

Reviewer #1:

We thank the reviewers for the positive feedback and helpful comments. Please find attached our point-to-point answers. We have made track changes in the text (blue) in the revised version of the manuscript.

1) The article is missing the new hypothesis proposed in this study.

Response: The hypothesis which we discuss in our manuscript suggests that measuring markers of cholesterol metabolism will demonstrate that especially patients 75 years and older have a higher ratio of cholesterol absorption to cholesterol synthesis and will therefore benefit in particular from inhibition of cholesterol absorption with ezetimibe. In order to point this out more clearly we have included a paragraph in the revised version of the manuscript in which we draw attention to a discussion with the TIMI Study Group in letters to the editor in the *Journal of the American College of Cardiology*:

We have therefore suggested to test the strategy of evaluating the ratio of cholesterol synthesis and absorption in IMPROVE-IT <sup>37</sup> as early as 2016. The analysis is under way as assured by the TIMI Study group and will provide important mechanistic insights <sup>38</sup>.

2) The authors describe the large studies conducted so far in which the treatment with statins was used as well as in combination with ezetimibe.

Response: we agree with this statement. But more importantly, we give mechanistic insights on why a combination of a statin and ezetimibe might be of particular benefit in patients with high sterol absorption.

3) In addition, understanding the factors influencing the aging process can improve the quality of life and reduce the number of risk factors for cardiovascular disease, as the incidence of atherosclerosis, myocardial infarction and stroke increases with age.

Response: We agree with this statement. On this background changes of cholesterol metabolism over lifetime and therapeutic consequences derived from these findings are of importance.

4) The article lacks clearly formulated methods of lowering cholesterol in patients over 75 years of age. There are no summary

conclusions from the analysis of the described clinical trials of cholesterol lowering in various disease states.

Response: Evidence from large scale prospective trials that ezetimibe in primary and secondary prevention reduces hard cardiovascular outcomes in patients 75 years and older should be included in future dyslipidemia recommendations. Current evidence indicates that ezetimibe should be the lipid-lowering drug of choice in this particular patient group. We have included a clear statement in our conclusions.

4) What are the unique insights presented in this study?

Response:

In this review we aimed to elucidate the most recent clinical trials demonstrating the benefit of ezetimibe (such as IMPROVE-IT and EWTOPIA-75). These studies change our view of lipid lowering therapy in elderly individuals. IMPROVE-IT demonstrated that the addition of ezetimibe to a statin is most effective in patients 75 years and older. Moreover, statins failed in primary prevention in the elderly (PROSPER, ALLHAT-LLT), ezetimibe, however, proved to be safe and effective in the reduction of cardiovascular events (EWTOPIA-75). We believe that these findings are important and guideline-changing.

Reviewer #2:

1) First what are the limitations of the study and its results?

The IMPROVE-IT Study in the elderly is a post hoc analysis. A prospective randomized trial investigating hard cardiovascular outcomes in patients 75 years or older is lacking. EWTOPIA 75 is such a trial for ezetimibe monotherapy. An analysis of markers of cholesterol metabolism in the IMPROVE-IT cohort, as suggested by our group earlier, will reveal important mechanistic insights and is under way. We have included a paragraph in the revised version of the manuscript:

We have therefore suggested to test the strategy of evaluating the ratio of cholesterol synthesis and absorption in IMPROVE-IT <sup>37</sup>as early as 2016. The analysis is under way as assured by the TIMI Study group and will provide important mechanistic insights <sup>38</sup>.

2) Second, what are the future directions of the topic depicted in this manuscript?

Response:

The future directions of the topic are:

1) individualized approach in lipid lowering therapy (it is known that there are several laboratory methods which allow to identify “hyperabsorbers”, who may not response to statins adequately).

2) elderly people require a different therapeutic approach and this should be taken into account in clinical practice

3) ezetimibe and statin combination demonstrated safety and effectiveness in the elderly. Therefore, in each individual 75 years and older this therapy option should at least be considered (independently from the LDL-C level).

Further, an individualized approach is necessary in lipid-lowering therapy. Measuring cholesterol absorption would allow defining “hyperabsorbers”, who would benefit from ezetimibe the most. Due to a low-cost effectiveness, these methods are currently used mostly only in clinical research. Further modifications of those methods to make them available in clinical routine would improve the decision-making in the lipid-lowering. Weingärtner et al. have already proposed to obtain data regarding the markers of cholesterol absorption in cohort of IMROVE-IT participants<sup>37</sup>. The TIMI Group investigators positively responded to this proposal and stated that the analysis of cholesterol production and absorption markers will be performed<sup>38</sup>.

3) I cannot find an answer in this publication what problems remain to be solved?

Response:

A more individualized approach to lipid-lowering therapy is needed.

There is a need to go beyond LDL-C - this problem can be solved by using lab methods, such as cholesterol absorption measurement available in routine clinical practice.

More randomized clinical trials are needed to evaluate the effectiveness of different lipid-lowering agents in elderly people, since many (but not all) large studies in this group are done secondarily (post-hoc analyses).

4) In my opinion this publication doesn't impact basic science and / or clinical practice.

Response:

Our manuscript calls for an individualized approach in lipid-lowering therapy, in which we look beyond LDL-C and determine cholesterol metabolism in more detail (gas-chromatography). Using these sophisticated techniques will provide the pathophysiological mechanisms that explain recent findings in large prospective studies that suggest that the addition of ezetimibe in patients over 75 years of age reduces cardiovascular risk.

„Another important point is that future clinicians need to “get personal” in their counseling and prescription, especially in patients 75 years and older, where ezetimibe should be the lipid-lowering drug of choice. Besides, the measurement of cholesterol absorption in large studies, such as IMROVE-IT and EWTOPIA 75 would be of high interest”.

We have previously proposed to measure markers of cholesterol absorption in the IMROVE-IT cohort (Weingärtner O, Lütjohann D, Elsässer A. Personalize and Optimize Lipid-Lowering Therapies. *J Am Coll Cardiol*. 2016 Jul 19;68(3):325-326. doi: 10.1016/j.jacc.2016.02.086. PMID: 27417013). The TIMI Study Group (Murphy SA, Cannon CP, Blazing MA, Giugliano RP, Tereshakovec AM, Braunwald E. Reply: Personalize and Optimize Lipid-Lowering Therapies. *J Am Coll Cardiol*. 2016 Jul 19;68(3):326. doi: 10.1016/j.jacc.2016.04.043. PMID: 27417014) positively responded to this proposal and stated that the analysis of cholesterol production and absorption markers will be performed.