PCSK9-AB and risk of neurocognitive events – comments to Robinson’s meta-analysis

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A pooled analysis [1] does not found worse safety profiles in patients reaching very low values of LDL-Cholesterol (<25 and <15 mg/dl) compared to higher LDL-Cholesterol levels. Authors concluded that aggressive alirocumab therapy seems generally well tolerated. We raise some methodological questions.

First, Authors’ analyses used propensity scores from regression models lacking in predictors of safety endpoints, while covariates must be associated to both outcome and exposition: associations with exposition only affect the analytical precision and do not adjust for possible confounders [2].

Second, limiting the evaluation to alirocumab therapies and focusing to very-low LDL-Cholesterol values subgroups reduces the power of comparisons and increases the risk of false negatives. The apparent lack of association between the LDL-Cholesterol <25 and <15 mg/dl and the risk of neurocognitive disorders can be due to the scarce power of these analyses. Indeed, the sample size of the groups exposed to those targets [1] can demonstrate with sufficient statistical power (≥80%), only very large hypothetical increases in risk of neurocognitive events (RRs ≥2.6 and ≥3.4 respectively).

PCSK9-abs are impressively effective in LDL-Cholesterol lowering, but their effectiveness on clinical major endpoints is uncertain. Our critical revision [3] of two PCSK9-abs meta-analyses [4,5] arouses more caution. After corrections, Navarese’s results [4] lost statistical significance and Lipinski’s results were resized [Death OR=0.51 (0.30-0.85); Neurocognitive Events OR=1.79 (1.05-3.06)].

Metaregression analyses [3] found no association between LDL-Cholesterol lowering and all-cause mortality [for every standard error of LDL-Cholesterol lowering: ratio of OR=0.99 (p=0.503)] and a significant log-linear association with neurocognitive events [for every standard error of LDL-Cholesterol lowering: ratio of OR=1.03 (p=0.042)]. (Figure 1)

Figure 1. Graph-Power analysis of comparisons between two sub groups of patients exposed to low LDL-CL values and 1894 controls

References

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