Trends in HbA1c thresholds for initiation of hypoglycemic agents: Impact of changed recommendations for older and frail patients

Martina Ambrož1 | Sieta T. de Vries1 | Klaas Hoogenberg2 | Petra Denig1

1Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
2Department of Internal Medicine, Martini Hospital, Groningen, The Netherlands

Abstract

Aims: Less strict glycated hemoglobin (HbA1c) thresholds have been recommended in older and/or frail type 2 diabetes (T2D) patients than in younger and less frail patients for initiating hypoglycemic agents since 2011. We aimed to assess trends in HbA1c thresholds at initiation of a first hypoglycemic agent(s) in T2D patients and the influence of age and frailty on these trends.

Materials and methods: The groningen initiative to analyze type 2 diabetes treatment (GIANTT) database was used, which includes primary care T2D patients from the north of the Netherlands. Patients initiating a first non-insulin hypoglycemic agent(s) between 2008 and 2014 with an HbA1c measurement within 120 days before initiation were included. The influence of calendar year, age, or frailty and the interaction between calendar year and age or frailty were assessed using multilevel regression analyses adjusted for confounders.

Results: We included 4588 patients. The mean HbA1c threshold at treatment initiation was 7.4% up to 2010, decreasing to 7.1% in 2011 and increasing to 7.4% in 2014. This quadratic change over the years was significant (P < 0.001). Patients aged 60 to 79 initiated treatments at lower HbA1c and patients of different frailty at similar HbA1c levels. The interaction between year and age or frailty was not significant (P > 0.05).

Conclusions: HbA1c thresholds at initiation of a first hypoglycemic agent(s) changed significantly over time, showing a decrease after 2010 and an increase after 2012. The HbA1c threshold at initiation was not influenced by age or frailty, which is in contrast with recommendations for more personalized treatment.

1 | INTRODUCTION

An important goal of type 2 diabetes (T2D) management is reducing the risk of complications by good control of blood glucose levels. This can be achieved with lifestyle changes but hypoglycemic agents have to be initiated when glucose control is insufficient. The success of T2D management is often monitored by regularly testing glycated hemoglobin (HbA1c) levels, which serve as a measure of chronic hyperglycemia.1 Several studies showed that the HbA1c level at initiation of a first hypoglycemic agent is the main predictor of achieving early glycemic control.2,3

Over the last decade, there have been several changes in treatment recommendations for patients with T2D (Supplementary...
Table 1 in Data S1). At first, achieving HbA1c levels below 7% was recommended for most patients. Between 2008 and 2010, performance measures assessing the percentage of patients achieving HbA1c levels below 7% was introduced in primary care in the Netherlands. Around 2009, several professional organizations started to advocate more personalized HbA1c targets, particularly in elderly patients. Diabetes guidelines started to recommend personalized HbA1c treatment targets in 2011. This personalization was based on the patients’ age and frailty. From 2011 onwards, guidelines recommended HbA1c targets ≤7.0% for non-frail patients younger than 70 years and between 7.0% and 8.5% for many patients older than 70 years with a longer diabetes duration and/or frail patients (Supplementary Table 1 in Data S1). These targets are also considered as thresholds for initiating treatment. The extent to which these recommendations have led to more personalized initiation of hypoglycemic treatment in clinical practice is unknown.

The aim of our study was to investigate trends in HbA1c thresholds at initiation of a first hypoglycemic agent(s) and the possible impact of more personalized treatment recommendations for older and frail patients with T2D. Given the introduction of performance measures and changes in treatment recommendations, we hypothesized that there would be a decrease in the overall mean HbA1c thresholds in the period 2008 to 2014 but that first hypoglycemic agent(s) would be initiated at higher HbA1c thresholds in older and frail patients after more personalized targets were introduced.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This was a repeated cross-sectional dynamic cohort study for the years 2008 to 2014. We used the data available from the GIANNT (www.giantt.nl) database, which contains anonymous primary care electronic medical records data from patients with T2D in the northern part of the Netherlands.

For each calendar year, patients were included if they had a confirmed diagnosis of T2D, were 18 years or older, and initiated treatment with a first hypoglycemic agent(s) in that year. This initiation was defined as a prescription for a non-insulin hypoglycemic agent (anatomic therapeutic chemical [ATC] classification codes A10B) without a prescription for any hypoglycemic agent in the preceding 365 days. Included patients had to have at least 1 year of history in the GIANNT database before initiation of hypoglycemic treatment. We excluded patients without a documented HbA1c level within 120 days before or on the day of treatment initiation. In addition, patients who had been diagnosed with T2D 10 or more years before treatment initiation and patients who initiated treatment with three or more hypoglycemic agents were excluded since it is unlikely that these patients were true initiators. An approval from the ethics committee is not needed for studies using anonymous medical records data in the Netherlands. We obtained an exemption letter from the University Medical Center Groningen Medical Ethics Review Board (reference number M19.235285).

2.2 | Outcome variable

The primary outcome was the patient’s most recent HbA1c level in the 120 days before or on the day of a first hypoglycemic agent(s) initiation.

2.3 | Explanatory variables

The following explanatory variables were included: calendar year of treatment initiation, age or frailty of the patient and the interaction between calendar year and age or frailty. Age was calculated on January 1 of the year in which the patient initiated treatment. We categorized age in four groups (<60 years, 60-69 years, 70-79 years, and ≥80 years old) based on the different cut-offs observed among guidelines (Supplementary Table 1 in Data S1). Frailty was calculated using an electronic frailty index (eFI), which is based on International Classification of Primary Care (ICPC) coded diagnoses. We excluded diabetes from the eFI, thus focusing on differences in additional frailty. A higher number for the eFI indicates a higher degree of frailty. Since there are no validated clinical cut-offs for the eFI, we categorized the scores in tertiles to compare low, medium, and high frailty patients.

2.4 | Confounders

There are several patient characteristics available in the GIANNT database that can be associated with age or frailty and may affect the prescribers’ decision to initiate a hypoglycemic agent. The following were included to correct for potential confounding: sex, duration of diabetes (0-1 year, 2-3 years, 4-5 years, 6-7 years, 8-9 years), presence of dyslipidemia (defined as low density lipoproteins [LDL] ≥2.5 mmol/L), systolic blood pressure level (<140 mm Hg or ≥140 mm Hg), estimated glomerular filtration rate (eGFR; ≤60 mL/min or >60 mL/min),
presence of albuminuria (albumin creatinine ratio ≥30 mg/g or albumin in 24 hours urine ≥300 mg), body mass index (BMI: <24.9 kg/m², 25-29.9 kg/m² or ≥30 kg/m²), blood pressure lowering treatment (no treatment, 1 class, 2 classes, ≥3 classes), lipid lowering treatment (no treatment or ≥1 classes) and number of all other prescribed chronic medications at initiation (used as a continuous variable). The most recent laboratory values available in the year before or 7 days after initiation were used for these variables. BMI was calculated from weight and height based on the data in the last 5 years or in the year after initiation or extracted as provided BMI from the database when weight and/or height were not available. The eGFR was calculated from serum creatinine using the Modification of Diet in Renal Disease-4 equation for the years 2008 and 2009, and using the Chronic Kidney Disease Epidemiology Collaboration equation from 2010 onwards, since the standard way of calculating eGFR in the Netherlands changed during the study period.14 In case serum creatinine was not available, the eGFR measurement was extracted as provided in the database. Prescribed chronic medication was assessed in the 120 days before or on the day of treatment initiation.

2.5 | Missing data

No data for the explanatory variables were missing. When confounders had less than 20% of missing values, they were imputed using multiple imputation by chained equation (MICE).15 For albuminuria, more than 20% of patients had a missing value. These patients were assumed as not having albuminuria, since conducting this test in the study period was less common in patients without suspected kidney problems.

2.6 | Analyses

Characteristics of included patients were analyzed descriptively per year. We conducted multilevel regression analyses with a two-level random intercept model to account for patients being nested within general practices. First, using the empty model that includes only the outcome variable, we calculated the intraclass correlation coefficient (ICC). The ICC assesses the proportion of variance attributed to general practices. Second, we created the trend model by adding the calendar year and the confounders to the model to assess the overall trend over the years. We compared linear and non-linear trend models using the Wald test to choose the best fitting final model. Next, we assessed the effect of age or frailty on these trends by adding the explanatory variables and the interaction between calendar year and age or frailty on HbA1c levels at initiation in this trend model. To assess changes over time in separate age and frailty groups, additional multilevel analyses were conducted per subgroup. In these models, the Bonferroni method was used to correct for multiple testing, with a significance level of $P < 0.0125$ when testing for trends per age group and of $P < 0.0167$ when testing for trends per frailty group.
A sensitivity analysis was conducted in which the eFI was used as a continuous variable in the final model.

The analyses were conducted in Stata version 14 (Stata Corp., College Station, Texas).

3 | RESULTS

We included 4588 patients who initiated a first hypoglycemic agent(s) between 2008 and 2014 (Table 1). The number of patients in each calendar year differed, whereas the patient characteristics were similar over the years (Supplementary Table 2 in Data S1). Around 90% of patients initiated treatment with metformin (Figure 1). The use of sulfonylureas slightly decreased over the years from 8% to 6%, mostly on the account of the newer medication that became available in this time period. Complete data were available for 74% of the patients.

3.1 | Trends in HbA1c thresholds

The mean HbA1c level before or at initiation of a first hypoglycemic agent(s) changed quadratically over the years ($\beta_{\text{year}} = -0.236$, 95% CI $-0.334$, $-0.138$, $P < 0.001$; $\beta_{\text{year}^2} = 0.021$, 95% CI $0.012$, $0.030$, $P < 0.001$; joint p using Wald test $<0.001$) and aged 60 to 69 years ($\beta_{\text{year}} = -0.216$, 95% CI $-0.360$, $-0.072$, $P = 0.003$; $\beta_{\text{year}^2} = 0.032$, 95% CI $0.016$, $0.049$, $P < 0.001$; joint p using Wald test $<0.001$), but this trend was not significant in the other two groups. All frailty groups initiated hypoglycemic treatment at similar HbA1c thresholds (Figure 2C; Table 2). The interaction between frailty and calendar year was not significant. In the analysis per frailty group, the HbA1c threshold changed significantly over the years in the least frail group ($\beta_{\text{year}} = -0.345$, 95% CI $-0.515$, $-0.176$, $P < 0.001$; $\beta_{\text{year}^2} = 0.032$, 95% CI $0.016$, $0.049$, $P < 0.001$; joint p using Wald test $<0.001$), but this trend was not significant in the other two groups. The sensitivity analysis, using frailty index as a continuous variable, showed similar non-significant results (Supplementary Table 3 in Data S1).

4 | DISCUSSION

The mean HbA1c level at initiation of a first hypoglycemic agent(s) decreased after 2010 and increased after 2012 until the end of our study period in 2014. Surprisingly, there were no differences in the trends for patients of different ages or frailty between 2008 and 2014.

The rising trend in HbA1c level at treatment initiation after 2012 is not in line with our hypothesis, since we expected a decrease in the overall HbA1c threshold throughout the study period. It is, however, in line with a recent study conducted in Denmark, which assessed the trends in pre-treatment HbA1c levels between 2000 and 2017, where a similar decreasing pattern up to 2011 with a slight increase...
thereafter was observed. Other studies have looked at trends in proportions of patients achieving target levels, showing either increases or non-significant changes over time. An intriguing finding of our study was that a drop in HbA1c levels was particularly seen between 2010 and 2011. This may be due to policy changes in the Netherlands. In 2008, performance measures were introduced as informative indicators for benchmarking the general practitioners (GPs) on achieving low targets in diabetes patients. In our study region, additional education and support was offered around 2010 to the GPs to improve their performance. We did not expect, however, that the HbA1c would increase after 2012. This could indicate that the performance measures and other activities only had a temporary effect.

Our study showed no differences in HbA1c levels at hypoglycemic treatment initiation in patients of different ages. This is not in line with our hypothesis and recommendations of using higher HbA1c targets for older T2D patients after 2011 (Supplementary Table 1). Surprisingly, the youngest and the oldest patients initiated treatment at similar slightly higher HbA1c levels. On the one hand, this could be due to more delay in diagnosing diabetes in younger as compared to older patients, who are more actively monitored. This would lead to higher HbA1c levels at diagnosis and subsequently at treatment initiation. It has indeed been shown that the HbA1c levels at diagnosis were higher in younger than in older patients. On the other hand, it was found that the time to initiation of a hypoglycemic agent increased with advancing age. Thus, the HbA1c level at treatment initiation can be higher in younger patients because of a delay in diagnosis, while it can be higher in older patients because of a delay in treatment initiation. Interestingly, the HbA1c level at initiation increased after 2012 in all age groups, with this increase being the highest in patients younger than 60 years. We can only speculate about the possible explanations. It could be that either the GPs or the patients prefer to try lifestyle changes for a longer period at a younger age, leading to higher HbA1c levels when deciding to initiate medication. It could also be that GPs became less strict in all patients because potential overtreatment for diabetes has been gaining a lot of attention in the last decade.

Similar to age, there were no significant differences between patients with different levels of frailty. Frailty has not been used in previous analyses of hypoglycemic treatment patterns, however, a recent study observed that patients with three or more comorbidities were more likely to have a tighter glycemic control than patients with no or only one comorbidity. We conducted a post-hoc analysis using the number of chronic medications at initiation as a proxy for frailty and found that patients receiving less than four (median) chronic medications initiated treatment at significantly higher HbA1c levels when compared to four or more chronic medications (Supplementary Figure 1 and Supplementary Table 4 in Data S1). Furthermore, the observed increase after 2012 particularly in patients prescribed less medication is again unexpected. These results do not support our hypothesis that less strict treatment thresholds were applied for frail patients. A possible explanation could be that frailty measured with the eFI score—or with the number of chronic medication—is not fully applicable or fitting in clinical practice. The eFI was comparable to the Groningen Frailty Index in the previous studies but it might not be in line with the GPs’ perception of the patient’s status. Also, frailty can easily be overlooked in practice due to its subtle manifestations and a
lack of consensus on how best to assess it. In addition, specific factors such as life expectancy, functional dependency, and risk of hypoglycemia, which are mentioned in relation to personalized treatment targets, may contribute more to the prescribers’ decisions to initiate treatment than frailty in general.

Our study provides important insights in prescribing trends and suggests that trends in initiation of a first hypoglycemic agent(s) may not be fully in accordance to changes in recommendations towards more personalized treatment. The lack of differentiation between patients of different ages and frailty is of concern. The increase in HbA1c thresholds after 2012 in older patients who do not benefit from tight control is encouraging but this trend was not observed in younger patients using real-world data from primary care. It is also a first study to examine trends in HbA1c level at initiation of a first hypoglycemic agent(s) and to compare patients of different ages and frailty. Our study has some limitations. First, the number of GPs included in each calendar year fluctuates. Since only little variation was explained at practice level, we do not expect that this affected our conclusions. Second, approximately 10% of patients initiating hypoglycemic therapy were excluded from our analysis because they initiated treatment with insulin. Although it is unlikely that these patients were true initiators, other studies have shown similar rates of initial therapy with insulin in patients with T2D. Therefore, we conducted a post-hoc analysis including only patients who initiated treatment with insulin, which revealed similar results (data not shown). Third, the observed time between diabetes diagnosis and treatment initiation was quite long for some patients. This could be due to persisting with lifestyle changes for several years before initiating medication treatment. We have to acknowledge, however, that some GPs may have included patients with early stages of diabetes or prediabetes in our cohort. We therefore conducted another post-hoc analysis including only patients with diabetes duration of 5 years or less (N = 3412), showing similar results (data not shown). Finally, we had some missing data but these were imputed using multiple imputation to reduce possible bias. Frailty, however, was probably underestimated due to incomplete coding of ICPC diagnoses in electronic medical records.

### Table 2

| FRAILTY | β     | 95% CI       | P     |
|---------|-------|--------------|-------|
|         | -0.223 | -0.321, -0.125 | <0.001 |
| Calendar year | 0.020 | 0.011 0.030 | <0.001 |
| Calendar year² | -0.005 | -0.090, 0.081 | 0.917 |
| Frailty 0.06-0.08 | 0.057 | -0.021, 0.134 | 0.151 |
| Frailty 0.11-0.36 | Reference group |
| Interaction year*frailty | None are significant |

Note: The intraclass correlation coefficient (ICC) calculated from the empty model was 0.064.

The age model was adjusted for sex, duration of diabetes, number of chronic medication at initiation, number of antihypertensive drug classes, systolic blood pressure, lipid lowering therapy, presence of albuminuria, presence of dyslipidemia, estimated glomerular filtration rate, and BMI.

Joint significance of calendar year and calendar year² using Wald test.

The frailty model was adjusted for sex, systolic blood pressure, duration of diabetes, number of antihypertensive drug classes, and lipid lowering therapy.
In conclusion, the observed HbA1c thresholds at initiation of a first hypoglycemic agent(s) changed significantly over time, showing a decrease after 2010 followed by an increase after 2012. This quadratic trend was not influenced by patients’ age or frailty, which is in contrast with changed recommendations for more personalized treatment targets in the study period. More research is needed to determine factors influencing decisions to initiate or refrain from initiating hypoglycemic treatment in general practice, particularly for frail patients. Furthermore, the reasons for initiating diabetes treatment at increasingly higher HbA1c levels in relatively young patients should be further investigated.

ETHICS STATEMENT
The authors state that no ethical approval was needed.

CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS
M.A. contributed to the development and formulation of the research question, conducted the analysis, contributed to the interpretation of data, wrote the manuscript, and reviewed and edited the manuscript. S.T.d.V. contributed to the development and formulation of the research question, conducted the analysis, contributed to the interpretation of data, and reviewed and edited the manuscript. K.H. contributed to the development and formulation of the research question, the interpretation of data, and reviewed and edited the manuscript. P.D. contributed to the development and formulation of the research question, development of the analysis, the interpretation of data, and reviewed and edited the manuscript.

REFERENCES

1. Shariq IS, Haseeb AK, Aishah E, Afshan M, Meena KS. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. Biomark Insights. 2016;2016(11):95-104.
2. Martono DP, Lub R, Heerspink HJL, Hak E, Wilffert B, Denig P. Predictors of response in initial users of metformin and sulphonylurea derivatives: a systematic review. Diabet Med. 2015;32(7):853-864.
3. Svensson E, Baggesen LM, Thomsen RW, et al. Patient-level predictors of achieving early glycaemic control in type 2 diabetes mellitus: a population-based study. Diabet Med. 2016;33(11):1516-1523.
4. Force IDFDCGT. Global guideline for type 2 diabetes: recommendations for standard, comprehensive and minimal care. Diabet Med. 2006;23(6):579-593.
5. Rutten G, De Grauw WJC, Nijpels G, et al. NHG-standaard diabetes mellitus type 2 [tweede herziening] [NHG standard diabetes mellitus type 2 (second review)]. Huisarts en Wetenschat. 2006;49(3):137-152.
6. Ryden L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary: the task force on diabetes and cardiovascular diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of diabetes (EASD). Eur Heart J. 2007;28(1):88-136.
7. de Vries ST, Voorham J, Haaijer-Ruskamp FM, Denig P. Potential overtreatment and undertreatment of diabetes in different patient age groups in primary care after the introduction of performance measures. Diabetes Care. 2014;37(5):1312-1320.
8. Struijs JN, van Tij JT, Baan CA. Experimenteren Met de Keten-Dbc Diabetes: de Eerste Zichtbare Effecten [Experimenting with a Bundled Payment System for Diabetes Care in the Netherlands: The First Tangible Effects]. Bilthoven, the Netherlands: National Institute for Public Health and the Environment (RIVM); 2009.
9. Verhoeven S, Blom LJG, van Hateren KJJ, Houweulng ST, Kleefstra N, van Meeteren J. Protocol: Diabeteszorg hoogbejaarden in verzorgings- en verpleeghuizen [protocol: diabetes care for the very elderly in care and nursing homes]. Diabeteszorg Spec 2009:1-8.
10. Teoh H, Home P, Leiter LA. Should A1C targets be individualized for all people with diabetes? Arguments for and against. Diabetes Care. 2011;34(Suppl 2):S191-S196.
11. Rutten G, De Grauw WJC, Nijpels G, et al. NHG-standaard diabetes mellitus type 2 [derde herziening] [NHG standard diabetes mellitus type 2 (third review)]. Huisartsen Wetenschap. 2013;10(56):512-525.
12. Sinclair AJ, Paolino G, Castro M, Bourdel-Marchasson I, Gadsby R, Rodriguez ML. European diabetes working party for older people 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. Diabetes Metab. 2011;37:S27-S38.
13. Verenso. Multidisciplinaire richtlijn diabetes. Verantwoord diabeteszorg bij kwetsbare ouderen thans en in verzorgings en Verpleeghuizen. Deel 1. [Multidisciplinary guideline diabetes. Responsible diabetes care in vulnerable elderly at home and in residential care or nursing homes. Part 1]. Utrecht, the Netherlands: Verenso; 2011.
14. Drubbel I, Bleijenberg N, Kranenburg G, et al. Identifying frailty: do the frailty index and Groningen frailty indicator cover different clinical perspectives? A cross-sectional study. BMC Fam Pract. 2013;14(1):64.
15. Nguyen DC, John BC, Katherine JL. Model checking in multiple imputation: an overview and case study. Emerg Themes Epidemiol. 2017;14(1):8-12.
16. Knudsen JS, Hulman A, Ronn PF, et al. Trends in HbA1c and LDL cholesterol in patients with type 2 diabetes receiving first-time treatment in northern Denmark, 2000-2017: population-based sequential cross-sectional analysis. Diabetes Care. 2020;43(2):e17-e19.
17. Heintjes EM, Houben E, Beekman-Hendriks WL, et al. Trends in mortality, cardiovascular complications, and risk factors in type 2 diabetes. Neth J Med. 2019;77(9):317-329.
18. Carls G, Huynh J, Tuttle E, Yee J, Edelman SV. Achievement of glycated hemoglobin goals in the US remains unchanged through 2014. Diabetes Ther. 2017;8(4):863-873.
19. Mata-Cases M, Franch-Nadal J, Real J, Mauricio D. Glycaemic control and antidiabetic treatment trends in primary care centres in patients with type 2 diabetes mellitus during 2007–2013 in Catalonia: a population-based study. BMJ Open. 2016;6(10):e012463.
20. Sinclair AJ, Alexander CM, Davies MJ, Zhao C, Mavros P. Factors associated with initiation of antihyperglycaemic medication in UKpatients with newly diagnosed type 2 diabetes. BMJ Endocr Disord. 2012;12(1):1.
21. Zhang Q, Rajagopalan S, Marrett E, Davies MJ, Radican L, Engel SS. Time to treatment initiation with oral antihyperglycaemic therapy in US patients with newly diagnosed type 2 diabetes. Diabetes Obes Metab. 2012;14(2):149-154.
22. Coons MJ, Greiver M, Alarzadeh B, et al. Is glycemias control in Cana- dians with diabetes individualized? A cross-sectional observational study. BMJ Open Diabetes Res Care. 2017;5(1):e000316.
23. Lee L, Patel T, Hillier LM, Maulkhan N, Slonim K, Costa A. Identifying frailty in primary care: a systematic review. Geriatr Gerontol Int. 2017;17(1358-1377).
24. Strain WD, Agarwal AS, Paldánius PM. Individualizing treatment targets for elderly patients with type 2 diabetes: factors influencing clinical decision making in the 24-week, randomized INTERVAL study. Aging. 2017;9(3):769-777.

25. Alvarez-Guisasola F, Cebrián-Cuenca AM, Cos X, et al. Calculating individualized glycaemic targets using an algorithm based on expert worldwide diabetologists: implications in real-life clinical practice. Diabetes Metab Res Rev. 2018;34(3):1–7.

26. Cahn A, Raz I, Kleinman Y, et al. Clinical assessment of individualized glycemic goals in patients with type 2 diabetes: formulation of an algorithm based on a survey among leading worldwide Diabetologists. Diabetes Care. 2015;38(12):2293-2300.

27. Delgado-Hurtado JJ, Cahn A, Raz I, Comi RJ. Comparison of HbA1c goals proposed by an algorithm to those set by different members of healthcare teams within the Dartmouth Hitchcock health system. Endocr Pract. 2018;24(8):705-709.

28. Montvida O, Shaw J, Atherton JJ, Stringer F, Paul SK. Long-term trends in antidiabetes drug usage in the U.S.: Real-world evidence in patients newly diagnosed with type 2 diabetes. Diabetes Care. 2018;41(1):69-78.

29. Ramzan S, Timmins P, Hasan SS, Babar Z-U-D. Trends in global prescribing of antidiabetic medicines in primary care: a systematic review of literature between 2000–2018. Prim Care Diabetes. 2019;13(5):409-421.

**SUPPORTING INFORMATION**

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

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