## PEER REVIEW HISTORY



## ARTICLE DETAILS

| | |
|---|---|
| **TITLE (PROVISIONAL)** | Effect of Fenofibrate on plasma apolipoprotein C-III levels: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials |
| **AUTHORS** | Sahebkar, Amir; Simental-Mendia, Luis; Katsiki, Niki; Reiner, Zeljko; Banach, Maciej; Pirro, Matteo; Atkin, Stephen |

## VERSION 1 – REVIEW

| | |
|---|---|
| **REVIEWER** | Shun Ishibashi<br>Jichi Medical University, Japan |
| **REVIEW RETURNED** | 07-Feb-2018 |

| | |
|---|---|
| **GENERAL COMMENTS** | Sahebakar A et al. performed a systemic review and meta-analysis of the effects of fenofibrate on plasma apoCIII levels. They found that fenofibtae reduced plasma apoCIII levels irrespective of the dose or duration of the studies.<br><br>Major comments<br>1) Given the effects of fenofibrate on plasma apoCIII levels are evident even in a small study of short duration, the reviewer does not think that a systematic review and meta-analysis are necessary to prove the premise. Relatively rare events such as ASCVD and thromboembolism or parameters of mixed results such as plasma LDL-C may be worth being studied by meta-analysis.<br>2) Most of the studies measured other apolipoproteins such as apoCII, apoE and apoB. The authors should include these parameters for the analyses.<br><br>Minor comments<br>p. 15, lines 5 and 3 from the bottom: APO3? |

| | |
|---|---|
| **REVIEWER** | Lisa Juntti-Berggren<br>The Rolf Luft Research Center for Diabetes and Endocrinology, Dept of Molecular Medicine and Surgery, Karolinska Institutet, Sweden |
| **REVIEW RETURNED** | 20-Mar-2018 |

| | |
|---|---|
| **GENERAL COMMENTS** | ApoCIII is interesting from several health aspects so this meta analysis has a value. I agree with the authors that unfortunately the number of subjects is small. To try to get as much information as possible out of this study I have some suggestions. I would include the total number of subjects in Table 1 instead of as now the n for females and the %,(so of course you can calculate the total n) write Total n and n for f/m. What I think would be of interest is if there is a gender difference in the response to the fibrate and |

| | |
|---|---|
| | if the numbers are too small to make any conclusion state that in the discussion. As Tgs are tightly related to apoCIII and even sometimes used as an indirect measure of apoCIII I suggest that you more clearly state what you found in the analysis. I think the sentence on p 14 and Fig 4 is too brief. Where there those where Tg decreased without effect on apoCIII and vice versa. Where the responses related to the baseline levels? |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name: Shun Ishibashi
Institution and Country: Jichi Medical University, Japan
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Sahebakar A et al. performed a systemic review and meta-analysis of the effects of fenofibrate on plasma apoCIII levels. They found that fenofibtae reduced plasma apoCIII levels irrespective of the dose or duration of the studies.

Major comments
1) Given the effects of fenofibrate on plasma apoCIII levels are evident even in a small study of short duration, the reviewer does not think that a systematic review and meta-analysis are necessary to prove the premise. Relatively rare events such as ASCVD and thromboembolism or parameters of mixed results such as plasma LDL-C may be worth being studied by meta-analysis.

*Thank you for that comment. As we detail, the strength of this study was the use of the meta-analysis that utilized the increased population size compared with individual studies that were small and, in some instances, underpowered to look at the effect of fenofibrate on plasma apo C-III. We agree that rare events such as ASCVD and thromboembolism would be worth their own meta-analysis separately*

2) Most of the studies measured other apolipoproteins such as apoCII, apoE and apoB. The authors should include these parameters for the analyses.

*Thank you for that comment. We agree that most of the studies measured other apolipoproteins that have been subject to other systematic reviews and meta-analyses, whilst apoC-III has not and hence the subject of this review*

Minor comments
p. 15, lines 5 and 3 from the bottom: APO3?

*This has been corrected*

Reviewer: 2
Reviewer Name: Lisa Juntti-Berggren

Institution and Country: The Rolf Luft Research Center for Diabetes and Endocrinology, Dept of Molecular Medicine and Surgery, Karolinska Institutet, Sweden
Please state any competing interests or state 'None declared': Participated in advisory boards for AstraZeneca, Sanofi and Novo Nordisk

Please leave your comments for the authors below
ApoCIII is interesting from several health aspects so this meta analysis has a value. I agree with the authors that unfortunately the number of subjects is small.

*Thank you for your positive comment and your very helpful suggestions.*

To try to get as much information as possible out of this study I have some suggestions. I would include the total number of subjects in Table 1 instead of as now the n for females and the %,(so of course you can calculate the total n) write Total n and n for f/m.

*Thank you this has been done as suggested*

What I think would be of interest is if there is a gender difference in the response to the fibrate and if the numbers are too small to make any conclusion state that in the discussion.

*Thank you this has been done as suggested. The Discussion reads "Finally, included the trials did not provide gender-stratified results for the impact of fenofibrate on plasma apo C-III levels; therefore, the presence of any gender effect on the apo C-III-lowering activity of fenofibrate needs to be evaluated in further studies."*

As Tgs are tightly related to apoCIII and even sometimes used as an indirect measure of apoCIII I suggest that you more clearly state what you found in the analysis.

*Thank you for that comment. The results have been amended in the meta-regrassion and now read "The results suggested a significant association between the apo C-III-lowering effect of fenofibrate with baseline apo C-III (slope: -0.40; 95% CI: -0.58, -0.22; p<0.001) and baseline triglyceride (slope: -0.02; 95% CI: -0.03, -0.01; p=0.001) concentrations. However, no significant association between the apo C-III-lowering and triglycerides-lowering effects of fenofibrate was found (slope: 0.11; 95% CI: -0.05, 0.27; p=0.185) nor were there any association with baseline LDL-C (slope: -0.02; 95% CI: -0.12, 0.08; p=0.677), HDL-C (slope: 0.35; 95% CI: -0.29, 0.98; p=0.284) and BMI (slope: -0.75; 95% CI: -2.08, 0.58; p=0.269) (Table 3)."*

I think the sentence on p 14 and Fig 4 is too brief. Where there those where Tg decreased without effect on apoCIII and vice versa. Where the responses related to the baseline levels?

*Thank you for that comment. The Discussion has been amended to read "Moreover, the apo C-III-lowering effect of fenofibrate was found to be directly proportional to baseline apo C-III and triglycerides levels, suggesting that greater effects on plasma apo C-III levels are anticipated in populations with hyperapolipoproteinemia C-III hypertriglyceridemia. However, there were no associations between apo C-III-lowering effect of fenofibrate with baseline BMI, LDL-C and HDL-C, and the changes in plasma triglycerides levels. The latter finding on the lack of any association between changes in plasma apo C-III and triglycerides levels could be attributed to the fact that not all VLDL particles (as the main carriers of apo C-III in plasma) contain apo C-III. It has been estimated that apo C-III is present in about 50% of plasma VLDL particles. This might justify the lack of apo C-III reduction proportional to triglycerides reduction following fenofibrate therapy 42."*

Reviewer: 3
Reviewer Name: Fabrizio D'Ascenzo
Institution and Country: DIvision of Cardiology, Turin
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The present is a pairwise meta-analysis aiming to describe impact of fenofibrate on apo C III levels, demosntrating a good reduction of levels.

*Thank you for your comment*

Some issues need to be appraised:

- meta-regression for baseline risk factors should be performed

*Thank you this has been performed in the Meta-regression section of the Results and reads "The results suggested a significant association between the apo C-III-lowering effect of fenofibrate with baseline apo C-III (slope: -0.40; 95% CI: -0.58, -0.22; p<0.001) and baseline triglyceride (slope: -0.02; 95% CI: -0.03, -0.01; p=0.001) concentrations. However, no significant association between the apo C-III-lowering and triglycerides-lowering effects of fenofibrate was found (slope: 0.11; 95% CI: -0.05, 0.27; p=0.185) nor were there any association with baseline LDL-C (slope: -0.02; 95% CI: -0.12, 0.08; p=0.677), HDL-C (slope: 0.35; 95% CI: -0.29, 0.98; p=0.284) and BMI (slope: -0.75; 95% CI: -2.08, 0.58; p=0.269) (Table 3)."*

- it is not clear if random or fixed effect was used

*A random effects model was used and this has been clarified in the manuscript*

- potential impact on plaque rupture (quote on PMID: 28605473) should be discussed

*Thank you for your comment that has been addressed in the Discussion that reads "It has also been shown that accumulation of apo C-III and triglycerides in the necrotic core predisposes to plaque vulnerability in patients with stable CAD; hence, the significant lowering effect of fenofibrate on both of these parameters might justify its potential efficacy in preventing plaque rupture and acute CV events, as shown for statin therapy [51]. In addition, there is evidence in vivo showing the stabilizing and regressing effects of fenofibrate[52 53] on the atherosclerotic plaque".*

**VERSION 2 – REVIEW**

| | |
|---|---|
| **REVIEWER** | Lisa Juntti-Berggren<br>The Rolf Luft Research Center for Diabetes and Endocrinology, Dept of Molecular Medicine and Surgery, Karolinska Institutet, Sweden |
| **REVIEW RETURNED** | 31-Jul-2018 |

| | |
|---|---|
| **GENERAL COMMENTS** | The revision of the mansucript has made it more clear for the readers and the limitations are mentioned. |

| | |
|---|---|
| **REVIEWER** | Fabrizio D'Ascenzo<br>Division of Cardiology, Turin |
| **REVIEW RETURNED** | 02-Jul-2018 |

| | |
|---|---|
| **GENERAL COMMENTS** | The authors fullfilled our requests |