Author's response to reviews

Title: The weight lowering effect of sibutramine and its impact on serum lipids in cardiovascular high risk patients with and without type 2 diabetes mellitus - an analysis from the SCOUT lead-in period

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Version: 4 Date: 3 December 2009

Author's response to reviews: see over
Dr. Sabina Alam, PhD.
Senior Scientific Editor,
BMC Endocrine Disorders

Regarding the Manuscript: 1278801374292037

The weight lowering effect of sibutramine and its impact on serum lipids in cardiovascular high risk patients with and without type 2 diabetes mellitus - an analysis from the SCOUT lead-in period

Dear editor, Dr. Sabina Alam,

Thank you for your positive reply and the very useful comments from the reviewers.

We have thoroughly addressed all of the comments and critique points raised by the reviewers and complied with proposed improvements to the manuscript. We have enclosed a point to point response.

We kindly request the editor to consider the revised manuscript for publication in BMC Cardiovascular Disorders. We hope you find our revision and changes to the manuscript satisfactory.

In the following the reviewers’ comments are formatted in Italic, black color and numbered (reviewers’ comments) followed by our reply in normal, green color characters (our replies to the reviewers’ comments).

Changes made to the manuscript are clearly marked by blue color text for newly added text (inserted text) and red and strikethrough for removed text (removed text). The revised manuscript has been uploaded (Text of manuscript: Lipids_BMC_July09_revised_Dec09). All authors have read and approved the revised version of the manuscript.

On behalf of all the authors, yours

Peter Weeke, MD
Referee no. 1:

Title: The weight lowering effect of sibutramine and its impact on serum lipids in cardiovascular high risk patients with and without type 2 diabetes mellitus – an analysis from the SCOUT lead-in period

Version: 3 Date: 25 September 2009

Reviewer: Zbigniew Gaciong

Reviewer's report:

The paper can be published after minor essential revisions listed below:

1. In the Methods section they wrote that treatment lasted 6 weeks while in Discussion 4 weeks of sibutramine administration was mentioned.

Our comment: We appreciate and acknowledge the reviewers comment regarding the treatment period. We are investigating a 4-week treatment period from the initial 6-week lead-in period, which is written in the methods section. However, in order to make this stand out more clearly we have made the following changes in the discussion section.

Changed text: Line 200, page 9

We found that T2D status had a significant influence on all lipids following four weeks of sibutramine treatment during the 6-week lead-in period of the study (Figure 3).

2. In the Discussion they missed the study by CA Dujovne et al (Effects of sibutramine on body weight and serum lipids: A double-blind, randomized, placebo-controlled study in 322 overweight and obese patients with dyslipidemia. Am Heart J 2001; 142: 489-97) which should be acknowledged.

Our comment: We agree with the reviewer that the study by Dujovne et al. is important and should be acknowledged. Thus, we have included the study in our discussion as it supports our findings together with previous findings regarding the changes in HDL-cholesterol following longer term (six months) weight loss with sibutramine treatment as an adjunct to a step I American Heart Association diet.

Changed text: Lines 230-231, page 10

Sibutramine was found to induce significant increases in HDL-C levels following six months of therapy[21, 22] but no acute changes during the initial period of weight loss.
Reviewer's report:

Major compulsory revisions:

1. The non diabetic subgroup revealed a baseline positive history of coronary heart disease (91.5%) and a significant higher prevalence of acute myocardial infarction (58.8% vs 37.1). The percentage of patients treated with statins is significantly higher in non diabetic subgroup. These data seem to justify an high cardiovascular risk profile of the analyzed population and furthermore the non diabetic LDL higher levels at baseline. For these reasons baseline characteristics need to be improved by analyzing the diagnosis of Metabolic Syndrome according to ATP-III (including fasting glycemia).

Our comment: A very insightful comment by the reviewer. We agree that the metabolic syndrome is of considerable interest in relation to cardiovascular risk. In order to improve the baseline characteristics we identified the number of patients with the metabolic syndrome according to predefined criteria of the Adult Treatment Panel III from the National Cholesterol Educational Programme as requested by the reviewer. Notably, the criteria for enrollment in the SCOUT study were largely the same criteria used to define the metabolic syndrome according to the Adult Treatment Panel III. We found that 84% (N=9033) of patients have 3 or more of the 6 risk factors defining the metabolic syndrome. One of these criteria is a fasting glucose level of ≥6.1 mmol/l.

Changed Text: Lines 155-157, page 8

Overall 84.2% (n=9033) of the patients had the metabolic syndrome according to the Adult Treatment Panel III defined criteria.[8] The majority (87.5%, n=7901) of the patients with T2D met the criteria whereas patients without T2D usually did not (12.5%, n=1132; p for difference <0.0001).
2. The antidiabetic oral therapy needs to be elucidated in relation to improvement on insulin resistance status and so in basal lipid profile.

Our comment: The reviewer has correctly pointed out that we have not elucidated the type of antidiabetic therapy in patients with type 2 diabetes. Thus, we have now added information on the percentage of patients receiving insulin therapy compared to oral antidiabetic therapy. In the SCOUT study no information on insulin resistance was available from the 6-week lead-in period which is why, unfortunately, we are unable to draw any conclusions on this matter.

Changed text: Line 148, page 7

The T2D group (n=8981) comprised 83.7% of the overall study population. Of these 30.4% (n=2734) were on treatment with insulin.

3. These data are of interest but limited by the potential influence on lipid profile exerted by performing venous sampling during the day.

Our comment: We agree that the results may be influenced by the venous sampling during the day. Thus, there may be day to day variation of the time of the sampling potentially influencing the lipid profile. As requested by the reviewer we, have addressed this further in our limitations section

Changed text: Lines 274-278, page 12

Patients were requested to be fasting for every visit that included blood samples and we have specific statements from the patients that they complied. were truly fasting. However, patient visits were carried out at different times during the day; for example, if the first visit was in the morning and the second in the late afternoon, this could potentially influence measured lipid levels. Thus, the lipid profile may have been influenced by the varying times of venous sampling.

Minor essential revisions:

1. viz line 13 page 10 please specify
Our comment: As noted by the reviewer the abbreviation ‘viz’ is a synonym for ‘namely’ or ‘as follows’. In order to improve the manuscript we have changed the abbreviation:

Changed text: line 220, page 10
These three features namely viz the greater fall in BMI, the use of statins and the greater hyperlipidaemia, therefore, seemed to have combined to induce the greater fall in TC and LDL-C in the patients without T2D.

2. **HDL-C dip line 2 page 11 please specify**

Our comment: We agree with the reviewer that our choice of words can be improved. The ‘HDL-C dip’ referred to by the reviewer is describing the finding from most studies investigating the changes in lipid profile following acute weight loss. These studies have demonstrated how HDL-C decrease immediately following acute weight loss. We have changed the sentence so that it now reads:

Thus, our results on HDL-C are concordant with previously described short term responses where an initial decrease in HDL-C is expected.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests
Referee no. 3:

Reviewer's report

Title: The weight lowering effect of sibutramine and its impact on serum lipids in cardiovascular high risk patients with and without type 2 diabetes mellitus – an analysis from the SCOUT lead-in period

Version: 3 Date: 29 October 2009

Reviewer: Kenneth Fujioka

Reviewer's report:

1. I would recommend a much shorter paper and try not to over reach the findings as again this study was designed to look at different end points, particularly trying to compare DM pts to non DM pts

Our comment: The reviewer has correctly pointed out that the SCOUT study was not designed to compare diabetes patients. This is a limitation which we have now addressed in our limitations section. Furthermore, we are willing to make the paper shorter if the editor would like us to. Currently we have not made the paper shorter as we believe it would influence the requests and wishes from the other reviewers. However, the paper has not been made longer after it has been revised.

Changed text: lines 283-284, page 12

Notably, the SCOUT trial was not specifically designed to compare lipid changes following four weeks of treatment with sibutramine as an adjunct to dietary advice and exercise; this is a limitation.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests
Referee no. 4:

Reviewer's report

Title: The weight lowering effect of sibutramine and its impact on serum lipids in cardiovascular high risk patients with and without type 2 diabetes mellitus – an analysis from the SCOUT lead-in period

Version: 3 Date: 17 November 2009

Reviewer: Davor Stimac

Reviewer's report:

Major Compulsory Revisions - In the paper are presented very interesant results about effect of anti obesity drug sibutramin and its impact on serum lipids in patients with and without type 2 diabetes. Analysis is made based on lead in period in SCOUT study - I found that section Introduction is enough informative, methods are correct results are well presented and discussion is fruitfull.

Discretionary Revisions

1. Figures should be technically better performed. I personnaly suggest to revise graphs.

Our comment: We agree with the reviewer that the graphs would benefit from revision. Thus, we have revised all figures to improve the quality.

Changed text: Please see revised figures

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'