ASSOCIATION BETWEEN APOLIPOPROTEIN B LOWERING AND CARDIOVASCULAR RISK REDUCTION: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background and aim: Several novel therapies that potently reduce plasma triglyceride levels by targeting the lipoprotein lipase (LPL) pathway are currently in development. Recent evidence from Mendelian randomization studies suggest that lowering plasma triglyceride levels through the LPL pathway and lowering low-density lipoprotein (LDL)-cholesterol through the LDL receptor pathway are associated with very similar proportional reductions in the risk of cardiovascular (CV) events for the same reduction in apolipoprotein B (apoB) containing lipoproteins. This finding implies that the clinical benefit of any lipid-lowering therapy should be proportional to the absolute change in apoB. Therefore, we sought to compare the clinical benefit of several different classes of lipid-lowering therapies per unit reduction in apoB, and to estimate the magnitude of the expected clinical benefit of lowering apoB for each class of therapy to inform the design of future randomized trials evaluating novel lipid-lowering therapies.

Methods: We conducted a study-level meta-analysis of randomized trials evaluating 6different classes of lipid-lowering therapies (statins, ezetimibe, PCSK9-inhibitors, CETP-inhibitors, niacin, and fibrates). We included all randomized trials that reported apoB levels for the entire study population, enrolled at least 1000 participants, had a least 1-year median follow-up and were designed to evaluate CV outcomes. The primary outcome for this meta-analysis was major CV events - defined as the first occurrence of CV death, non-fatal myocardial infarction, stroke or coronary revascularization. We estimated the relative risk (RR) of major CV events standardized for a 30 mg/dl reduction in apoB using fixed effect inverse-variance weighted meta-analysis (adjusted for study duration) separately for each class of therapy and in a combined analysis including all classes of lipid-lowering therapies. Heterogeneity of the observed clinical benefit per unit reduction in apoB between the different classes of lipid-lowering therapies was measured with the I^2statistic.

Results: A total of 25trials that enrolled 285,241participants (mean age: 63.3years; female sex: 24.7%) who experienced 40,244first major CV events were included in the analysis. Among the included trials, the mean baseline LDL-cholesterol level was 100.7mg/dL and the mean baseline apoB level was 93.9mg/dL. The mean absolute difference in apoB between the treatment and comparison groups at one year was 24.1mg/dL. Among all included trials, the overall RR per 30 mg/dL reduction in apoB levels was 0.79(95% confidence intervals (CI) 0.77-0.81) for major CV events. Examining separately the components of the composite endpoint, the risk of non- fatal myocardial infarction was reduced by 24% (RR 0.76, 95% CI 0.73-0.79), the risk of coronary revascularization and of stroke by 21% (RR 0.79, 95% CI 0.76-0.81and RR 0.79, 95% CI 0.74-0.83, respectively), and the risk of CV death by 13% (RR 0.87, 95% CI 0.82-0.92). There was no significant heterogeneity in the clinical benefit per 30 mg/dl reduction in apoB among the six different lipid-lowering therapies, either for the primary composite outcome or for any of the individual components of the primary composite outcome.

Conclusions and relevance: Statins, ezetimibe, PCSK9-inhibitors, CETP-inhibitors, niacin, and fibrates are all associated with very similar reductions in the risk of major CV events per unit change in apoB. The results of this study suggest that the clinical benefit of all lipid-lowering therapies does appear to be proportional to the achieved absolute reduction in apoB, regardless of the observed changes in other lipids. This study also demonstrates that each 30 mg/dl absolute reduction in plasma apoB concentration is associated with an approximately 20% reduction in the risk of major CV events. The results of this study can be used to inform the design of randomized trials evaluating novel lipid-lowering therapies.