Author's response to reviews

Title: Antihyperglycaemic treatment patterns, observed glycaemic control and determinants of treatment change among patients with type 2 diabetes in the United Kingdom primary care: a retrospective cohort study

Authors:

Andrew Maguire (andrew.maguire@oxonepi.com)
Beth D Mitchell (mitchell_beth_d@lilly.com)
Javier Cid Ruzafa (Javier.cid@evidera.com)

Version: 4
Date: 16 July 2014

Author's response to reviews: see over
Author's response to reviews

Title: Antihyperglycaemic treatment patterns, observed glycaemic control and determinants of treatment change among patients with type 2 diabetes in the United Kingdom primary care: a retrospective cohort study

Authors:
Andrew Maguire (andrew.maguire@oxonepi.com)
Beth D Mitchell (mitchell_beth_d@lilly.com)
Javier Cid Ruzafa (javier.cid@evidera.com)

Version: 3
Date: 10 July 2014

Author’s response to reviews: see over
Dear Sir or Madam,

We are pleased to resubmit our manuscript entitled “Antihyperglycaemic treatment patterns, observed glycemic control and determinants of treatment change among patients with type 2 diabetes in the United Kingdom primary care: a retrospective cohort study”, for your consideration as an original article to be published in BMC Endocrine Disorders. Our manuscript was revised according to the two reviewers’ comments, suggestions and guidelines (please see details below).

We have been commissioned by Eli Lilly and Company to research the antihyperglycaemic treatment patterns in the UK among patients with type 2 diabetes. Therefore, we used available epidemiologic data at the population level to describe such treatment patterns, the observed glycaemic control on the corresponding patients and the determinants of treatment change.

We describe antyhperglycaemic treatment patterns in the UK between 2006 and 2011 and conclude that, whilst there is a notable improvement in glycaemic control at the patient level following OAD initiation, a majority of patients remain above the HbA1c levels recommended by NICE and there is a group of patients whose glycaemic control worsens. The robustness of our results is derived from the use of five recent years of data from a large population-based reputable data source in the UK. We believe that our results have implications for type 2 diabetic patients and how they are treated and monitored.

This manuscript has not been previously published and is not under consideration in the same or substantially similar form by any other journal. Partial results of this study were reported as abstracts at two scientific conferences, including oral presentation at the European Association for the Study of Diabetes in Berlin 2012. All authors are listed in order of their contributions and declare no substantial conflicts of interest.

We look forward to receiving your comments. Please notify us as soon as possible if you have any comments or questions or require additional documentation.

Sincerely,

Andrew Maguire, Beth D Mitchell and Javier Cid Ruzafa

**Corresponding author:**

Dr. Andrew Maguire  
OXON Epidemiology Ltd.  
The Euston Office  
1 Euston Square, 40 Melton Street  
London NW1 2FD UK  
Email: andrew.maguire@oxonepi.com
Reviewer #1: Martin Gulliford

Reviewer's report:

This paper analyses utilisation of oral hypoglycaemic drugs among diabetes patients in the UK registered with the CPRD. The study focuses on predictors of treatment switching or augmentation. The findings are of interest because of the frequency of the condition and the high costs of OHA use.

Major revisions

The main statistical analysis has been done using multinomial logistic models with odds ratios as the main measure of association. The paper notes 'Multinomial logistic regression models were applied to estimate the association between each covariate and the likelihood of each of the treatment outcomes as compared to no change in treatment during the timeframe of interest. The timeframes for which models were applied included the baseline period (first six months after index date) and yearly intervals since index. It was not possible to execute the models for time periods beyond one year since index date due to the decreasing numbers of patients over time.'

In the CPRD data observations may be censored either at left or right as patients enter and leave the database. Analysis in a time to event framework would be more usual. This would overcome some of the difficulties encountered. As a minimum, if a logistic model is to be used then the paper needs to justify this, and explain how many days in a year were required for patients to be considered at risk.

It would be optimal to take into account clustering by general practice, since treatment decision may be correlated within practices. The confidence intervals presented may be artificially narrow. In Stata the 'svy set' or 'robust, cluster' options may be used.

We performed both survival analyses and multinomial logistic regression. For this manuscript we reported the results of the multinomial logistic regression and in the interest of space we decided not to report the survival analyses. Multinomial logistic regression provides intuitive results when patients can have one of several interrelated outcomes (i.e. switch, augmentation or discontinuation vs. persistence) whilst survival analyses are limited to one single event and censors all other outcomes (i.e. discontinued vs. did not discontinue). We were also able to account for the change in HbA1c, as a predictor for treatment pattern change using the HbA1c associated with the timeframe in which the change occurred, in a simpler way than if survival analyses were used only considering one outcome at a time. We accept the limitation of using logistic regression in that variable follow-up is not accounted for. Nevertheless, the patients who were included in these analyses all had to have had at least 15 months of follow-up and the outcome is specifically defined in the time window comprising 6 months to 18 months since OAD initiation. Hence in order to be considered the patients have to comply with similar criteria regarding their follow-up.
We agree that data analysis taking into consideration clustering by general practice would have provided insight into potential bias resulting from variable data quality and confidence intervals that could have a different width than reported. We find reassuring that others have reported little evidence of such potential bias after matching on practice (Haynes K et al, *Pharmacoepidemiology and Drug Safety* 2011). Likewise, the use of matching on general practice could result in wider confidence intervals but it could also reduce variability overall (Walker AM, *J Clin Epidemiol* 2013).

We have included these considerations in the manuscript.

The main results are of interest, but I did not find these surprising. The paper might emphasise the novelty of the results. Data on drug selection at the augmentation stage would be of interest, particularly in terms of the use of newer drugs.

- Data on drug selection at the augmentation stage was not studied specifically because it was not the main goal of our project, i.e. to identify determinants of treatment change following initiation of non-insulin anti-hyperglycaemic treatment. We agree that it would be a topic of interest for another manuscript.

The paper should avoid words that suggest causation. For example, 'association' would be a better word than 'influence'.

- We appreciate the reviewer’s suggestion and have revised the manuscript to avoid using words that suggest causation.

The lines in Figure 2 are not sufficiently labelled. Also, it is not clear that the same patients have increased HbA1c values at each time point, which is implied by the graph. The text should perhaps note some reservations about constructing these subgroups, as there may be problems with the initial measure. It does not seem necessary to include the histogram in either Figure 1 nor 2.

- The Figure 2 has been updated according to the suggestions. At each time point the patients who have HbA1c values is indicated by the corresponding N at the bottom of the Figure, not necessarily the same patients. The initial HbA1c measure is obtained similarly across patients and over time, from the test results in the patient’s records in the database. We agree that the histogram in Figure 2 could be removed but we consider the histogram in Figure 1 to be informative of the shape of the HbA1c distribution at baseline.

Minor revisions

In the introduction it reads 'Our objective was to identify determinants of initial treatment change following initiation of non-insulin anti-hyperglycaemic treatment for UK patients with T2D.'

The first use of the word 'initial' is redundant,
The redundant word has been removed.