Author's response to reviews

Title: Insulin Use and Persistence in Patients with Type 2 Diabetes Adding Mealtime Insulin to a Basal Regimen: A Retrospective Database Analysis

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Version: 2 Date: 9 December 2010

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December 9, 2010

To Whom It May Concern:

We are pleased to submit the accompanying revised manuscript, titled, “Insulin Use and Persistence in Patients with Type 2 Diabetes Adding Mealtime Insulin to a Basal Regimen: A Retrospective Database Analysis” to BioMed Central Health Services Research for publication consideration. We have addressed the reviewers’ comments below and throughout the revised manuscript. As with the initial submission, this is an original study that is not currently under consideration for publication.

Each of the authors approve of this revised manuscript. Below is a summary of the contributions of each author, in addition to providing feedback on manuscript drafts and revisions:

- Bonafede: Principal investigator
- Kalsekar: Study conception, data interpretation
- Pawaskar: Study conception, data interpretation
- Ruiz: Data analysis and interpretation
- Torres: Study concept operationalization, data analysis and interpretation
- Kelly: Study design, clinical relevance, data interpretation
- Curkendall: Data interpretation, oversight of study

We have no competing interest to report but have added relevant employer information to the competing interests section of the paper.

The manuscript is 16 pages long, including the title page, and 22 pages long, including the 3 tables and 2 figures.

Funding for the study was provided by Eli Lilly and Company. Some of this information was previously presented at the 12th Annual European Congress at Le Palais des Congrès de Paris in Paris, France, October 24-27, 2009.

Please do not hesitate to contact me for any additional information or clarification.

Sincerely,

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Reviewer Comments and Responses

Reviewer: Richard Rubin

Reviewer's report:
The question posed by the authors is well defined. The editors should note that the authors recently published a paper (Patient Preference and Adherence 2010; 4:147-156) using the same database and identical methodology. The earlier paper considered a different insulin regimen. The earlier paper is not cited in the current manuscript, but it should be (compulsory).

Response: We have added a reference, highlighting that this methodology has been previously published. The following text was added to the Methods section:

The methods used in this current study were employed in a similar analysis of insulin naïve patients with type 2 diabetes using the same datasource and study design.

The methods are appropriate and well described, though the authors should provide readers with a sense of what non-persistence means in terms of the amount of insulin a person should have taken (compulsory). This estimate cannot be precise, but as it stands the reader is left without a sense of the clinical implications of the defined non-persistence.

Response: We have added text surrounding this to the discussion section. Recommended insulin dose per day, whether it be total or mealtime, depends on patient characteristics that are not included in the dataset (not the least of which is weight). However, we do know that the average insulin per day among non-persistence patients in this study is below what we would reasonably expect; average total insulin per day was 0.30mL and average mealtime insulin per day was 0.13mL, both of which are lower when using measure 2 to define insulin persistence (0.37mL and 0.10mL, respectively). We have added this information to the discussion section.

The manuscript adheres to relevant standards for reporting and data deposition, though the authors should provide 95% CI for OR in text and in table 3 (compulsory).

Response: We have added the 95% confidence intervals for the OR to table 3 and throughout the text.

The discussion and conclusions are generally balanced and adequately supported by the data, though the issues noted above must be addressed in these sections and the authors should discuss the clinical relevance of the statistically significant findings they report (compulsory).

Response: We have addressed the issues above, including the discussion of how non-persistence translates into much lower average daily insulin doses.

The authors do not acknowledge their published paper (noted above).
Response: As mentioned above, we have added a reference to our previously published paper.

Reviewer: Howard Moffet
Reviewer's report:
This paper examined Insulin Use and Persistence in Patients with Type 2 Diabetes Adding Mealtime Insulin to a Basal Regimen. The paper is well-written, but exposures of interest (claims) and outcomes (persistence) could be clearer in their definitions.

Minor Essential Revisions
1. It would be most helpful to differentiate clearly the following: prescriptions (written or ordered by provider) vs dispensings (fills and refills). As written, it suggests that persistence depends on the prescriptions being written rather the dispensings. ("Patients were required to have a second mealtime insulin prescription...") You measured claims as a measure of utilization/dispensings. The use of "claims" or "dispensings", not "prescriptions", as the outcome of interest should be consistent and clear throughout the manuscript.

   Response: This is a great suggestion and one that we have applied throughout the revised manuscript. As the reviewer points out, the database in the study contains only adjudicated claims; unfortunately, the database does not have information on prescriptions that were written but not filled. Prescriptions and claims are not one in the same and this revision should help prevent confusion.

2. The description of measure 2 in the abstract is "1 prescription (dispensing?) per quarter" but this does not seem to be in the text and the definition(s) in the text does not easily distill into 1/quarter. The definition of measure 1 in the text might be aided by an example; I had a hard time grasping the definition as written. ["For example, if a patient had a refill at (index date + 2 months) but did not have another fill within the next 90 days (i.e. index + 5 months), that patient would be nonpersistent." ] The definition of measure 2 could be clearer; does the count (e.g. At least 2 mealtime insulin claims in first 4 months) include the index fill? Should the bullets for Persistent at 6 months be joined by "and"? If so, perhaps simply state as a sentence (e.g., Do you mean, "At least 3 mealtime insulin claims (including index or not?) in first 7 months INCLUDING At least one mealtime insulin claim in months 1-3 AND At least one mealtime insulin claim in months 4-6")? Also, start a new paragraph on page 6 at the beginning of definition of Measure 2.

   Response: We have incorporated these suggestions into the text to make this section more clear, including adding an example for Measure 1. Your interpretation is correct, on all counts. Measure 2 is strictly one claim per quarter for persistence at 12 months (the primary study outcome) but not for evaluating persistence at 3 or 6 months. We have not changed the abstract, due partly to space constraints, but moreso due to the fact that this manuscript does not focus on persistence at 3 or 6 months.
3. In Results, suggest simply identifying those with type 2 dm those with no evidence of type 1 or GDM and then identify those with required prescriptions of basal insulin. It is distracting to read of those with type 2 dm who have evidence of type 1 or gdm.

Response: The current description of the sample follows the steps in the building of the analytic file as they relate to the index event (i.e., mealtime insulin claim). These steps were completed at the start of the file build and the start of the project, meaning that we can’t generate the prevalence of each exclusion criteria in a different order than they are presented here. The only alternative would be to exclude this information from the Results section, which we are reluctant to do as it describes where our study sample fits into the larger database and patient populations.

Discretionary Revisions

4. It was surprising that the two measures of adherence have such different results, since they appear to be so similar at first look. Perhaps you can say more to explain the difference or why it might matter.

Response: The two approaches were designed to provide a higher and lower estimate of persistence. Measure 1 uses a fairly standard approach where the presence of a 90-day gap indicates non-persistence. Measure 1, however, is strict in that it doesn’t allow pauses in therapy or filling of prescriptions far in advance. Measure 2 requires the same number of scripts per year (4), requiring that the average gap between refills is no more than 90 days, but allows for more variation in the refill pattern. Measure 2 also allows for increasing flexibility throughout the one year follow-up; method 2 should show a higher rate of persistence. In short, real-world persistence in a similar population shouldn’t be much higher than we found using Measure 2 or much lower than we found using Measure 1. That said, as a team, we were reluctant to state that one measure is better than the other, nor did we want to.