Dear Editor,

Thank you for the reviews, please find below our responses:

Reviewer 1:

Well written article

No changes made, thank you.

Reviewer 2:

This paper reflects the current Knowledge on the use of fibrates in patients with hypertriglyceridaemia. The Problems with the Elevation of HDL-C induced by fibrates are clearly described. The reviewer suggests that the authors should add some Points:

1. A severely impaired renal function is an accepted contraindication against fibrates - this should be clearly stated. The authors describe an Elevation of creatinine under fibrates.

Thank you, we accept this as a valid point. To page 9 this has been added: Fibrates also cause reversible elevations in creatinine levels and, though this is not usually a contraindication for use, fibrate dose should be reduced or the drug withheld in those with renal impairment as recommended by the manufacturer[47]. Doses of fibrates should be reduced or withheld in those with renal impairment as per manufacturer's advice.

2. Some remark on the role of Nutrition (fats, Body weight) should be made.

Thank you, the following has been added to page 7.

Indeed, the various phenotypes of the syndrome prompt the use of specific therapies. For example, the syndrome is characterised by weight gain that may be ameliorated by nutritional advice resulting in weight loss and reduced hypertriglyceridaemia and increased HDL. Such advice and intervention should be first line treatment which is continued throughout treatment even if initial efforts are unsuccessful. Insulin resistance and hypertension may also be improved by this approach.

3. The role of postprandial TG Levels should be discussed - should they be measured in the practice? What is the effect of fibrates on them?

Thank you, we have added this on page 26.

Further elucidation, of the role of TG and CVD, may also occur with the introduction of non-HDL in the recent NICE guidance on lipid guidance and CVD risk assessment[3]. This will

lead to postprandial hypertriglyceridaemia being represented in CVD risk assessment[3]. Data suggest that postprandial hypertriglyceridaemia is an independent CVD risk factor and that it is non-fasting TG, rather than fasting TG, that provide the main risk[105]. There is evidence that fibrates are useful in ameliorating vascular damage caused by postprandial elevations in TG level by targeting TG metabolism, although the evidence is not conclusive at the current time with robust outcome data lacking[106,107,108]

4. A HTG also may induce pancreatitis - this should be mentioned.

This has been added to page 10:

Fibrates also have a role in preventing the hypertriglyceridaemia associated with pancreatitis. Guidelines do suggest fibrates as first-line TG lowering treatment to reduce the risk of pancreatitis, with nicotinic acid, omega 3 supplements and statins also considered[60].

The clinical efficacy of fibrates in CVD risk management will now be examined.

5. A recently published paper dealt with data obtained in HTG patients in a lipidologic Center - this paper should be discussed as well: Scholz, M., Tselmin, S., Fischer, S., and Julius, U. Hypertriglyceridemia in an outpatient department - Significance as an atherosclerotic risk factor. Atheroscler.Suppl. 18:146-53. doi: 10.1016/j.atherosclerosissup.2015.02.011., 146-153. 2015. Here the effect of TG lowering on CVE has been described also.

Thank you this has been added to page 21:

Our finding is complemented by a recent retrospective study by Scholz et al which highlighted the risk posed by elevated TG levels in the metabolic syndrome and pointed to TG lowering by fibrates and omega 3 fatty acids being potentially an important mechanism of cardiovascular event reduction[88].

6. The role of fish oils should be discussed.

Thank you, we decided to focus on fibrates specifically but it is a good point for completeness. Therefore added to page 26:

Future Developments

Other existing TG medications such as omega-3 fatty acids have a less clear evidence base than fibrates in regards to CVD risk reduction. This may be due to lack of specific efficacy or that the benefit is not mediated directly by TG reduction but by other unidentified mechanisms. Further, research is required to answer these questions and also the effects in combination with fibrates.

7. New developments (Lipase gene therapy, antisense apo CIII) should be mentioned - their Position with that of fibrates should be discussed.

Pg 26 – we have included this following the section on fish oils addressed in point 6.

Future Developments

Development of novel agents that treat hypertriglycerideamia (including genetic hypertriglyceridaemic states) with greater efficacy may clarify the role of TG reduction in CVD risk management. For example gene therapy with lipoprotein lipase replacement may well reduce pancreatitis in those with familial lipoprotein lipase deficiency, however, long term data and larger patient numbers are required to establish their role regards CVD outcomes[104].

The paper contains a few spelling Errors:

1. A space is lacking several times - e. g. before mmol/L.

Thank you, spaces added.

2. Page 12 Line 21: (62) should be in upper case

Thank you, changed, reference removed.

3. Page 17 Line 16: not - what is meant here?

Thank you it has been changed. The study looked at those with ECG changes indicating an MI which had been asymptomatic; they appeared to gain more benefit than those with no evidence of a silent MI.

4. Page 22 Line 6: LTTs (LTTS is written)

I am sorry but unable to spot this mistake. Thank you.

5. In the capture of Figure 3 "only" is redundant once

Thank you, one has been removed.

6. References 10 and 69: no authors

Thank you, added

7. Reference 73: end page lacking

Thank you, however this is how it is cited with no end page. If you enter the article it is numbered pages 1-5 but citation does not include that information.

8. Reference 81: volume and pages lacking

Thank you, yes the article has yet to be published but I have made that clearer etc.

In regards to an audio core tip we are struggling to get hold of a suitable technology to do this. Would you like me to keep chasing this, is it essential? We are also struggling with cross check, none of us have access to this via our institutions.