also used to identify a hypoglycaemia episode. Furthermore, hypoglycaemia was identified by the presence of administration of intramuscular glucagon, indicated by National Drug Code (NDC) and Healthcare Common Procedure Coding System (HCPCS) codes. Early hypoglycaemia was defined as ≥1 hypoglycaemic event occurring during the period from the index date through to month 6 of the follow-up period.

Other additional outcomes of interest included adherence and persistence over 12-month follow-up periods (adherence and persistence were measured over a 36-month follow-up period in the sensitivity analysis). Adherence to BI was assessed using the proportion of days covered (PDC) measure. PDC was calculated by spreading the reported days’ supply from each insulin prescription from the fill date to the date the supply would have been exhausted, and then calculating whether each day in the period was covered by any insulin prescription fill. Patients were defined as adherent to BI with a PDC ≥0.80. A treatment gap was identified when a patient’s claims data indicated a continuous gap of ≥90 days with no supply of any BI. Persistence with BI was defined as the time from BI initiation to first 90-day gap (ie days with continuous treatment without gaps of ≥90 days) or to the end of the follow-up period.

2.4 Statistical analysis and covariates

Descriptive sample characteristics were generated for the sample of patients initiating a new BI. ANOVA and χ² tests were used to assess differences between patients with and without early hypoglycaemia. Multivariable logistic regressions were used to examine factors associated with early hypoglycaemia and the association between early hypoglycaemia and binary outcomes of adherence and the continuous ≥90-day BI gap. Multivariable Cox regression was used to analyze the association between early hypoglycaemia and time to first continuous ≥90-day BI gap. Multivariable logistic regressions and Cox regression were adjusted for sociodemographics, clinical variables, Part D plan benefit-related variables, Part D plan formulary characteristics, and index year.

Sociodemographic variables included the beneficiary’s age, sex, race, reason for Medicare eligibility (because of age, disability or end-stage renal disease), Medicare Part D low-income subsidy (LIS) status (eligible for full LIS or not eligible for LIS), census region of residence, metropolitan status, per capita income (US$), number of primary care doctors per 10 000 residents, and education level in the beneficiary’s county of residence.

Clinical variables included diabetes complications (ie hypoglycaemia, neuropathy, nephropathy or retinopathy) or other co-morbidities (ie myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue/rheumatic disease, peptic ulcer, mild or moderate-to-severe chronic liver disease, paraplegia and hemiplegia, chronic renal disease, non-metastatic or metastatic cancer, HIV/AIDS, hypertension, hyperlipidaemia or obesity) during the baseline period, adapted Diabetes Complications Severity Index (aDCSI),20 non-insulin antidiabetes medication used during the baseline period, number of hospitalizations with type 2 diabetes as the primary diagnosis in the baseline period, and prescription drug hierarchical condition category (RxHCC) risk score,21 which has been used to adjust for potential selection biases in drug-use studies among Medicare patients.22–24 Clinical variables were coded based on claims during the 12-month baseline period; all other variables were coded during the year of the index date (index year). Part D prescription drug plan benefit-related variables included Medicare Part D plan type (defined standard benefit, actuarially equivalent standard, basic alternative and enhanced alternative), plan coverage for coverage gap (defined by no coverage or unknown, coverage for generic drugs, and coverage for brand and generic drugs), Part D plan formulary coverage for BI, and plan utilization management tools (mean proportion of BI subjected to prior authorization, step therapy, or quantity limits in the plan).

3 RESULTS

3.1 Sample characteristics

A total of 14 466 patients met the final study criteria (Figure S1). The mean age of all patients was 69 ± 13 years; most patients were Caucasian (75.64%); approximately 40% qualified for Medicare primarily as a result of disability; approximately 60% had Medicare Part D LIS status; and approximately 66% were from the south or midwest regions (Table 1). In this sample, 1315 (9.1%) patients experienced hypoglycaemia during the first 6 months of BI therapy. Patients who experienced early hypoglycaemia more likely to have full LIS status (63.65% vs 58.65%, P < 0.001). They were also more likely to have a history of hypoglycaemia and co-morbid illnesses (e.g. myocardial infarction, congestive heart failure, and peripheral vascular disease, cerebrovascular disease, peptic ulcer disease, and chronic renal disease) during the baseline period.

3.2 Factors associated with early hypoglycaemia

Baseline factors associated with early hypoglycaemia in the multivariable logistic regression were female sex (P = 0.026), being a full LIS patient (P = 0.043), having a larger number of inpatient claims with type 2 diabetes (P = 0.003), having a high adapted Diabetes Complications Severity Index (aDCSI) (P = 0.029), the presence of connective tissue disease/rheumatic disease (P = 0.002), and having hypoglycaemia during the baseline period (P < 0.001; Table 2).

3.3 Association of early hypoglycaemia and insulin adherence and persistence

Over the 12-month follow-up, patients with early hypoglycaemia were less likely to be adherent to observed adherence 20.6% vs 25%; odds ratio [OR] based on multivariable logistic regression 0.81 [95% confidence interval [CI] 0.70–0.93]) and more likely to discontinue
| Characteristic                      | No hypoglycaemia within the 6-mo. follow-up n = 13,151 | Hypoglycaemia within the 6-mo. follow-up n = 1,315 | P-value |
|------------------------------------|--------------------------------------------------------|--------------------------------------------------|---------|
| Mean age, years, (SD)              | 69.16 (12.66)                                          | 71.03 (13.07)                                    | <.001   |
| Age group, years                   |                                                        |                                                  | <.001   |
| <65                                | 3627 (27.58%)                                          | 323 (24.56%)                                     |         |
| 65–69                              | 2303 (17.51%)                                          | 175 (13.31%)                                     |         |
| 70–74                              | 2651 (20.16%)                                          | 247 (18.78%)                                     |         |
| 75–79                              | 1928 (14.66%)                                          | 230 (17.49%)                                     |         |
| ≥80                                | 2642 (20.09%)                                          | 340 (25.86%)                                     |         |
| Sex                                |                                                        |                                                  |         |
| Female                             | 7767 (59.06%)                                          | 834 (63.42%)                                     | .002    |
| Race                               |                                                        |                                                  | .005    |
| White                              | 10,215 (77.67%)                                        | 968 (73.61%)                                     |         |
| Black                              | 1677 (12.75%)                                          | 190 (14.45%)                                     |         |
| Latino                             | 616 (4.68%)                                            | 72 (5.48%)                                       |         |
| Other                              | 643 (4.89%)                                            | 85 (6.46%)                                       |         |
| Reason for Medicare eligibility    |                                                        |                                                  | <.001   |
| Age ≥ 65 years                     | 7699 (58.54%)                                          | 796 (60.53%)                                     |         |
| Disability                         | 5264 (40.03%)                                          | 481 (36.58%)                                     |         |
| ESRD                               | 188 (1.43%)                                            | 38 (2.89%)                                       |         |
| Part D LIS status                  |                                                        |                                                  | <.001   |
| Non-LIS                            | 5438 (41.35%)                                          | 478 (36.35%)                                     |         |
| Full LIS                           | 7713 (58.65%)                                          | 837 (63.65%)                                     |         |
| Census region of residence         |                                                        |                                                  | .286    |
| Northeast or unknown               | 2173 (16.52%)                                          | 218 (16.58%)                                     |         |
| Midwest                            | 3437 (26.13%)                                          | 355 (27.00%)                                     |         |
| South                              | 5372 (40.85%)                                          | 505 (38.40%)                                     |         |
| West                               | 2169 (16.49%)                                          | 237 (18.02%)                                     |         |
| Co-morbidities                     |                                                        |                                                  |         |
| Myocardial infarction              | 1437 (10.93%)                                          | 177 (13.46%)                                     | .005    |
| Congestive heart failure           | 3403 (25.88%)                                          | 460 (34.98%)                                     | <.0001  |
| Peripheral vascular disease        | 2375 (18.06%)                                          | 330 (25.10%)                                     | <.0001  |
| Cerebrovascular disease            | 2850 (21.67%)                                          | 392 (29.81%)                                     | <.0001  |
| Dementia                           | 976 (7.42%)                                            | 151 (11.48%)                                     | <.0001  |
| Chronic pulmonary disease          | 3947 (30.01%)                                          | 462 (35.13%)                                     | .0001   |
| Connective tissue disease/rheumatic disease | 649 (4.93%)              | 105 (7.98%)                                     | <.0001  |
| Peptic ulcer disease               | 340 (2.59%)                                            | 56 (4.26%)                                       | .000    |
| Paraplegia and hemiplegia          | 341 (2.59%)                                            | 55 (4.18%)                                       | .001    |
| Chronic renal disease              | 3310 (25.17%)                                          | 477 (36.27%)                                     | <.0001  |
| Cancer (non-metastatic)            | 1562 (11.88%)                                          | 176 (13.38%)                                     | .109    |
| Cancer (metastatic)                | 127 (0.97%)                                            | 20 (1.52%)                                       | .056    |
| Mild chronic liver disease         | 184 (1.40%)                                            | 17 (1.29%)                                       | .753    |
| Moderate or severe chronic liver disease | 264 (2.01%)              | 35 (2.66%)                                       | .112    |
| AIDS/HIV                           | 63 (0.48%)                                             | Not reportedb                                    | .617    |
| Hypertension                       | 12 138 (92.30%)                                        | 1228 (93.38%)                                    | .156    |
| Hyperlipidaemia                    | 10 909 (82.95%)                                        | 1065 (80.99%)                                    | .072    |
| Obesity                            | 2912 (22.14%)                                          | 291 (22.13%)                                     | .991    |

(Continues)
| Characteristic                                                                 | No hypoglycaemia within the 6-mo. follow-up n = 13 151 | Hypoglycaemia within the 6-mo. follow-up n = 1315 | P-value |
|--------------------------------------------------------------------------------|--------------------------------------------------------|---------------------------------------------------|---------|
| Diabetes complications                                                         |                                                        |                                                   |         |
| Hypoglycaemia                                                                  | 962 (7.32%)                                            | 385 (29.28%)                                       | <.0001  |
| Neupathy                                                                       | 2706 (20.58%)                                          | 350 (26.62%)                                       | <.0001  |
| Nephropathy                                                                    | 1324 (10.07%)                                          | 196 (14.90%)                                       | <.0001  |
| Retinopathy                                                                    | 1557 (11.84%)                                          | 171 (13.00%)                                       | .215    |
| Antidiabetes medication use during baseline period                              |                                                        |                                                   |         |
| GLP-1 RA                                                                       | 760 (5.78%)                                            | 67 (5.10%)                                         | .308    |
| DPP4 inhibitors                                                                 | 3422 (26.02%)                                          | 319 (24.26%)                                       | .164    |
| Biguanides                                                                      | 9568 (72.75%)                                          | 896 (68.14%)                                       | .000    |
| Thiazolidinediones                                                              | 4209 (32.01%)                                          | 425 (32.32%)                                       | .816    |
| Sulfonylurea                                                                    | 10 336 (78.59%)                                        | 1044 (79.39%)                                      | .501    |
| Meglitinide (prandial glucose regulators)                                       | 616 (4.68%)                                            | 71 (5.40%)                                         | .245    |
| α-Glucosidase inhibitors                                                       | 177 (1.35%)                                            | 24 (1.83%)                                         | .157    |
| Prandial insulin                                                                | 166 (1.26%)                                            | 28 (2.13%)                                         | .009    |
| aDCSI                                                                           | 2.1 (1.7)                                              | 2.7 (1.9)                                          | <.0001  |
| RxHCC risk score, mean (SD)                                                    | 1.2 (0.4)                                              | 1.4 (0.4)                                          | <.0001  |
| Number of inpatient claims with type 2 diabetes as the primary diagnosis       | 0.04 (0.21)                                            | 0.11 (0.37)                                        | <.0001  |
| Plan type, n                                                                   |                                                        |                                                   | .524    |
| Defined standard benefit                                                        | 1342 (10.2%)                                           | 133 (10.11%)                                       |         |
| Actuarially equivalent standard                                                 | 4886 (37.15%)                                          | 513 (39.01%)                                       |         |
| Basic alternative                                                               | 4187 (31.84%)                                          | 396 (30.11%)                                       |         |
| Enhanced alternative                                                            | 2736 (20.8%)                                           | 273 (20.76%)                                       |         |
| Plan coverage for coverage gap, n                                              |                                                        |                                                   | .195    |
| No coverage or unknown                                                          | 11 797 (89.70%)                                        | 1190 (90.49%)                                      |         |
| Coverage for generic drugs                                                      | 142 (1.08%)                                            | 19 (1.44%)                                         |         |
| Coverage for brand and generic drugs                                           | 1212 (9.22%)                                           | 106 (8.06%)                                        |         |
| Education level in the county of residence                                      |                                                        |                                                   | .986    |
| Low<sup>a</sup>                                                                 | 2187 (16.65%)                                          | 219 (16.67%)                                       |         |
| Metropolitan status                                                             |                                                        |                                                   | .040    |
| Urban                                                                           | 9037 (68.79%)                                          | 940 (71.54%)                                       |         |
| Part D plan formulary characteristics, mean (SD)                                |                                                        |                                                   | .378    |
| Mean proportion of BI on formulary                                              | 90 (13.8)                                              | 89.4 (14.6)                                        |         |
| Part D plan utilization management tools for BI, mean (SD)                      |                                                        |                                                   | .448    |
| Mean proportion of BI subjected to prior authorization                         | 6 (16.2)                                               | 6.4 (17)                                           |         |
| Mean proportion of BI subjected to step therapy                                 | 0.1 (1.2)                                              | 0.1 (1.3)                                          | .763    |
| Mean proportion of BI subjected to quantity limits                              | 6.3 (24)                                               | 7.1 (25.3)                                         | .211    |
| Per capita income, US$, mean (SD)                                              | 38 384.7 (10 962.2)                                    | 39 126.4 (11 354.4)                                | .001    |
| Number of PCP per 10 000 residents                                              | 0.6 (0.3)                                              | 0.6 (0.3)                                          | .112    |
| Index year                                                                      |                                                        |                                                   | .361    |
| 2008                                                                             | 2552 (19.41%)                                          | 267 (20.30%)                                       |         |
| 2009                                                                             | 2401 (18.26%)                                          | 264 (20.08%)                                       |         |
| 2010                                                                             | 2567 (19.52%)                                          | 249 (18.94%)                                       |         |
their insulin therapy (observed discontinuation rates 13.5% vs 10.1%; OR based on multivariable logistic regression 1.33 [95% CI 1.07–1.66]) (Tables 3 and 4).

Multivariable analysis results over the 36-month follow-up period similarly showed that patients with early hypoglycaemia had higher odds of insulin discontinuation (OR 1.31 [95% CI 1.03–1.67]). There was no statistically significant association between early hypoglycaemia and 3-year adherence (OR 0.84; \(P = .226\)). Consistent with logistic regressions on ≥90-day gap, Cox regression showed that early hypoglycaemia was associated with a higher hazard ratio (HR) of time to insulin discontinuation during the 12-month follow-up (HR 1.31; [95% CI 1.07–1.61]) and during the 36-month follow-up (HR 1.22 [95% CI 1.04–1.44]).

### 4 | DISCUSSION

This study is the first to provide a nationally representative analysis of the Medicare-insured population that examines the incidence of hypoglycaemia in new initiators of BI, factors associated with hypoglycaemia, and the association between early hypoglycaemia and patient adherence to and persistence with treatment. Our findings are consistent with a recent electronic medical record data analysis showing that patients with type 2 diabetes who have hypoglycaemia that occurs within the first 6 months after initiating BI were at an increased risk of discontinuing insulin compared with those who did not experience early hypoglycaemia.\(^{15}\) We found that early hypoglycaemia occurred in 9.1% of Medicare patients with type 2 diabetes who initiated BI. The real rate of hypoglycaemia is probably even higher as hypoglycaemia events that were not captured in claims data were not included, with the result that the incidence of hypoglycaemia is underreported.\(^{19,25}\) The risk for early hypoglycaemia was significantly associated with female sex, LIS status, inpatient resource use, higher aDCSI, presence of connective tissue/rheumatic disease, and hypoglycaemia during the baseline period. Some of these factors, such as prior hypoglycaemia, have been associated with hypoglycaemia risk in previous studies.\(^{26,27}\) In terms of the findings related to connective tissue disease, it is possible that the patients prone to hypoglycaemia have undiagnosed latent autoimmune diabetes of adults. Therefore, their total daily insulin need is low and thus hypoglycaemia occurs early in the process of titration. A unique finding of the present study is the observed association between increased hypoglycaemia risk and Medicare LIS. Potential reasons may be lower education and higher co-morbidity burden among patients who received the LIS, with such factors consistent with social deprivation, which is itself a risk factor for hospitalization for hypoglycaemia.\(^{27}\) Episodes of early hypoglycaemia may be modifiable by wider utilization of diabetes self-care management education. This information may be useful for targeting physicians’ efforts to improve treatment persistence among type 2 diabetes patients in these vulnerable groups.

Policy and guidelines could also be modified to address early hypoglycaemia in Medicare patients. Suitable measures might include a focus on vulnerable patient populations, such as females and those with the LIS. Although initiating insulin is an indication for diabetes education, only a small minority of patients access their Medicare diabetes education benefits.\(^{28}\) Barriers may include the limit of 10 hours of diabetes education per enrollee and lack of availability of certified diabetes education classes. As a result, many patients may not be receiving the assistance they require to successfully transition to insulin use. Insulin titration guidelines may also need to be considered as contributors to early hypoglycaemia with BI. The recommended approach to initiating BI involves patient self-titration to their fasting blood glucose. This approach may lead to hypoglycaemia in patients with variable blood sugars throughout the day. Another option is to consider BIs that are less likely to result in hypoglycaemia in vulnerable populations. The wider adoption of second-generation BIs, which offer favourable pharmacokinetic/pharmacodynamic profiles and potential benefits on the incidence of hypoglycaemia,\(^{29,30}\) might also alleviate the issue of hypoglycaemia in Medicare patients with type 2 diabetes.

There are several limitations inherent to this claims database analysis. First, the adherence and ≥ 90-day gap measures were based on claims filled for BI that did not indicate whether the BI was taken by the patients as prescribed. Furthermore, as is the case with all administrative claims database studies, we did not have information on the reasons for non-adherence or gaps for BI. Additionally, claims data do not include clinical details and, therefore, fail to capture important disease indicators, such as HbA1c and renal function markers. Furthermore, claims data are often inherently prone to underrepresenting hypoglycaemia as only ICD-9-CM/ICD-10-CM codes associated with a healthcare encounter are captured.\(^{19,25,31}\) In addition, this was an

### TABLE 1 (Continued)

| Characteristic | No hypoglycaemia within the 6-mo. follow-up n = 13 151 | Hypoglycaemia within the 6-mo. follow-up n = 1315 | P-value |
|---------------|------------------------------------------------------|-----------------------------------------------|---------|
| 2011          | 2728 (20.74%)                                        | 265 (20.15%)                                  |         |
| 2012          | 2903 (22.07%)                                        | 270 (20.53%)                                  |         |

Note: Numbers are reported per Centers for Medicare and Medicaid Services data use agreement because of cell size ≤10.

Abbreviations: BI, basal insulin; DPP4, dipeptidyl peptidase-4; ESRD, end-stage renal disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LIS, low-income subsidy; PCP, primary care practitioner; aDCSI, Adapted diabetes complication severity index; RxHCC, prescription drug hierarchica condition categories; SD, standard deviation.

\(^{a}\)≤25% of residents aged 25–64 years in the county had neither a high school diploma nor General Education Development.

\(^{b}\)Numbers are reported per Centers for Medicare and Medicaid Services data use agreement due to cell size of ≤10.
| Characteristic                                      | OR    | 95% CI    | P-value |
|----------------------------------------------------|-------|-----------|---------|
| **Age group, years**                               |       |           |         |
| <65 Reference                                      |       |           |         |
| 65–69                                              | 0.89  | 0.71-1.11 | .291    |
| 70–74                                              | 1.04  | 0.82-1.32 | .731    |
| 75–79                                              | 1.15  | 0.87-1.52 | .322    |
| ≥80                                                | 1.12  | 0.86-1.46 | .412    |
| **Sex**                                            |       |           |         |
| Female                                             | 1.16  | 1.02-1.32 | .026    |
| **Race**                                           |       |           |         |
| White Reference                                    |       |           |         |
| Black                                              | 1.10  | 0.90-1.34 | .341    |
| Latino                                             | 1.08  | 0.79-1.48 | .624    |
| Other                                              | 1.20  | 0.93-1.54 | .164    |
| **Reason for Medicare eligibility**                |       |           |         |
| Old age ≥65 years Reference                        |       |           |         |
| Disability                                         | 0.98  | 0.81-1.18 | .813    |
| ESRD                                               | 1.17  | 0.78-1.75 | .459    |
| **Part D LIS status**                              |       |           |         |
| None-LIS Reference                                  |       |           |         |
| Full-LIS                                           | 1.20  | 1.01-1.43 | .043    |
| **Census region of residence**                     |       |           |         |
| Northeast or unknown Reference                     |       |           |         |
| Midwest                                            | 1.15  | 0.95-1.39 | .164    |
| South                                              | 1.01  | 0.84-1.22 | .903    |
| West                                               | 1.11  | 0.89-1.38 | .355    |
| **Co-morbidities**                                 |       |           |         |
| Myocardial infarction                              | 0.90  | 0.74-1.10 | .316    |
| Congestive heart failure                           | 1.07  | 0.91-1.25 | .414    |
| Peripheral vascular disease                        | 1.06  | 0.89-1.24 | .525    |
| Cerebrovascular disease                            | 1.04  | 0.89-1.22 | .607    |
| Dementia                                           | 1.08  | 0.86-1.36 | .501    |
| Chronic pulmonary disease                          | 1.03  | 0.88-1.21 | .703    |
| Connective tissue disease/rheumatic disease        | 1.43  | 1.14-1.79 | .002    |
| Peptic ulcer disease                               | 1.23  | 0.89-1.69 | .211    |
| Paraplegia and hemiplegia                          | 1.19  | 0.87-1.63 | .275    |
| Chronic renal disease                              | 1.13  | 0.95-1.34 | .156    |
| Cancer (non-metastatic)                            | 1.05  | 0.88-1.26 | .583    |
| Cancer (metastatic)                                | 1.44  | 0.83-2.50 | .19     |
| Mild chronic liver disease                         | 0.67  | 0.37-1.22 | .188    |
| Moderate or severe chronic liver disease           | 1.18  | 0.78-1.80 | .429    |
| AIDS/HIV                                           | 0.64  | 0.23-1.75 | .384    |
| Hypertension                                       | 0.86  | 0.68-1.09 | .227    |
| Hyperlipidaemia                                    | 0.86  | 0.73-1.00 | .05     |
| Obesity                                            | 0.90  | 0.78-1.05 | .168    |
(Continues)
| Characteristic                                           | OR    | 95% CI     | P-value |
|---------------------------------------------------------|-------|------------|---------|
| **Diabetes complications**                              |       |            |         |
| Hypoglycaemia                                           | 4.24  | 3.63–4.96  | <.001   |
| Neuropathy                                              | 1.02  | 0.87–1.19  | .825    |
| Nephropathy                                             | 1.03  | 0.84–1.27  | .75     |
| Retinopathy                                             | 0.87  | 0.71–1.06  | .161    |
| **Antidiabetes medication use during baseline period**  |       |            |         |
| GLP-1 RA                                                | 1.11  | 0.85–1.44  | .461    |
| DPP4 inhibitors                                         | 0.98  | 0.86–1.13  | .788    |
| Biguanides                                              | 1.01  | 0.88–1.16  | .9      |
| Thiazolidinediones                                      | 1.02  | 0.90–1.16  | .746    |
| Sulfonyurea                                             | 1.00  | 0.86–1.16  | .989    |
| Meglitinide (prandial glucose regulators)               | 1.01  | 0.77–1.31  | .965    |
| α-glucosidase inhibitors                                | 1.32  | 0.83–2.08  | .237    |
| Prandial insulin                                        | 1.29  | 0.87–1.93  | .207    |
| aDCSI                                                   | 1.08  | 1.01–1.15  | .029    |
| RxHCC risk score                                        | 1.14  | 0.91–1.42  | .251    |
| **Number of inpatient claims with type 2 diabetes as the primary diagnosis** | 1.38  | 1.11–1.71  | .003    |
| **Plan type**                                           |       |            |         |
| Defined standard benefit                                | 0.73  | 0.56–0.96  | .027    |
| Actuarially equivalent standard                         | 0.80  | 0.63–1.02  | .066    |
| Basic alternative                                       | 0.79  | 0.64–0.98  | .028    |
| Enhanced alternative                                    | Reference |          |         |
| **Plan coverage for coverage gap**                      |       |            |         |
| No coverage or unknown                                  | Reference |          |         |
| Coverage for generic drugs                              | 0.79  | 0.60–1.04  | .089    |
| Coverage for brand and generic drugs                    | 1.42  | 0.90–2.24  | .128    |
| **Education level in the county of residence**          |       |            |         |
| Low                                                     | 0.94  | 0.78–1.12  | .483    |
| **Metropolitan status**                                 |       |            |         |
| Urban                                                   | 0.99  | 0.86–1.16  | .94     |
| Bi on formulary                                          | 1.00  | 0.99–1.00  | .088    |
| Prior authorization                                     | 1.00  | 1.00–1.00  | .663    |
| Step therapy                                            | 0.98  | 0.93–1.04  | .537    |
| Quantity limits                                         | 1.00  | 1.00–1.00  | .711    |
| **Per capita income, US$**                              | 1.00  | 1.00–1.00  | .201    |
| **Number of PCP per 10 000 residents**                  | 0.98  | 0.75–1.26  | .85     |
| **Year of index date**                                  |       |            |         |
| 2008                                                    | Reference |          |         |
| 2009                                                    | 1.07  | 0.89–1.28  | .487    |
| 2010                                                    | 0.96  | 0.80–1.15  | .653    |
| 2011                                                    | 0.90  | 0.73–1.10  | .302    |
| 2012                                                    | 0.89  | 0.73–1.09  | .249    |

Abbreviations: BI, basal insulin; CI, confidence interval; DPP4, dipeptidyl peptidase-4; ESRD, end-stage renal disease; LIS, low-income subsidy; OR, odds ratio; PCP, primary care practitioner; aDCSI, Adapted diabetes complication severity index; RxHCC, prescription drug hierarchical condition categories; SD, standard deviation.
observational study instead of a randomized controlled trial. If there are unmeasured confounders, such as disease severity, that correlated with early hypoglycaemia and adherence/persistence outcomes, the estimated correlation between hypoglycaemia and outcomes will be biased. To reduce this concern, we conducted a comprehensive risk adjustment by coding from the claims data information on patients’ co-morbidities, diabetes complications/severity, preindex medication use, and other risk factors (eg, age). Moreover, pharmacy claims data were only recorded for prescriptions that were paid for by the patients’ Part D plans. Claims datasets are, therefore, unable to capture instances when patients paid in cash for their prescription or received free drug samples. For the purposes of the present study, it was assumed that patients’ prescriptions were filled as the drug was needed, and patients were not discarding, hoarding or wasting unused insulin. Regardless, there is no reason to believe that these rates would have varied significantly between the two comparison groups in our study.

In this analysis, almost 1 in 10 Medicare Part D patients starting BI therapy experienced hypoglycaemia within 6 months of initiation. Moreover, patients who experienced early hypoglycaemia had poorer adherence to and persistence with BI treatment. Reducing the incidence of early hypoglycaemia has the potential to improve insulin adherence and outcomes for patients with type 2 diabetes. Therefore, it is important for clinicians to consider the hypoglycaemia risks associated with BI preparations and to work to minimize hypoglycaemia in older patients starting BI treatment, for example, through emphasizing the importance of blood glucose monitoring and adequate patient education to better manage the transition to insulin use. Given that this study showed that patients who experienced early hypoglycaemia had poorer adherence and persistence, such patients may benefit from more frequent and less aggressive insulin titration, more frequent healthcare professional visits and specialist referrals during the first year of BI initiation to address diabetes education and specialist care needs, and to improve glycaemic control, without the high risk of early hypoglycaemia. Prospective studies are needed to confirm these data, while additional research will allow a better understanding of the impact of hypoglycaemia on clinical outcomes associated with poor adherence and persistence.

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CONFLICT OF INTEREST

J.W. is an employee and stockholder of Sanofi. J.A.D. has served as an advisory board member or consultant for Allergan, Ironwood Pharmaceuticals, Kite Pharma, Merck, Otsuka, Regeneron, Sage Therapeutics, Sanofi, Shire, and Vertex; and has received research funding from Abbvie, Biogen, Humana, Janssen, Novartis, PhRMA, Regeneron, and Valeant, all unrelated to the content of this article. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

P.L. and J.A.D. designed the study. P.L., V.P.L. and J.A.D. acquired the data. All authors analyzed/interpreted the data and critically revised the manuscript.

| Characteristic                  | Without early hypoglycaemia | With early hypoglycaemia | P-value |
|--------------------------------|----------------------------|--------------------------|---------|
| Adherence to insulin (PDC ≥0.80), n (%) |                              |                          |         |
| During 12-mo. follow-up         | 25.0                        | 20.6                     | <.001   |
| During 36-mo. follow-up         | 16.1                        | 14.0                     | .197    |
| Having a ≥ 90-day gap on insulin, n (%) |                              |                          |         |
| During 12-mo. follow-up         | 10.1                        | 13.5                     | .007    |
| During 36-mo. follow-up         | 44.3                        | 50.3                     | .029    |

Abbreviation: PDC, proportion of days covered.

*Patients having a gap within the 6-mo. postindex period were excluded.

TABLE 3 Observed insulin adherence and persistence among those with and without early hypoglycaemia during the follow-up period

| Characteristic                  | With early hypoglycaemia (vs without as reference) | P-value |
|--------------------------------|---------------------------------------------------|---------|
| Logistic regression             | OR (95% CI)                                       |         |
| Adherence (PDC ≥0.80) to insulin| 0.81 (0.70–0.93)                                  | .003    |
| During 12-mo. follow-up         |                                                   |         |
| During 36-mo. follow-up         | 0.84 (0.64–1.11)                                  | .226    |
| Having ≥90-day gap on insulin   | 1.33 (1.07–1.66)                                  | .01     |
| During 12-mo. follow-up         |                                                   |         |
| During 36-mo. follow-up         | 1.31 (1.03–1.67)                                  | .025    |
| Cox regression (time to ≥90-day gap) | 1.31 (1.07–1.61)                                  | .01     |
| During 12-mo. follow-up         |                                                   |         |
| During 36-mo. follow-up         | 1.22 (1.04–1.44)                                  | .014    |

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; PDC, proportion of days covered.

*Patients having a gap within the 6-mo. postindex period were excluded.
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SUPPORTING INFORMATION

Additional supporting information may be found in the Supporting Information section at the end of this article.

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