Reviewer's report

Title: Recent findings on the health effects of omega-3 fatty acids and statins, and their interactions. Do statins inhibit omega-3?

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Reviewer: Clemens von Schacky

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de Lorgeril et al provide an article that is partly review, partly hypothesis. The authors propose an interaction of statins with n-3 fatty acids, and discuss the pros, but hardly the cons, of this concept. The manuscript is very strongly opinionated, and, in parts, does not conform to scientific standards.

Major comments

The direct comparison of fatty acid measurements from different labs is not possible. What is 1% in one lab, may be 1,5% in another. The lab-to-lab variability was found to be that large (Harris WS et al, unpublished).

Both OMEGA and SU.FOL.OM3 were underpowered. By definition this precludes conclusions on the therapeutic effect of omega-3 fatty acids. It is unclear, whether the trial or the therapeutic effect was too small.

In JELIS, a significant treatment effect was seen, as was demonstrated very convincingly, e.g. in the Kaplan Meier curves. Clearly, however, the overall risk, especially for fatal events in JELIS was low, lower than in comparable Western populations (e.g. in HOPE or EUROPA). This should be interpreted as an effect of the high background intake of omega-3 fatty acids in Japan, rather than as eicosapentaenoic acid being ineffective.

That statins have no effect in GISSI-HF cannot be called a surprise. It had previously been demonstrated in the CORONA trial (N Engl J Med. 2007;357:2248-61). Also, if looking at the causes of death in both CORONA and GISSI-HF, almost no deaths fell into the category that statins can prevent, e.g. a myocardial infarction. This has nothing to do with an inhibition of the action of omega-3’s by statins.

The relation between red cell arachidonic acid and coronary events is J-shaped (Am Heart J. 2008;156:1117-23). The higher arachidonic acid, the higher the risk is not supported by these data.

“most experts and opinion-makers do have major conflicts of interest and strong links with the pharmaceutical industry and/or various sponsors does not help shedding light on the true statin benefit/risk ratio in the everyday medicine” This is general mud-slinging and not scholarly writing.

Statins have limited efficiency, and are no panacea. After statins were
established in cardiovascular prevention, it became unethical to perform placebo-controlled studies with statins in that area. Industry then tried to push the envelope by performing trials in populations less prone to the effects of statins, e.g. congestive heart failure, chronic kidney failure asf. Not surprisingly, the results of these trials were neutral. The verbiage used on page 12 insinuates a conspiracy of enormous size, something that would include unethical and unscientific behaviour by large numbers of persons involved in clinical trials. If there is direct evidence for such a conspiracy, it should be brought forward. Insinuating a conspiracy by relying only on plausibility is not acceptable.

Minor comments:
A negative trial is a trial with a negative result, i.e. intervention worse than comparator. Recent trials with omega-3’s were neutral.

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
CvS founded Omegametrix, a laboratory for fatty acid analyses. He received speakers honoraria from Trommsdorff, Solvay/Abbott, Martek and DSM. Through the University of Munich, his research was supported by Sanofi-Aventis and Smartfish. No other competing interests.