Published in final edited form as:

Curr Med Res Opin. 2017 July ; 33(7): 1309–1316. doi:10.1080/03007995.2017.1318121.

Persistence with rapid-acting insulin and its association with A1C level and severe hypoglycemia among elderly patients with type 2 diabetes

Usha Sambamoorthi¹, Rahul Garg¹, Arijita Deb¹, Tao Fan², and Anders Boss²

¹Department of Pharmaceutical Systems and Policy, School of Pharmacy, West Virginia University, Morgantown, WV, USA

²Sanofi US, Inc., Bridgewater, NJ, USA

Abstract

Objective—To examine the persistence with rapid-acting insulin (RAI) and its association with clinical outcomes among elderly patients with type 2 diabetes (T2D).

Methods—This observational, retrospective cohort study analyzed RAI persistence and its association with change in A1C and risk of severe hypoglycemia among elderly (≥ 65 years) Medicare beneficiaries with T2D who added RAI to their basal insulin regimen.

Results—Among T2D patients with >1 RAI prescriptions (n=3,927), only 21% were persistent. Baseline factors positively associated with RAI persistence (Adjusted Odds Ratio [95% CI]) were: age ≥ 75 vs 65–74 years: 1.20 [1.01–1.43]; use of ≥ 3 oral antidiabetes drugs: 1.63 [1.16–2.28]; cognitive impairment: 1.34 [1.03–1.73]; and A1C >9.0%: 1.58 [1.15–2.17]. Elderly T2D patients having emergency department visits (0.73 [0.59–0.91]) and higher RAI out-of-pocket costs (≥ \$75 vs \$0 to <\$6.40: 0.56 [0.44–0.70]) were less likely to be persistent. Persistent RAI users had a significantly higher reduction in A1C (beta coefficient [standard error]: –0.24 [0.10]) and lower odds of severe hypoglycemia (Adjusted Odds Ratio [95% CI]): 0.73 [0.53–0.99].

Conclusion—Among elderly T2D patients, persistence with RAI added to basal insulin was associated with improved glycemic control, with lower risk of severe hypoglycemia. Despite treatment effectiveness, RAI persistence was poor and might be improved by reducing RAI out-of-pocket costs.

Correspondence: Usha Sambamoorthi, Department of Pharmaceutical Systems and Policy, School of Pharmacy, PO Box 9510, West Virginia University, Morgantown, WV 26506, USA. usambamoorthi@hsc.wvu.edu.

Contribution statement

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Transparency

Any opinions, findings, and conclusions or recommendations expressed in this manuscript are those of the authors and do not necessarily reflect the views of the organizations that supported the study.

Declaration of financial/other relationships

AD and RG have disclosed that they have no conflict of interest. US has disclosed that she has received grant funding from Sanofi US, Inc. to perform this study. TF and AB have disclosed that they are employees of Sanofi US, Inc., and AB was an employee of MannKind Corporation at the time of this research, is a stock holder of MannKind Corporation and Novo Nordisk, Inc. and holds several methods of use patents for inhaled insulin.

Keywords

Type 2 diabetes; rapid-acting insulin; persistence; hypoglycemia; A1C; elderly

Introduction

Current evidence-based clinical guidelines for patients with type 2 diabetes (T2D) recommend the addition of rapid-acting insulin (RAI) to basal insulin (BI) if postprandial glycemic goals are not met with BI or oral antidiabetes drugs (OADs) alone^{1–3}. Clinical trials have demonstrated the efficacy of RAI in achieving optimal postprandial A1C levels^{4,5}.

The chronic, progressive nature of T2D means that achieving and maintaining glycemic control depends on the persistent use of antidiabetes drugs, which eventually requires intensification over time. Most of the previous studies in this research area have evaluated persistence with OADs⁶, and only a few studies have examined persistence with BI in patients with T2D^{7–10}. Poorer persistence was found in T2D patients who initiated antidiabetes treatment with BI as compared to OADs (35.0% vs 69.2%, respectively)⁷. Although adding RAI to BI is a recommended clinical practice^{1–3}, only one study identified RAI persistence of 19.1% in patients with T2D who added RAI to their BI regimen¹¹. However, this study did not evaluate the effect of patients' clinical characteristics such as baseline A1C levels and hypoglycemia on RAI persistence, which are the most important guiding factors for RAI initiation and persistence. Further, the effect of RAI persistence on clinical outcomes such as change in A1C levels and risk of severe hypoglycemia have not been evaluated previously.

Research focusing on RAI use and persistence among elderly patients with T2D is critical because of the heterogeneity in the health status of this patient population and the effect of this heterogeneity on the management of T2D. The American Geriatrics Society, for example, recommends that geriatric syndromes (e.g., cognitive impairment, depression, falls and falls risk, polypharmacy, and urinary incontinence) should be considered in the management of elderly patients with diabetes¹². However, the effect of geriatric syndromes on RAI persistence is unknown. Therefore, we conducted this study to assess the factors associated with RAI persistence among elderly (≥ 65 years) patients with T2D who added RAI to their BI regimen, and to examine the effect of RAI persistence on change in A1C levels and risk of severe hypoglycemia over 12 months.

Patients and methods

Study design

This was an observational, retrospective cohort study utilizing medical, pharmacy, and laboratory claims data from Humana Medicare Advantage Prescription Drug (MAPD) plans. The study population comprised elderly (≥ 65 years) Medicare beneficiaries with T2D having one or more inpatient visits or two or more outpatient physician visits at least 30 days apart, and a primary or secondary diagnosis of T2D [International Classification of Diseases, 9th

Revision, Clinical Modification (ICD-9-CM) code 250.x0 or 250.x2]. Patients with 18 months' continuous enrollment in MAPD plans and two or more claims for BI during the baseline period, who newly added RAI to their BI treatment between July 2007 and December 2011, were included in this study. The first observed RAI prescription date (RAI index date) was used to define the baseline and follow-up periods; the baseline period was 6 months before the RAI index date, and the follow-up period was 12 months after the index date. Patients were excluded if they used inhaled insulin or insulin mixture during the baseline or follow-up periods, were enrolled in commercial insurance plans, or their gender or insurance plan type was unknown.

Measures

RAI persistence and clinical outcomes—Persistence with RAI was defined as the absence of any 90-day gap between RAI prescriptions among patients with two or more prescriptions for RAI during the follow-up period of 12 months¹¹. The clinical outcome variables included the change in A1C levels from baseline to follow-up (calculated for patients with A1C values available during both baseline and follow-up periods) and severe hypoglycemia. Severe hypoglycemia rather than any hypoglycemia was included in the analysis, as claims databases may not capture hypoglycemic events that do not require clinical intervention.

Baseline and follow-up independent variables—Clinical characteristics of interest during the 6-month baseline period were severe hypoglycemia (hypoglycemia requiring external assistance, identified using ICD-9-CM codes 250.8, 251.0, 251.1, and 251.2 in inpatient and emergency department [ED] settings)¹³, A1C values, diabetes complications (measured by the adapted Diabetes Complications Severity Index [aDCSI] score)¹⁴, healthcare utilization (any inpatient or ED visit), medication use, and the following complexities specific to elderly patients¹²: polypharmacy (>13 drugs during a 90-day period)¹⁵, cognitive impairment (using ICD-9-CM codes for Alzheimer's disease, dementia, Huntington's disease, Parkinson's disease, schizophrenia, bipolar disorder, and psychosis), major depression, falls and falls risk (ICD-9-CM E-codes¹⁶ and V-codes¹⁷), and urinary incontinence (ICD-9-CM diagnosis codes¹⁸) (Appendix 1). Other independent variables assessed at baseline were demographic characteristics (age, gender, race/ethnicity, and region) and insurance plan type. The 12-month follow-up independent variable included average out-of-pocket costs for RAI prescriptions (quartiles: \$0 to <\$6.40, \$6.40 to <\$39.60, \$39.60 to <\$75, \$75).

Statistical analyses

Descriptive analyses were conducted using frequency distributions. Chi-square tests (for categorical variables) and Student *t*-tests (for continuous variables) were used to assess the unadjusted subgroup differences. Factors associated with RAI persistence were analyzed using multivariate logistic regression. Clinical outcomes of change in A1C levels and severe hypoglycemia at 12 months were analyzed using ordinary least squares (OLS) and binary logistic regressions, respectively, with adjustment for selection bias using inverse probability treatment weights (IPTW). Statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline patient demographic and clinical characteristics

A total of 4,979 patients were included in the study. The baseline demographics and clinical characteristics of the study population are summarized in Table 1. Gender distribution was fairly even, patients aged ≥ 75 years accounted for two-thirds of the population and over a half lived in the Southern United States. One-third of the patients were enrolled in health maintenance organizations (HMOs), had an inpatient visit, or an ED visit. A small number of patients had a complexity specific to the elderly, which included: cognitive impairment; major depression; falls and falls risk; polypharmacy; and urinary incontinence. With regard to medication use, one-third did not use any OADs and a small number used three or more OADs. Baseline A1C values were available for 1,792 patients with over a half having A1C levels $>8.0\%$.

Follow-up measures

RAI Persistence—Of the study population, 3,927 patients (78.9%) had two or more RAI prescriptions during the 12-month follow-up period, 815 (20.8%) of whom were persistent with RAI (Table 2). Multivariable logistic regression analysis revealed that patients with the following baseline factors were more likely to be persistent: older age (≥ 75 years), higher baseline A1C ($>9.0\%$), use of three or more OADs, and cognitive impairment (Table 3). Patients were significantly less likely to be persistent with RAI if they were enrolled in a preferred provider organization (PPO) or other plans, had any ED visit, or had higher average out-of-pocket costs per RAI prescription (\$6.40 – $<\$39.60$, $\$39.60$ – $<\$75.0$, or $\$75.0$ as compared to 0 – $\$6.40$).

A1C levels—Among patients with one or more RAI prescriptions and A1C values available for both baseline and 12-month follow-up periods ($n=1,792$), mean (standard deviation [SD]) A1C values were 8.6% (1.71) at baseline and 8.2% (1.50) at 12 months, with a mean (SD) change in A1C levels of -0.5% (1.42). In unadjusted analyses of patients with two or more RAI prescriptions and A1C values available for both the baseline and 12-month follow-up periods ($n=1,117$), persistent RAI users had a significantly greater reduction in A1C levels (mean [SD]) compared with non-persistent users (-0.8% [1.55] vs -0.4% [1.41]), respectively; ($p<0.01$). This finding remained significant in IPTW-adjusted OLS regression analyses (Table 4). The IPTW-adjusted analysis of change in A1C revealed that a significantly greater reduction in A1C from baseline was associated with persistence with RAI therapy, living in the Midwestern region, lower aDCSI score (0–1), and higher baseline A1C levels ($>8.0\%$) (Table 4). Elderly patients with African American race, HMO or PPO enrollment, higher OADs (≥ 3) had a significantly higher elevation in A1C.

Severe hypoglycemia—Overall, 8.1% of the study population ($n=318$) experienced severe hypoglycemia during the 12-month follow-up period. IPTW-adjusted logistic regression analysis of severe hypoglycemia revealed that persistent RAI users were less likely to have severe hypoglycemia as compared to nonpersistent users ($p=0.046$) (Table 4). The odds of having severe hypoglycemia were significantly lower for patients who had HMO insurance plans and those who had a lower aDCSI score (0–1) (Table 4). African

American patients, patients with higher baseline A1C (>9.0%), baseline any hypoglycemia, inpatient visits, ED visits, and cognitive impairment had higher odds of severe hypoglycemia (Table 4).

Discussion

This observational study of elderly Medicare beneficiaries with T2D who newly added RAI to their BI regimen revealed that persistence with RAI was low during the year following RAI initiation. We identified older age, higher A1C levels, use of multiple OADs, and cognitive impairment as baseline factors significantly associated with RAI persistence. Factors significantly associated with nonpersistence were PPO enrollment, ED visits at baseline, and higher average RAI out-of-pocket costs. The persistence rate in our study (20%) is similar to the only other study conducted in patients with T2D who added RAI to BI¹¹; this study, however, was conducted in patients of all ages with commercial or Medicare insurance as compared to our study population comprising Medicare beneficiaries only. Further, in contrast to our observations, Bonafede et al.¹¹ identified older age, polypharmacy, and mental illness to be barriers to RAI persistence. Our observation of higher costs as a barrier to persistence agrees with the Bonafede study and is in line with previous research^{19–21} reporting higher RAI out-of-pocket costs as a barrier to RAI continuation and persistence. This finding suggests that value-based insurance designs that eliminate copays or lower copays may encourage RAI persistence.

We found that those with cognitive impairment were more likely to be persistent with RAI. This result is consistent with our previous study on RAI persistence among elderly Medicare beneficiaries with T2D who added RAI to OAD²². One plausible explanation could be the high dependence on caregiver's assistance among those with cognitive impairment leading to more close monitoring of RAI administration. Future studies examining the persistence with RAI among elderly with cognitive impairment and other mental health conditions are warranted.

The rate of RAI persistence was low in our study. A possible explanation is that the RAI use can be dynamic; patients and providers might adjust RAI doses after initiation, leading to prescriptions lasting longer than the duration indicated in the original prescriptions. Patients for whom doses are lowered may not need to refill prescriptions within the 90-day limit imposed by the definition of persistence applied. Many individuals in our analysis continued to fill RAI prescriptions even after a 90-day gap, suggesting that our persistence measure may be an underestimate of actual persistence.

Patients who were more persistent with RAI treatment experienced a greater reduction in A1C levels, with a lower risk of severe hypoglycemia, compared with non-persistent users. Continuing treatment with antidiabetes medication, irrespective of treatment class, is known to positively influence outcomes. Numerous recent studies have reported associations between persistence/adherence and glycemic control, resource use, mortality, and cost, in patients with T2D^{23–28}. Our results suggest that policy makers should consider implementing interventions targeted to increase persistence to RAI, which may translate into better outcomes.

It is interesting to note that the greater reduction in A1C levels associated with persistent RAI use observed in our study was accompanied by a lower risk of severe hypoglycemia. The finding of a low risk of hypoglycemia associated with insulin use is in line with other studies that reported lower hypoglycemia risk with insulin added to OADs compared with OADs alone²⁹ or no increase in hypoglycemia with insulin compared with OADs^{30,31}. This finding has implications for programs and interventions focused on reducing barriers to RAI initiation and persistence, as the fear of adverse effects (such as hypoglycemia) is one of the reasons for not initiating insulin therapy among both physicians and patients^{32–35}. The lower risk of severe hypoglycemia among persistent RAI users may alleviate these concerns regarding insulin therapy. Our finding of a significant reduction in A1C with a decreased risk of severe hypoglycemia highlights the beneficial effects of RAI persistence.

Our study is subject to some limitations. The use of ICD-9-CM diagnosis codes in medical claims to identify T2D, diabetes severity complications, and hypoglycemia may have been affected by coding errors (e.g., under- or over-coding). Patients with increased hypoglycemia may have discontinued the treatment, which could have led to a biased observation. In addition, not all drug prescriptions are added to claims databases³⁶, which may be the case for RAI prescriptions as well. Another potential limitation is that many patients may pay out of pocket for the RAI prescriptions, thus preventing the generation of a health claim³⁷. The nature of claims data means that prescriptions for medications, rather than actual use of medications, are recorded, and the 90-day gap measure may underestimate the level of RAI persistence. It is plausible that physicians may adjust RAI dose depending on the adverse event profile between prescription refills; such adjustment may not be captured in the claims database, and therefore, RAI persistence may be underestimated. Also, a lack of T2D diagnosis dates meant that time from T2D diagnosis to RAI initiation could not be controlled in the analyses. Clinical reasons for RAI initiation were not examined in this study, and, as this study included elderly Medicare beneficiaries enrolled in Humana MAPD plans, results may not be generalizable to all elderly Medicare beneficiaries with T2D. Further, A1C data were not available for all of the patients included in the study, a factor that also affects the generalizability of the study findings. It is possible that weight gain due to medication use may affect persistence. However, we did not control for patient's body weight because the information was not available in the dataset. Finally, the Humana MAPD plan does not include information on the number of daily RAI injections, which can be a significant barrier to RAI persistence. Hence, we could not examine the association of number of RAI injections with RAI persistence in this study.

Conclusions

Clinical guidelines for patients with T2D recommend the addition of RAI to BI if postprandial glycemic goals are not met with BI or OADs alone. The effect of RAI persistence on clinical outcomes such as change in A1C levels and risk of severe hypoglycemia, which are the most important guiding factors for RAI initiation and persistence, have not been evaluated previously. This observational, retrospective cohort study found that among elderly patients with T2D using BI, persistence with RAI over 12 months was poor. However, patients that were persistent with RAI therapy had a beneficial effect as they had a greater mean A1C reduction at the end of the 12-month period compared

with non-persistent RAI users, with a lower incidence of severe hypoglycemia during the 12-month follow-up period between the two groups. Therefore, it would be advantageous to target factors significantly associated with non-persistence that were identified in this study: PPO enrollment, ED visits at baseline, and higher average RAI out-of-pocket costs. In addition, the information derived from this study: the lower risk of severe hypoglycemia among persistent RAI users, may assist clinicians in reducing barriers to RAI initiation and persistence, as the fear of adverse effects (such as hypoglycemia) is one of the reasons for not initiating insulin therapy among both clinicians and patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Declaration of funding

Sponsorship for this study and article processing charges were funded by Sanofi US, Inc

The authors thank Steve Zhou of Sanofi US, Inc., for his critical revision of this manuscript. The authors received writing and editorial support in the preparation of this manuscript from Pim Dekker, PhD, and Rasilaben Vaghjiani, PhD, of Excerpta Medica, funded by Sanofi US, Inc.

References

1. 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; 38:140–49. [PubMed: 25538310]
2. Raccach D. Options for the intensification of insulin therapy when basal insulin is not enough in type 2 diabetes mellitus. *Diabetes Obes Metab*. 2008; 10(Suppl 2):76–82. [PubMed: 18577159]
3. Monnier L, Colette C. Addition of rapid-acting insulin to basal insulin therapy in type 2 diabetes: indications and modalities. *Diabetes Metab*. 2006; 32:7–13. [PubMed: 16523182]
4. Kazda C, Hülstrunk H, Helsberg K, et al. Prandial insulin substitution with insulin lispro or insulin lispro mid mixture vs. basal therapy with insulin glargine: a randomized controlled trial in patients with type 2 diabetes beginning insulin therapy. *J Diabetes Complications*. 2006; 20:145–52. [PubMed: 16632233]
5. Riddle M, Pencek R, Charenkavanich S, et al. Randomized comparison of pramlintide or mealtime insulin added to basal insulin treatment for patients with type 2 diabetes. *Diabetes Care*. 2009; 32:1577–82. [PubMed: 19502544]
6. Iglay K, Cartier SE, Rosen VM, et al. Meta-analysis of studies examining medication adherence, persistence, and discontinuation of oral antihyperglycemic agents in type 2 diabetes. *Curr Med Res Opin*. 2015; 31:1283–96. [PubMed: 26023805]
7. Hertz RP, Unger AN, Lustik MB. Adherence with pharmacotherapy for type 2 diabetes: a retrospective cohort study of adults with employer-sponsored health insurance. *Clin Ther*. 2005; 27:1064–73. [PubMed: 16154485]
8. Brown JB, Nichols GA, Glauber HS, Bakst A. Ten-year follow-up of antidiabetic drug use, nonadherence, and mortality in a defined population with type 2 diabetes mellitus. *Clin Ther*. 1999; 21:1045, =57. [PubMed: 10440626]
9. Wei W, Pan C, Xie L, Baser O. Real-world insulin treatment persistence among patients with type 2 diabetes. *Endocr Pract*. 2014; 20:52–61. [PubMed: 24013990]

10. Buysman E, Conner C, Aagren M, et al. Adherence and persistence to a regimen of basal insulin in a pre-filled pen compared to vial/syringe in insulin-naïve patients with type 2 diabetes. *Curr Med Res Opin.* 2011; 27:1709–17. [PubMed: 21740289]
11. Bonafede MM, Kalsekar A, Pawaskar M, et al. Insulin use and persistence in patients with type 2 diabetes adding mealtime insulin to a basal regimen: a retrospective database analysis. *BMC Endocr Disord.* 2011; 11:3. [PubMed: 21226935]
12. Brown AF, Mangione CM, Saliba D, et al. Guidelines for improving the care of the older person with diabetes mellitus. *J Am Geriatr Soc.* 2003; 51(5 Suppl Guidelines):S265–80. [PubMed: 12694461]
13. Ginde AA, Blanc PG, Lieberman RM, Camargo CA Jr. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. *BMC Endocr Disord.* 2008; 8:4. [PubMed: 18380903]
14. Chang HY, Weiner JP, Richards TM, et al. Validating the adapted Diabetes Complications Severity Index in claims data. *Am J Manag Care.* 2012; 18:721–6. [PubMed: 23198714]
15. Goldberg JF, Brooks JO 3rd, Kurita K, et al. Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. *J Clin Psychiatry.* 2009; 70:155–62. [PubMed: 19210946]
16. Mehta S, Chen H, Johnson ML, Aparasu RR. Risk of falls and fractures in older adults using antipsychotic agents. *Drugs Aging.* 2010; 27:815–29. [PubMed: 20883062]
17. Tinetti ME, Gordon C, Sogolow E, et al. Fall-risk evaluation and management: challenges in adopting geriatric care practices. *Gerontologist.* 2006; 46:717–25. [PubMed: 17169927]
18. Anger JT, Saigal CS, Madison R, et al. Increasing costs of urinary incontinence among female Medicare beneficiaries. *J Urol.* 2006; 176:247–51. [PubMed: 16753411]
19. Davies MJ, Gagliardino JJ, Gray LJ, et al. Real-world factors affecting adherence to insulin therapy in patients with Type 1 or Type 2 diabetes mellitus: a systematic review. *Diabet Med.* 2013; 30:512–24. [PubMed: 23323988]
20. Janes R, Titchener J, Pere J, et al. Understanding barriers to glycaemic control from the patient's perspective. *J Prim Health Care.* 2013; 5:114–22. [PubMed: 23748392]
21. Nam S, Chesla C, Stotts NA, et al. Barriers to diabetes management: patient and provider factors. *Diabetes Res Clin Pract.* 2011; 93:1–9. [PubMed: 21382643]
22. Sambamoorthi U, Deb A, Zhou S, Garg R, Fan T, Boss A. Rapid acting insulin use and persistence among elderly type 2 diabetes patients adding rai to oral antidiabetes drug regimens. *J Diabetes Res.* 2016; 2016:5374931. [PubMed: 27761472]
23. Egede LE, Gebregziabher M, Dismuke CE, et al. Medication nonadherence in diabetes: longitudinal effects on costs and potential cost savings from improvement. *Diabetes Care.* 2012; 35:2533–9. [PubMed: 22912429]
24. Egede LE, Lynch CP, Gebregziabher M, et al. Differential impact of longitudinal medication non-adherence on mortality by race/ethnicity among veterans with diabetes. *J Gen Intern Med.* 2013; 28:208–15. [PubMed: 22948932]
25. Egede LE, Gebregziabher M, Echols C, Lynch CP. Longitudinal effects of medication nonadherence on glycemic control. *Ann Pharmacother.* 2014; 48:562–70. [PubMed: 24586059]
26. Gibson TB, Song X, Alemayehu B, et al. Cost sharing, adherence, and health outcomes in patients with diabetes. *Am J Manag Care.* 2010; 16:589–600. [PubMed: 20712392]
27. Jha AK, Aubert RE, Yao J, et al. Greater adherence to diabetes drugs is linked to less hospital use and could save nearly \$5 billion annually. *Health Aff (Millwood).* 2012; 31:1836–46. [PubMed: 22869663]
28. McAdam-Marx C, Bellows BK, Unni S, et al. Impact of adherence and weight loss on glycemic control in patients with type 2 diabetes: cohort analyses of integrated medical record, pharmacy claims, and patient-reported data. *J Manag Care Spec Pharm.* 2014; 20:691–700. [PubMed: 24967522]
29. Papa G, Fedele V, Chiavetta A, et al. Therapeutic options for elderly diabetic subjects: open label, randomized clinical trial of insulin glargine added to oral antidiabetic drugs versus increased dosage of oral antidiabetic drugs. *Acta Diabetol.* 2008; 45:53–9. [PubMed: 18180864]

30. Chen HS, Wu TE, Jap TS, et al. Beneficial effects of insulin on glycemic control and beta-cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. *Diabetes Care*. 2008; 31:1927–32. [PubMed: 18556343]
31. Lingvay I, Legendre JL, Kaloyanova PF, et al. Insulin-based versus triple oral therapy for newly diagnosed type 2 diabetes: which is better? *Diabetes Care*. 2009; 32:1789–95. [PubMed: 19592630]
32. Polonsky WH, Jackson RA. What's so tough about taking insulin? Addressing the problem of psychological insulin resistance in type 2 diabetes. *Clin Diabetes*. 2004; 22:147–50.
33. Nam S, Chesla C, Stotts NA, et al. Factors associated with psychological insulin resistance in individuals with type 2 diabetes. *Diabetes Care*. 2010; 33:1747–9. [PubMed: 20435797]
34. Korytkowski M. When oral agents fail: practical barriers to starting insulin. *Int J Obes Relat Metab Disord*. 2002; 26(Suppl 3):S18–24.
35. Khunti K, Nikolajsen A, Thorsted BL, et al. Clinical inertia in intensifying therapy among people with type 2 diabetes treated with basal insulin. *Diabetes Obes Metab*. 2016; 18:401–9. [PubMed: 26743666]
36. Martin CB, Shewale A. Validity of electronic prescription claims records: A comparison of commercial insurance claims with pharmacy provider derived records. *Inov Pharm*. 2014; 5:184.
37. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol*. 2005; 58:323–37. [PubMed: 15862718]

Appendix

Appendix 1. ICD-9-CM codes for complexities specific to elderly patients

Complexity	ICD-9-CM codes ¹
Cognitive impairment	331.83
Alzheimer's disease	331.0
Dementia	290.0
Huntington's disease	333.4
Parkinson's disease	332.0
Schizophrenia	295.0
Bipolar disorder	296.7
Psychosis	298.9
Major depression	296.3
Falls and falls risk	E880–E888 V15.88
Urinary incontinence	788.30

Reference

¹ICD9data.com. 2015 Medical Coding Reference. Available at: <http://www.icd9data.com/>. [Last accessed 29 January 2016].

Table 1

Description of elderly patients with T2D who newly added RAI to their basal insulin regimen

Characteristic	All patients (N = 4,979)	Patients with A1C values at baseline (n = 1,792)
Gender, n (%)		
Female	2,666 (53.5)	970 (54.1)
Male	2,313 (46.5)	822 (45.9)
Race, n (%)		
White	3,901 (78.3)	1,359 (75.8)
African American	705 (14.2)	277 (15.5)
Hispanic, other	219 (4.4)	105 (5.9)
Unknown	154 (3.1)	51 (2.8)
Age group, n (%)		
65–74 years	3,524 (70.8)	1,233 (68.8)
75 years	1,455 (29.2)	559 (31.2)
United States region, n (%)		
Midwest	1,444 (29.0)	276 (15.4)
South	2,834 (56.9)	1,277 (71.3)
Northeast, west, other	701 (14.1)	239 (13.3)
Type of Medicare plan, n (%)		
HMO	1,836 (36.9)	1,113 (62.1)
PPO, other	1,297 (26.1)	385 (21.5)
PFFS	1,846 (37.1)	294 (16.4)
Clinical characteristics		
Severe hypoglycemia, n (%)	356 (7.2)	110 (6.1)
aDCSI score, n (%)		
0–1	1,491 (29.9)	458 (25.6)
2	890 (17.9)	530 (29.6)
3–4	1,333 (26.8)	280 (15.6)
5–12	1,265 (25.4)	524 (29.2)
A1C, n (%)		
<8.0%	727 (14.6)	727 (40.6)
8.0–9.0%	443 (8.9)	443 (24.7)
>9.0%	622 (12.5)	622 (34.7)
Data not available	3,187 (64.0)	–
Healthcare utilization		
Any inpatient visit, n (%)	1,816 (36.5)	572 (31.9)
Any ED visit, n (%)	1,926 (38.7)	615 (34.3)
Number of OADs, n (%)		
1	1,758 (35.3)	615 (34.3)
2	1,253 (25.2)	503 (28.1)
3	285 (5.7)	124 (6.9)
No OAD	1,683 (33.8)	550 (30.7)

Characteristic	All patients (N = 4,979)	Patients with A1C values at baseline (n = 1,792)
Complexities specific to elderly patients		
Cognitive impairment, n (%)	544 (10.9)	153 (8.5)
Major depression, n (%)	578 (11.6)	191 (10.7)
Falls and falls risk (%)	198 (4.0)	48 (2.7)
Polypharmacy (>13 drugs), n (%)	619 (12.4)	198 (11.0)
Urinary incontinence, n (%)	205 (4.1)	68 (3.8)
Average RAI out-of-pocket costs, n (%)		
\$0 to <\$6.40	1,243 (25.0)	521 (29.1)
\$6.40 to <\$39.60	1,246 (25.0)	431 (24.1)
\$39.60 to <\$75.0	1,244 (25.0)	407 (22.7)
\$75.0	1,246 (25.0)	433 (24.2)

aDCSI, adapted Diabetes Complications Severity Index; ED, emergency department; HMO, health maintenance organization; OAD, oral antidiabetes drug; PFFS, private fee-for-service; PPO, preferred provider organization; RAI, rapid-acting insulin; T2D, type 2 diabetes.

Table 2

Description of elderly patients with T2D who newly added RAI to their basal insulin regimen by RAI persistence during the 12-month follow-up period.

Characteristic	Persistent, n (Row %)	Non-persistent, n (Row %)	p-value	Persistent, IPTW wt. row %	Non-persistent, IPTW wt. row %	p-value
All (N = 3,927)*	815 (20.8)	3,112 (79.2)		20.8	79.2	
Gender			0.383			0.913
Female	450 (21.3)	1,665 (78.7)		20.9	79.1	
Male	365 (20.1)	1,447 (79.9)		20.8	79.2	
Race			0.482			0.790
White	647 (21.0)	2,432 (79.0)		20.9	79.1	
African American	97 (18.2)	435 (81.8)		21.3	78.7	
Hispanic, other	39 (21.1)	146 (78.9)		18.0	82.0	
Unknown	32 (24.4)	99 (75.6)		21.6	78.4	
Age group, years			0.005			0.884
65–74	546 (19.6)	2,242 (80.4)		20.9	79.1	
75	269 (23.6)	870 (76.4)		20.7	79.3	
United States region			0.658			0.765
Midwest	250 (21.6)	906 (78.4)		21.4	78.6	
South	448 (20.3)	1,761 (79.7)		20.8	79.2	
Northeast, west, or other	117 (20.8)	445 (79.2)				
Type of Medicare plan			<0.001			0.806
HMO	318 (22.3)	1,105 (77.7)		21.0	79.0	
PPO, other	167 (16.1)	873 (83.9)		21.2	78.8	
PFFS	330 (22.5)	1,134 (77.5)		20.4	79.6	
Clinical characteristics						
Severe hypoglycemia	56 (20.5)	217 (79.5)	0.919			
a1DCSI score			0.519			0.984
0–1	235 (19.8)	950 (80.2)		20.7	79.3	
2	143 (19.8)	579 (80.2)		20.6	79.4	
3–4	218 (21.1)	813 (78.9)		21.3	78.7	
5–12	219 (22.1)	770 (77.9)		20.8	79.2	
A1C			0.005			0.796

Characteristic	Persistent, n (Row %)	Non-persistent, n (Row %)	p-value	Persistent, IPTW wt. row %	Non-persistent, IPTW wt. row %	p-value
<8.0%	86 (15.3)	475 (84.7)		20.3	79.7	
8.0–9.0%	68 (19.6)	279 (80.4)		22.1	77.9	
>9.0%	111 (21.9)	396 (78.1)		22.0	78.0	
Not available	550 (21.9)	1,962 (78.1)		20.5	79.5	
Healthcare utilization						
Any inpatient visit	303 (22.3)	1,054 (77.7)	0.077	20.8	79.2	0.998
Any ED visit	294 (19.9)	1,180 (80.1)	0.333	21.4	78.6	0.485
Number of OADs 1	244 (18.8)	1,055 (81.2)		21.0	79.0	
2	297 (21.5)	1,084 (78.5)		20.8	79.2	
3	213 (21.0)	803 (79.0)		21.7	78.3	
No OAD	61 (26.4)	170 (73.6)		20.6	79.4	
Complexities specific to elderly patients						
Cognitive impairment	119 (26.7)	327 (73.3)	0.001			
Major depression	100 (22.2)	351 (77.8)	0.430	20.6	79.4	0.885
Falls and falls risk	32 (21.5)	117 (78.5)	0.824	22.1	77.9	0.686
Polypharmacy (>13 drugs)	121 (25.1)	362 (74.9)	0.013	20.4	79.6	0.815
Urinary incontinence	31 (19.6)	127 (80.4)	0.719	20.6	79.4	0.928
Average RAI out-of-pocket costs						
\$0 to <\$6.40	290 (28.2)	739 (71.8)	<0.001	20.8	79.2	0.963
\$6.40 to <\$39.60	152 (17.2)	732 (82.8)		20.8	79.2	
\$39.60 to <\$75.0	197 (19.7)	805 (80.3)		20.4	79.6	
\$75.0	176 (17.4)	836 (82.6)		21.4	78.6	

aDCSI, adapted Diabetes Complications Severity Index; ED, emergency department; HMO, health maintenance organization; OAD, oral antidiabetes drug; PFFS, private fee-for-service; PPO, preferred provider organization; RAI, rapid-acting insulin; T2D, type 2 diabetes; IPTW, Wt% Inverse Probability Treatment Weighted percentages.

* Based on 3,927 elderly Medicare beneficiaries who had two or more claims for RAI during the 12-month follow-up period.

Table 3

Logistic regression analysis of RAI persistence during the 12-month follow-up period among patients with T2D who added RAI to their basal insulin regimen.

Characteristic	Adjusted OR (95% CI)	p-value
All (N = 3,927) *		
Gender		
Female	1.05 (0.89–1.23)	0.558
Male	Ref.	
Race		
African American	0.78 (0.61–1.01)	0.058
Other	0.87 (0.60–1.27)	0.477
White	Ref.	
Age group, years		
75	1.20 (1.01–1.43)	0.037
65–74	Ref.	
United States region		
Midwest	0.99 (0.77–1.28)	0.955
South	0.89 (0.70–1.13)	0.325
Northeast, west, other	Ref.	
Type of Medicare plan		
HMO	1.10 (0.89–1.36)	0.362
PPO, other	0.71 (0.57–0.88)	0.002
PFFS	Ref.	
Clinical characteristics		
Any hypoglycemia		
Yes	0.96 (0.74–1.24)	0.740
No	Ref.	
aDCSI score		
0–1	0.93 (0.73–1.19)	0.566
2	0.91 (0.71–1.19)	0.499
3–4	0.99 (0.79–1.24)	0.927
5–12	Ref.	
A1C		
8.0–9.0%	1.32 (0.92–1.88)	0.127
>9.0%	1.58 (1.15–2.17)	0.005
<8.0%	Ref.	
Healthcare utilization		
Any inpatient visit		
Yes	1.16 (0.92–1.46)	0.207
No	Ref.	
Any ED visit		

Characteristic	Adjusted OR (95% CI)	p-value
Yes	0.73 (0.59–0.91)	0.005
No	Ref.	
Number of OADs		
1	1.18 (0.97–1.43)	0.093
2	1.16 (0.94–1.43)	0.174
3	1.63 (1.16–2.28)	0.004
No OAD	Ref.	
Complexities specific to older patients		
Cognitive impairment		
Yes	1.34 (1.03–1.73)	0.027
No	Ref.	
Major depression		
Yes	0.89 (0.69–1.15)	0.364
No	Ref.	
Falls and falls risk		
Yes	1.01 (0.66–1.54)	0.957
No	Ref.	
Polypharmacy (>13 drugs)		
Yes	1.17 (0.92–1.49)	0.209
No	Ref.	
Urinary incontinence		
Yes	0.83 (0.55–1.26)	0.388
No	Ref.	
Average RAI out-of-pocket costs		
\$0 to <\$6.40	Ref.	
\$6.40 to <\$39.60	0.53 (0.42–0.67)	<0.001
\$39.60 to <\$75.0	0.65 (0.52–0.81)	<0.001
\$75.0	0.56 (0.44–0.70)	<0.001

aDCSI, adapted Diabetes Complications Severity Index; CI, confidence interval; ED, emergency department; HMO, health maintenance organization; OAD, oral antidiabetes drug; OR, odds ratio; PFFS, private fee-for-service; PPO, preferred provider organization; RAI, rapid-acting insulin; ref. reference, T2D type 2 diabetes.

* Based on 3,927 elderly Medicare beneficiaries who had two or more claims for RAI during the 12-month follow-up period.

Table 4

Persistence with RAI and clinical outcomes during the 12-month follow-up in patients with T2D who added RAI to their basal insulin regimen.

Characteristic	Change in A1C from baseline to 12-month follow-up		Severe hypoglycemia during 12-month follow-up	
	Beta coefficient	SE	p-value	Adjusted OR(95% CI)
All (N = 3,927)*				
RAI persistent				
Yes	-0.24	0.10	0.013	0.73 (0.53–0.99)
No	Ref.			Ref.
Gender				
Female	0.02	0.08	0.829	0.99 (0.77–1.26)
Male	Ref.			Ref.
Race				
African American	0.25	0.11	0.019	1.55 (1.12–2.13)
Other	0.24	0.13	0.078	0.88 (0.56–1.39)
White	Ref.			Ref.
Age group, years				
65–74	Ref.			Ref.
75	0.04	0.08	0.621	1.19 (0.93–1.54)
United States region				
Midwest	-0.30	0.15	0.042	0.99 (0.67–1.45)
South	-0.03	0.11	0.755	0.87 (0.61–1.26)
Northeast, west, other	Ref.			Ref.
Type of Medicare plan				
HMO	0.25	0.12	0.035	0.67 (0.49–0.92)
PPO, other	0.31	0.13	0.022	0.78 (0.57–1.06)
PFFS	Ref.			Ref.
Clinical characteristics				
Any hypoglycemia				
Yes	0.13	0.12	0.281	2.08 (1.55–2.78)
No	Ref.			Ref.
aDCSI score				
0–1	-0.26	0.12	0.029	0.58 (0.39–0.87)

Characteristic	Change in A1C from baseline to 12-month follow-up			Severe hypoglycemia during 12-month follow-up		
	All (N = 3,927) *	Beta coefficient	SE	p-value	Adjusted OR(95% CI)	p-value
2		-0.09	0.12	0.456	0.86 (0.59–1.25)	0.429
3–4		-0.04	0.10	0.708	0.82 (0.61–1.11)	0.202
5–12		Ref.			Ref.	
A1C						
<8.0%		Ref.			Ref.	
8.0–9.0%		-0.46	0.10	<0.001	1.60 (0.96–2.68)	0.073
>9.0%		-1.57	0.09	<0.001	1.66 (1.04–2.65)	0.034
Healthcare utilization						
Any inpatient visit						
Yes		-0.15	0.11	0.181	1.58 (1.13–2.21)	0.007
No		Ref.			Ref.	
Any ED visit						
Yes		-0.17	0.10	0.108	1.56 (1.13–2.14)	0.007
No		Ref.			Ref.	
Number of OADs						
1		0.07	0.10	0.495	0.97 (0.73–1.29)	0.814
2		0.19	0.10	0.053	1.00 (0.73–1.37)	0.999
3		0.40	0.16	0.012	0.79 (0.44–1.42)	0.433
No OADs		Ref.			Ref.	
Complexities specific to older patients						
Cognitive impairment						
Yes		0.18	0.15	0.221	1.95 (1.43–2.65)	<0.001
No		Ref.			Ref.	
Major depression						
Yes		0.17	0.13	0.216	1.06 (0.76–1.48)	0.737
No		Ref.			Ref.	
Polypharmacy (>13 drugs)						
Yes		0.02	0.13	0.871	1.21 (0.88–1.66)	0.250
No		Ref.			Ref.	

Characteristic	Change in AIC from baseline to 12-month follow-up		Severe hypoglycemia during 12-month follow-up	
All (N = 3,927) *	Beta coefficient	SE	Adjusted OR(95% CI)	p-value
Falls and falls risk [†]				
Yes	NA		1.42 (0.90–2.25)	0.130
No			Ref.	
Urinary incontinence [‡]				
Yes	NA		0.86 (0.51–1.47)	0.592
No			Ref.	

aDCSI, adapted Diabetes Complications Severity Index; CI, confidence interval; ED, emergency department; HMO, health maintenance organization; NA, Not Applicable; OAD, oral antidiabetes drug; OR, odds ratio; PFFS, private fee-for-service; PPO, preferred provider organization; RAI, rapid-acting insulin; ref., reference; SE, standard error; T2D, type 2 diabetes.

* Based on 3,927 elderly Medicare beneficiaries who had two or more claims for RAI during the 12-month follow-up period.

[†]Not included in the logistic regression model for change in AIC.