Can Dropping LDL-C Cause Regression of Atherosclerosis or Should Toxic LDL-C Be Eradicated?

A Pooled Study of Plaque Burden Reduction in Lipid-Lowering Trials

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Background and Aims:

To evaluate the minimum valuable threshold for reduction of LDL-C in lipid-lowering trials.

Methods:

This hypothesis-generating pooled analysis comparatively evaluates trends in Caucasian (7 Classic studies which were conducted by the group of Nicholls/ Nissen, 18 clinical studies with Caucasian population), and 13 trials with East Asian populations (EAP) of the different Y-DNA haplogroups in 38 intravascular ultrasound (IVUS) imaging studies (N = 9,146).

Results:

A $-1.67 \pm 5.99\%$ mean absolute reduction of PB reported in all 38 studies with a -18.46 (SD 20.35%) decrease of LDL-C. A pooled linear regression analysis revealed moderate association between LDL-C and mean change of the plaque burden ($r = 0.3314$, $p = 0.008$) with a LDL-C threshold of 106 mg/dl. The LDL-C threshold in EAP was substantially higher vs Caucasians achieving 123 mg/dl vs 84 mg/dl. Unlike the modest $0.14 \pm 0.94\%$ (0.22% ; 95% CI: -1.70 , 1.97 ; $p=0.89$) progression of atherosclerosis in classic studies (with a $-19.89 \pm 24.75\%$ (-6.65% ; 95% CI: -68.40 , 28.62 ; $p=0.11$) LDL-C reduction), the EAP demonstrate a $-1.99 \pm 3.57\%$ (-1.80% ; 95% CI: -8.99 , 5.01 ; $p=0.19$) regression of

-35.80%; 95% CI: -

61.99, 0.60; $p < 0.0001$) decrease of LDL-C. The dramatic regression of atherosclerosis was confirmed for invasive studies with a mean $-6.12 \pm 13.25\%$ (-1.10% ; 95% CI: $-32.10, 19.86$) reduction of PB ($p = 0.056$).

The strategy with a reduction of LDL-C below a threshold of 106 mg/dl is not effective for the regression of atherosclerosis. Further clinical studies are required to estimate the role of very low LDL-C for clinical outcomes.

Figure 1. Regression analysis of the associations between low-density lipoprotein (LDL) cholesterol vs. coronary plaque progression—regression documented by the intravascular imaging.

Figure 2. Geographic and dominating Y-DNA haplogroup distribution of 38 intravascular imaging studies with the evaluated bias among Caucasian and East Asian populations.

Figure 3. Comparative analysis of the Caucasian and East Asian populations in intravascular imaging studies testing artery remodeling under lipid-lowering or invasive therapy of atherosclerosis.

Major points to debate:

- 1) **Can we reverse atherogenesis with lipid-lowering strategies?** *Not yet there... Angiographic (Brown BG et al, Circulation 1993) and Intravascular Imaging (Williams KJ et al, Nature 2008; Elshazly MB et al, Curr Opin 2016; Andrews J et al, CDT 2016) studies demonstrate very moderate a - 1.22% (SD 3.04; $p = 0.01$) accomplishments reducing plaque burden despite substantial attenuation of the LDL-C metabolism (-31.29%, SD 16.47; $p = \text{NS}$) raising a question about feasibility*
- 2) **Should we upgrade our strategy with LDL-C eradication?** *Prof. Kastelein (AMC, Amsterdam, NL) this year introduced the concept of “cumulative LDL-C exposure” underlining that LDL-C is toxic. LDL-C lowering makes a sense in all patients and LDL-C eradication – in among those with a high lifetime ACSVD risk. The lifelong low LDL-C is safe (Newman CB, ATVB 2019). High-intensity statins are associated with a CV risk reduction and survival benefit (Rodriguez F et al, JAMA 2016; Sabatine MS et al, JAMA 2018; Navarese EP et al, JAMA 2018).*
- 3) **Observational studies must not be considered for clinical decision making** (Frieden TR, NEJM 2017; Nissen SE et al, EHJ 2018)
- 4) **Plaque -omics studies (e.g. PlaqOmics) and medical devices have a potential to revolutionize the field**

This poster was prepared exclusively for EAS 2019, Maastricht, The Netherlands, May 26-29, 2019

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