Analysis of prescription rates of insulin glargine (IG), per product and presentation type, by general practitioners (GPs) in England and its association with health determinants (2013–2018)

Ion Agirrezabal[1,2], Juan Manuel Cabasés[1], Eduardo Sánchez-Iriso[1]

[1]Public University of Navarre, Pamplona/Iruña (Spain); [2]Covance Market Access, London (UK)

Introduction

- Approximately 4 million people in England have diabetes, of whom approximately 10% and 90% have type 1 diabetes and type 2 diabetes, respectively.[1-3]
- People from deprived areas or part of an ethnic minority within the UK are more likely to have diabetes.[1] For instance, South Asian or black people are two to four times more likely to have type 2 diabetes than white people.[1]
- Insulin glargine (IG) is a long-acting insulin analogue used for the treatment of diabetes in adults, adolescents and children aged two years and above:[4]
  - For adults with type 1 diabetes, basal-bolus insulin regimens are recommended, with once-daily IG recommended if twice-daily insulin detemir basal injection is not acceptable or not tolerated to the person or if insulin detemir is not tolerated.[2]
  - For adolescents and children with type 1 diabetes, IG is recommended as part of a basal-bolus regimen.[5]
  - For adults with type 2 diabetes, insulin regimens are only recommended as second intensification treatments (after initial treatment and first intensification) and only in certain conditions; IG is considered a treatment option as an alternative to neutral protamine Hagedorn (NPH) insulin in certain situations.[3]
- Prescribed in both primary (general practitioner [GP] practice) and secondary care, IG is administered subcutaneously and is available in the UK in various forms (vials, syringes and pre-filled pens) and strengths (100 and 300 units/ml);[6] biosimilars of IG have also been available since September 2015.[7]
- According to the National Diabetes Audit, care processes for people with diabetes varies greatly across England's Clinical Commissioning Groups (CCGs). Similarly, there is a substantial variation across CCGs in terms of achievement of treatment targets.[1]

Objectives

- To understand prescription rates of different IG formulations in England at GP practice level, as well as their temporal trends.
- To analyse whether key health determinants (i.e. income deprivation, sex, age, rural-urban classification and ethnic group composition) are significant predictors of IG prescription rates.
- To evaluate whether inequalities in IG prescription rates exist by means of concentration indices (CIs).

Methods

Data sources

- In May 2019, the list of all IG prescriptions by GPs in England between April 2013 and December 2018 was extracted from publicly available UK Government databases. Monthly datasets were available, which included the following variables: number of items prescribed, by IG formulation and by GP practice, as well as the CCG to which the GP practice belongs.[8]
- The following variables were collected from publicly available databases:
  - Total number of patients, age (mean years) and sex (percentage of females) of patients registered with each GP practice, available monthly.[9]
  - Income score, or percentage income-deprived, of the area where each GP practice is located (i.e. the lower-layer super output area [LSOA]), obtained from the 2015 version of the Index of Multiple Deprivation (IMD).[10]
  - Rural-urban classification (dichotomous) and ethnicity (percentage of white people) of LSOAs where GP practices are located, obtained from the Office for National Statistics. Data from 2011 were available.[11,12]

Data analysis

- **Exploratory analyses.** Total IG prescriptions were calculated, as well as total IG prescriptions by formulation. Prescription rates were calculated by income deprivation decile. Exploratory analyses allowed the visual analysis of temporal trends.
- **Regression analyses.** Mixed-effects Poisson regression models (one per IG formulation) were implemented to understand potential associations between prescription rates and health determinants. All health determinants plus time (month and year) and the number of patients registered per GP practice were incorporated as fixed effects; the models included random intercepts for GP practice and CCGs.

$$\text{items}_{tij} = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{number of patients}_{tij}\ \beta_3 \times \text{income score}_{ij} + \beta_4 \times \text{sex}_{tij} + \beta_5 \times \text{age}_{tij} +$$

$$+ \beta_6 \times \text{rural-urban category}_{ij} + \beta_7 \times \text{ethnicity}_{ij} + u_{i|j} + u_j$$

$$u_{i|j} \sim N(0, \sigma^2_{\text{intercept:GP practice}})$$

$$u_j \sim N(0, \sigma^2_{\text{intercept: CCG}})$$

  - items_{tij} represents the number of prescriptions of a given product prescribed at time t, by a GP practice i which belongs to CCG j; β_0 through β_7 represent the fixed intercept and the fixed effects of covariates included in the model.
  - The distribution of random effects associated with GP practices nested within a given CCG is represented by $u_{i|j}$, where $\sigma^2_{\text{intercept:GP practice}}$ represents the variance of the random GP practice-specific intercepts. The distribution of random effects associated with CCGs is represented by u_j, with $\sigma^2_{\text{intercept: CCG}}$ indicating the variance of the random CCG-specific intercepts.
  - Models without random effects for CCGs were implemented to evaluate whether different prescribing behaviours exist across CCGs.
- **Concentration indices.** Concentration curves were generated, plotting cumulative number of prescriptions vs the cumulative number of patients ranked by income deprivation. The area under the curve (AUC) was calculated with the trapezoidal rule, and the CIs were then calculated as: CI = 2* (0.5 - AUC).

Results

Exploratory analyses

- The GP practice level prescribing datasets included the following IG formulations: Lantus® 100 units/ml solution for injection in three forms (cartridges, vials and SoloStar® pre-filled pen); Toujeo® 300 units/ml solution for injection in SoloStar® pre-filled pen; and Abasaglar® (IG biosimilar) 100 units/ml solution for injection in two forms (cartridges and KwikPen® pre-filled pen).
  - A very small number of Lantus OptiSet® and Lantus OptiClik® prescriptions were captured in the time frame analysed, despite being withdrawn from the market by the manufacturer following the commercialisation of Lantus SoloStar® in December 2011. For this reason, the former were excluded from any further analyses.
  - The more-recently launched Toujeo DoubleStar® and Semglee® (IG biosimilar) were not captured in the time frame analysed.
  - The datasets contained IG prescriptions without recording the brand name. These amounted to 13.1% of total prescriptions and were excluded from the analyses to avoid assumptions about whether these corresponded to originator or biosimilar IG.
- Lantus SoloStar® was the most frequently prescribed IG product, with approximately constant prescription rates since 2013 (Figure 1). A trend was observed according to income deprivation, with GPs in the most income-deprived areas prescribing Lantus SoloStar® relatively more frequently compared with less income-deprived areas (Figure 1).
- Toujeo SoloStar® and Abasaglar KwikPen® prescription levels steeply increased from first prescription in 2015, with a quicker uptake by GP practices in the most income-deprived areas (Figure 1).

Regression analyses

  - Regression analyses showed an association between IG prescription rates and the variables studied (Table 1).
  - Income deprivation had a positive effect on prescription levels of all products, this being statistically significant for Lantus® (cartridges and SoloStar®) and Abasaglar KwikPen®. These results demonstrate that GPs prescribed relatively more IG per population in more income-deprived areas compared with less income-deprived areas.
  - Sex had a positive effect on prescription levels of all products, i.e. the higher the percentage of females, the higher levels of IG prescriptions.
  - Uptake of the newest IG formulations (Toujeo SoloStar®, Abasaglar® cartridges and Abasaglar KwikPen®) was quicker, with relatively more prescribed, in urban areas compared with rural areas; Lantus SoloStar® was also relatively more prescribed in urban areas.
  - The impact of age and ethnicity varied across products.
  - Time trends were aligned with exploratory analyses presented in Figure 1.
- Results from regression analyses implied that different prescribing behaviours may exist across CCGs (results not shown).

Figure 1. Prescription rates, over time, for each product and by income deprivation decile (from 1, the most deprived, to 10, the least deprived)

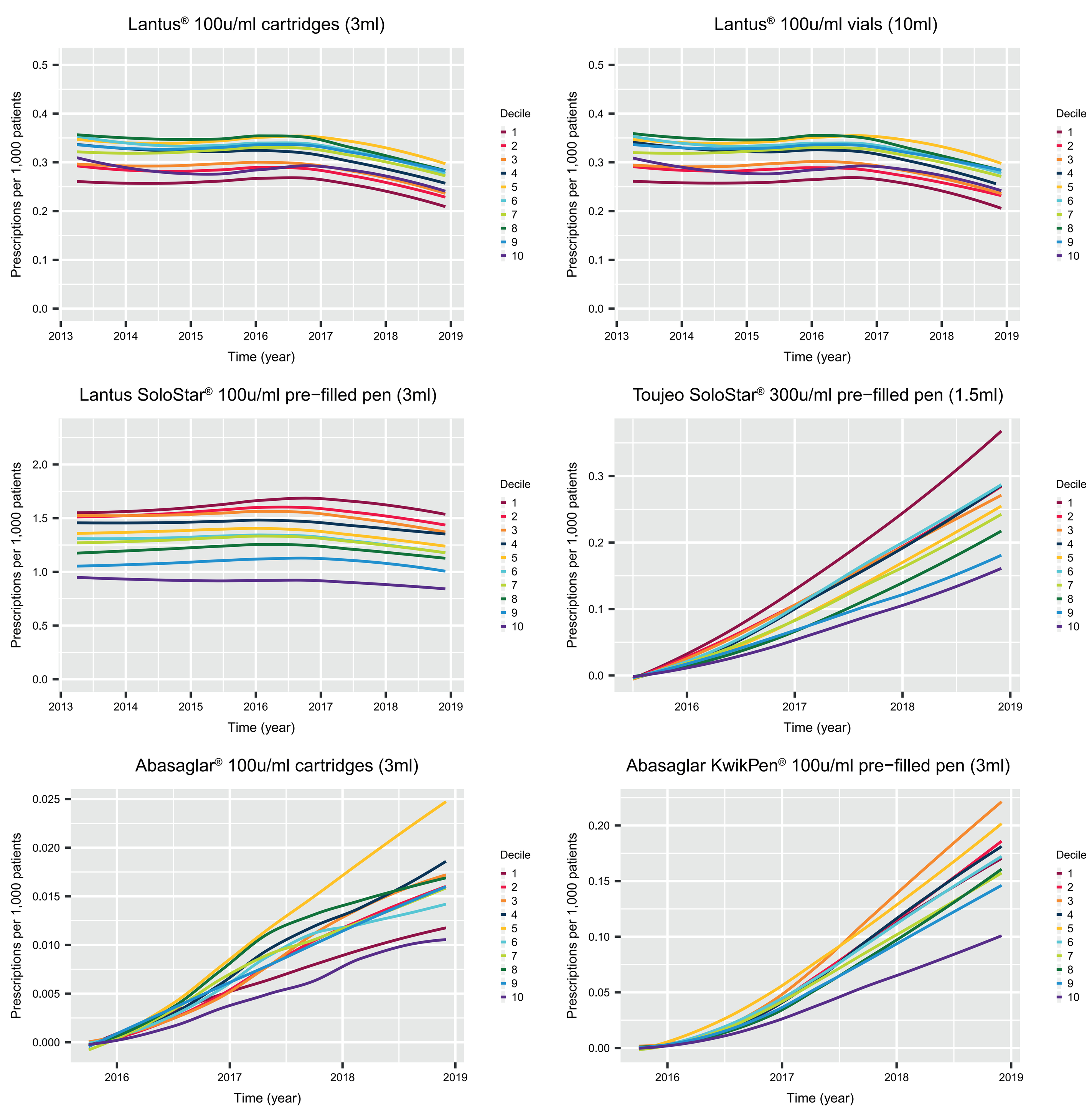

Table 1. Mixed-effects regression model results: estimates and 95% confidence intervals

	Lantus® 100u/ml cartridges (3ml)	Lantus® 100u/ml vials (10ml)	Lantus SoloStar® 100u/ml pre-filled pen (3ml)	Toujeo SoloStar® 300u/ml pre-filled pen (1.5ml)	Abasaglar® 100u/ml cartridges (3ml)	Abasaglar KwikPen® 100u/ml pre-filled pen (3ml)
Intercept	**35.5 (34.5; 36.4)*** **	**206.1 (197.0; 215.2)*** **	-0.552 (-1.127; 0.024)	**-1,594.0 (-1,603.0; -1,584.0)*** **	**-1,607.0 (-1,646.2; -1,567.8)*** **	**-1,946.0 (-1,948.1; -1943.9)*** **
Time (year and month)	**-0.019 (-0.020; -0.019)*** **	**-0.106 (-0.111; -0.101)*** **	-0.0001 (-0.0004; 0.0002)	**0.788 (0.784; 0.793)*** **	**0.792 (0.773; 0.811)*** **	**0.962 (0.961; 0.963)*** **
Patients (1,000s)	**0.055 (0.054; 0.056)*** **	**0.055 (0.052; 0.059)*** **	**0.048 (0.047; 0.048)*** **	**0.047 (0.044; 0.049)*** **	**0.093 (0.084; 0.103)*** **	**0.046 (0.042; 0.050)*** **
Income score (% deprived)	**0.002 (0.001; 0.004)** **	0.001 (-0.004; 0.005)	**0.004 (0.003; 0.005)*** **	0.003 (-0.001; 0.007)	0.001 (-0.007; 0.009)	**0.006 (0.002; 0.011)** **
Sex (% females)	**0.043 (0.041; 0.046)*** **	**0.041 (0.032; 0.051)*** **	**0.036 (0.035; 0.038)*** **	**0.024 (0.018; 0.029)*** **	**0.039 (0.017; 0.062)*** **	**0.055 (0.046; 0.064)*** **
Age (mean years)	**0.016 (0.013; 0.018)*** **	**0.041 (0.032; 0.051)*** **	**0.019 (0.018; 0.020)*** **	-0.0004 (-0.007; 0.006)	-0.004 (-0.024; 0.015)	0.003 (-0.006; 0.013)
Rural-urban category (rural=0)	-0.013 (-0.060; 0.034)	-0.080 (-0.214; 0.053)	**0.040 (0.013; 0.067)** **	**0.351 (0.248; 0.454)*** **	**0.248 (0.033; 0.462)* **	**0.161 (0.149; 0.173)** **
Ethnicity (% white)	**0.300 (0.175; 0.425)*** **	-0.005 (-0.311; 0.301)	**-0.414 (-0.475; -0.352)*** **	0.088 (-0.181; 0.357)	-0.121 (-0.657; 0.416)	**-0.414 (-0.705; -0.124)** **
N	525,322	525,332	525,332	311,686	288,458	288,458

*p<0.05, **p<0.01, ***p<0.001

NOTE: Cells in green indicate a significant result at the 5% significance level; N represents the total number of data points analysed, i.e. the sum of the number of GP practices at each time point.

Concentration indices

- Concentration indices were approximately constant over time and did not indicate any inequalities in the distribution of IG prescriptions across the population (results not shown).

Conclusions

- Results demonstrate that the way GPs in England prescribed IG between 2013 and 2018 was associated with the characteristics of the patients they served. In line with previously reported studies, this included income deprivation which is associated with increased prevalence of diabetes and which was here shown to have a positive effect on prescription levels of all IG products.[1] In general, these relationships do not seem to vary greatly across products, including IG biosimilars.
- Potential variations in prescription levels across CCGs may be related to individual CCG prescribing policies, as it has been shown to occur in other disease areas.[13] These variations may also reflect the epidemiology of the populations served by the CCGs.
- This analysis had some limitations:
  - Some prescriptions (13.1%) were excluded from the analysis due to the lack of brand name associated with the prescription records.
  - Income deprivation (2015 version of the IMD), rural-urban classification (2011) and ethnicity (2011) data were only available in the public domain at single points in time.
- In the regression model, variables such as time can be implemented in several ways. The current model (i.e. considering time as a fixed effect) allows the interpretation of results in a straightforward manner; however, alternative models (e.g. considering time within CCG and GP practice level hierarchy levels or even including an interaction term between these two and time) could also be considered.
- In summary, this study brings new light to understanding potential variations in prescription levels of IG across GP practices and CCGs. This evidence, along with potential future analyses that identify the cause of these variations, could help inform decision making to ensure an equitable primary healthcare system in England.

References

1) Diabetes UK: Tackling the crisis: transforming diabetes care for a better future (England). http://www.diabetes.org.uk/resources-s3/2019-04/Diabetes%20UK%20Tackling%20the%20Crisis.pdf? (2019). **2)** National Institute for Health and Care Excellence: Type 1 diabetes in adults: diagnosis and management. https://www.nice.org.uk/guidance/ng17 (2015). Accessed June 26th 2019. **3)** National Institute for Health and Care Excellence: Type 2 diabetes in adults: management. https://www.nice.org.uk/guidance/ng28 (2015). Accessed June 26th 2019. **4)** Electronic Medicines Compendium: Lantus 100 units/ml solution for injection. https://www.medicines.org.uk/emc/medicine/32853/SPC# (2019). Accessed June 26th 2019. **5)** National Institute for Health and Care Excellence: Diabetes (type 1 and type 2) in children and young people: diagnosis and management. https://www.nice.org.uk/guidance/ng18 (2015). Accessed June 27th 2019. **6)**Electronic Medicines Compendium. https://www.medicines.org.uk/emc/search?q=%22insulin+glargine%22 (2019). Accessed June 26th 2019. **7)** National Institute for Health and Care Excellence: Diabetes mellitus type 1 and type 2: insulin glargine biosimilar (Abasaglar). https://www.nice.org.uk/advice/esnm64/chapter/Key-points-from-the-evidence (2015). Accessed June 26th 2019. **8)** NHS Digital: Practice Level Prescribing Data. https://digital.nhs.uk/data-and-information/publications/statistical/practice-level-prescribing-data (2019). Accessed May 15th 2019. **9)** NHS Digital: Numbers of Patients Registered at a GP Practice (practice level, 5 year age groups). https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/general-practice-data-hub/patients-registered-at-a-gp-practice (2019). Accessed May 15th 2019. **10)** Government Digital Service: English indices of deprivation 2015. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 (2015). Accessed May 15th 2019. **11)** Office for National Statistics: Census Data on Nomis. https://www.nomisweb.co.uk/ (2011). Accessed May 15th 2019. **12)** Office for National Statistics: Rural Urban Classification (2011) of Lower Layer Super Output Areas in England and Wales. https://data.gov.uk/dataset/b1165cea-2655-4cf7-bf22-dfbd3cdeb242/rural-urban-classification-2011-of-lower-layer-super-output-areas-in-england-and-wales (2011). Accessed May 15th 2019. **13)** Walker, A.J. et al: Trends, geographical variation and factors associated with prescribing of gluten-free foods in English primary care: a cross-sectional study. BMJ open 8(3), e021312 (2018). doi:10.1136/bmjopen-2017-021312.