Author's response to reviews

Title: Use of aspirin for primary and secondary prevention of cardiovascular disease in diabetic patients in an ambulatory care setting in Spain

Authors:

Antoni Sicras-Mainar (asicras@bsa.gs)
Ruth Navarro-Artieda (rnavarro.germanstrias@gencat.net)
Xavi Frias-Garrido (xfrias@bsa.gs)
Rafael Ruiz-Riera (rruiz@bsa.gs)
Javier Rejas-Gutierrez (javier.rejas@pfizer.com)
Jaime Fernandez-de-Bobadilla (jaime.fernandez@pfizer.com)

Version: 3 Date: 19 July 2007

Author's response to reviews: see over
Dear Editor,

We really appreciate and thank you the comments and suggestions made on this manuscript. As you can see, the format of manuscript has been reviewed and modified accordingly with journal guidelines.

# 0 - Senior Assistant Editor (Dr Chrissie Kouremenou)
To this regard, title page has been corrected. A new paragraph dealing with signed consent has been included in section Material & Methods, and 'Competing interests' section has been added between the Conclusions and Authors' contributions (financial & non-financial). Finally, it has been completed the section Authors' contributions before the Acknowledgements and Reference list.

# Reviewer 2: Jun Ma

Major Compulsory Revisions

Commentary 1: The Introduction pays inadequate attention to numerous studies already published on the same subjects and does not address why this study is needed and how it advances the scientific knowledge.

- A new paragraph has been added in the section Introduction before the reference to the objectives of the study. It is the following: “… The rationale of the study was to review to what extent these recommendations/guidelines, which are evidence base medicine, are implemented in real world standard condition of care in a primary care setting”.

Commentary 2: Aspirin is contraindicated in individuals < 21 years because of increased risk of Reye's syndrome, yet the study sample included patients >= 18 years.
- In Spain aspirin is contraindicated in subjects less than 16 years, instead of 21 years old.
  … In addition we deleted ‘under 21 years’ in the introduction section.

Commentary 3: It is also unclear how patients with other known contraindications to aspirin were handled in the analysis. These contraindications include: aspirin allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease.
- This was a research based on real world data from an extensive database and, as a consequence, included variables are limited and it is not possible to determine whether patients were taking a medication different from aspirin because of a contraindication or because of other medical criteria. However, we recognize this gap in the limitations section of manuscript.

Commentary 4: The definition of “regular use” of aspirin is unspecified, yet it is critical to the understanding and interpretation of the study findings. Also, in certain passages it is stated “aspirin was prescribed” whereas in other passages it is stated “aspirin was taken.” These two phrases imply entirely different measurements and implications. The former is medical prescription data and measures physician prescribing behaviour, whereas the latter is typically by patient self-report and measures patient adherence.
- The reviewer is right. We have modified the methods section in order to add a definition for regular use of aspirin as follows: “Aspirin regular use by a patient was established when a physician prescribed
Commentary 5: No data are provided regarding the representativeness of the primary care centers and the patients in the study. As a result, no judgement may be made regarding the generalizability of the findings. In the Discussion, it is stated that "...the sample size achieved in our study, among the largest in the reviewed series, suggests that the results found should not differ too much from the actual results." It must be noted that sample size alone does not guarantee representativeness or generalizability.
- The reviewer is right. We have deleted the sentence "the sample size achieved in our study, among the largest in the reviewed series, suggests that the results found should not differ too much from the actual results" from the discussion section in order to avoid any possible confusion or misunderstanding.

Commentary 6: A number of statistical methods are listed for bi-variate analyses. But, it is unclear which methods were used for what variables and the rationale is not provided. For example, why is it necessary to perform a correlation with polynomial trend when visual inspection and simple statistics would sufficiently show that most PP patients have 2 or 3 risk factors? Also, it is interesting that diabetes was included as one of the risk factors in Figure 1 when the entire sample had diabetes to begin with.
- The reviewer is right. We have rewritten the section statistical methods in order to gain clarity. Also mentions to polynomial correlation have been deleted from figure and text as well.

Commentary 7: In Figure 2, the PP and SP groups showed quite similar patterns. The reason that the trend test did not reach statistical significance for the SP group could very likely due to lack of power associated with a much smaller sample size compared to the PP group. The value of Figures 1 and 2 is not apparent and this reviewer recommends their omission.
- The reviewer is right. We have deleted figure 2 as recommended by reviewer. However, figure 1 and table 1 are kept in the manuscript in order to gain more information on patient distribution of cardiovascular risk factors. Also mentions to polynomial correlation have been deleted from figure and text as well.

Commentary 8: The forward (or backward) stepwise logistic regression method utilizes the likelihood ratio test (chi-square difference) to determine automatically which variables to add or drop from the model. This brute-force method runs the risk of modelling noise in the data and is considered useful only for exploratory purposes. Selecting model variables on a theoretic basis and using the "Enter" method is preferred. However, problems of overfitting the model to noise in the current data may be mitigated by cross-validation, fitting the model to one a test subset of the data and validating the model using a hold-out validation subset. Authors are recommended to consult a qualified statistician.
- We used to procedure to run the regression analysis; one using the enter procedure and the other using a backward stepwise procedure. Results were equivalent and we decided to maintain in the manuscript results observed in the regression model using the enter procedure.

Commentary 9: The thresholds quoted in the text and for statistical analysis were different from those enumerated in Table 1 for several clinical parameters (e.g., total cholesterol and HbA1c) and no justification is given.
- The reviewer is right. We have modified typographic mistake on HbA1c. Also, regarding the thresholds used for analysis, these were the one commented on methods section, while the data on table 1 become from a Medical Society.

**Minor Essential Revisions**
The manuscript needs thorough editing and proofreading.
- Done
# Reviewer 1: James Sowers

**Major Compulsory Revisions**
None

**Minor Essential Revisions**
Please comment on temporal changes in ASA use over the duration of this retrospective analysis.
- see reviewer 2 comment on this topic above.