Reviewer 1:

The manuscript summarizes findings, described in various studies with lipid-lowering drugs, pointing to a differing efficacy of these drugs on outcome data in dependence on the vascular situation (especially polyvascular disease), CABG, diabetes, age, and the morphology of plaques. They recommend not to focus solely on the LDL-C levels when adding another drug to a statin. The interpretation of these findings by the authors sounds reasonable. Though some heterogeneity between the PCSK9i studies cannot be ignored. Economic aspects – the newer lipid-lowering drugs are more expensive – are also mentioned. In general, the reviewer accepts the argumentation of the authors – but more randomized controlled studies focusing on the major aspects of this manuscript are clearly needed.

We thank the Reviewer for summarising the main points of the Review article. We agree with the Reviewer that future randomized clinical trials are needed to assess this approach. We have now added the following paragraph to reflect this suggestion:

"Future randomised clinical trials are needed to assess whether the proposed approach would prove to be cost-effective. The use of atherosclerotic disease characteristics to guide decision making for intensive, yet, expensive lipid-lowering therapy is a step toward more personalised and precision medicine."

Another approach would be to take into account other risk factors, like VLDL remnants, lipoprotein(a), Cystatin C, C-reactive protein, and others in order to define groups of patients who need an additional lipid-lowering drug therapy.

We thank the Reviewer for this comment. We have highlighted the potential role of other lipoprotein particles in the risk of atherosclerotic disease in Page 12. Nonetheless, targeting some of these risk markers, such as HDL-c, did not translate into reduction in future risk. The complex interactions among lipoprotein and non-lipoprotein biomarkers would render a single marker less precise in predicting future cardiovascular events. We agree with the Reviewer that certain markers would be able to identify high risk patients in relation to this marker such as CRP and lipoprotein (a), and therefore, targeting these markers may be associated with a significant reduction in future cardiovascular outcomes. We have now added this paragraph to the manuscript:

"This approach is promising as certain markers such as lipoprotein (a) would identify high risk patients and, therefore, targeting this particular biomarker maybe associated with a reduction in future cardiovascular events."

Minor comments Page 5 Line 8:) in patients with monovascular disease and LDL-c ≤100. the dimension is missing after 100

We thank the Reviewer for highlighting this point. We have now added mg/dL.

References 21, 47, 51: volume and pages are lacking

We thank the Reviewer for highlighting this point. We have now added the volume and pages to the above references.

Science Editor

Self-cited references: There are 12 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated;

We thank the Editor for highlighting this point. We have now removed 4 self-citation references from the manuscript. The remaining references are essential and support the main argument regarding the use of intensive lipid-lowering therapy in certain patients' groups.

The title is too long, and it should be no more than 18 words;

The current title has only 8 words *"intensive lipid-lowering therapy, time to think beyond LDL-c"*.

The "Author Contributions" section is missing. Please provide the author contributions

We have added the following paragraph to reflect patient contribution:

Conceptualization, methodology and project administration MA. Resources AZ & MA. Writing original draft and preparation AAW & AAA. Writing review and editing all authors.

Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references.

We have now added the DOI citation number alongside all authors list to the reference list.