Journal of Integrative Cardiology

Letter to Editor

ISSN: 2058-3702

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*: a*ssociations 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)

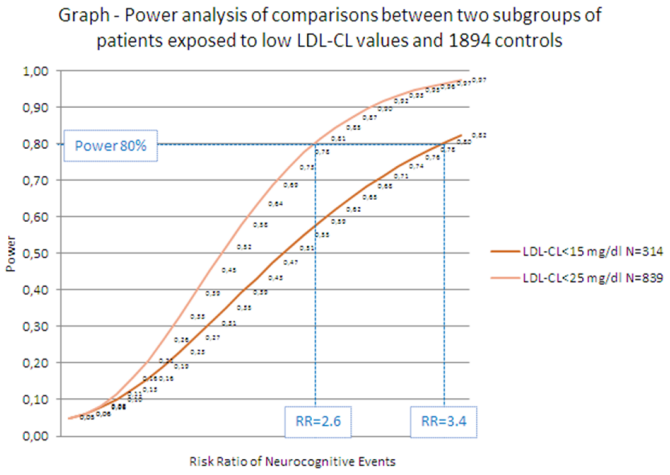

Figure 1. Graph-Power analysis of comparisons between two sub groups of patients exposed to low LDL-CL values and 1894 controls

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Received: March 04, 2017; **Accepted:** March 15, 2017; **Published:** March 17, 2017