Circulation

LETTER TO THE EDITOR

Letter by Weingärtner et al Regarding Article, "Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized, Controlled Trial"

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To the Editor:

We congratulate Ouchi et al[1] for their excellent analysis of the EWTOPIA 75 (Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older) trial. Patients older than 75 years of age are of particular interest because they represents the largest group of those hospitalized for an acute coronary syndrome, and with the aging of the population, that number continues to grow.

Only recently, Bach et al[2] reported results of IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) in patients older than 75 years of age. In this analysis, the number needed to treat by the addition of ezetimibe–simvastatin was only 11, whereas it was 125 in patients younger than 75 years. These results illustrate the life-saving capacity of adding a cholesterol absorption inhibitor in this particular patient group. Moreover, both trials reported an unexpected magnitude of observed cardiovascular risk reductions by the addition of ezetimibe, which could not be explained by differences of low-density lipoprotein cholesterol between the groups.

These results, however, do not come as a surprise, because cholesterol metabolism changes during lifetime: midlife is characterized by high synthesis and low cholesterol absorption, whereas cholesterol synthesis deteriorates with increasing age.[3]

As early as 2006, Strandberg et al[4] reported the results of the DEBATE (Drugs and Evidence-Based Medicine in the Elderly) study. In this study of home-dwelling elderly patients, low cholesterol absorption (independent from total cholesterol and low-density lipoprotein) was associated with fewer cardiovascular events and better survival. Strandberg et al concluded that patients over the age of 75 years should be treated with an additional cholesterol absorption inhibitor such as ezetimibe.[4]

Only recently, we reported findings in a cohort representative for patients undergoing cardiac catheterization in Germany with a mean age of 64 years. We found that low serum levels of lathosterol (a marker for endogenous cholesterol synthesis) correlated with cardiovascular events and all-cause mortality, whereas campesterol and sitosterol (markers of increased cholesterol absorption) showed a trend but did not reach significance yet.[5]

On the background of these results, testing the strategy of determining the ratio of campesterol to lathosterol (cholesterol absorption and synthesis, respectively) before starting lipid-lowering treatment has become a necessity. We expect that this ratio will personalize and optimize lipid-lowering therapy and improve cardiovascular outcomes in primary, as well as in secondary, prevention.[3] To verify this hypothesis, an analysis needs to be performed in the biobank of the EWTOPIA 75 cohort.

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ARTICLE INFORMATION

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Disclosures

Oliver Weingärtner serves on advisory boards for AMGEN and Sanofi.

REFERENCES

1. Ouchi Y, Sasaki J, Arai H, Yokote K, Harada K, Katayama Y, Urabe T, Uchida Y, Hayashi M, Yokota N, et al. Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): a randomized, controlled trial. *Circulation*. 2019;140:992–1003. doi: 10.1161/CIRCULATIONAHA.118.039415
2. Bach RG, Cannon CP, Giugliano RP, White JA, Lokhnygi Y, Bohula EA, Califf RM, Braunwald E, Blazing MA. Effect of simvastatin-ezetimibe compared with simvastatin monotherapy after acute coronary syndrome among patients 75 years or older: a secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2019; 4: 846-854. doi: 10.1001/jamacardio.2019.2306
3. Lütjohann D, Stellaard F, Mulder MT, Sijbrands EJG, Weingärtner O. The emerging concept of "individualized cholesterol-lowering therapy": a change in paradigm. *Pharmacol Ther.* 2019;199:111–116. doi: 10.1016/j.pharmthera.2019.03.004
4. Strandberg TE, Tilvis RS, Pitkala KH, Miettinen TA. Cholesterol and glucose metabolism and recurrent cardiovascular events among the elderly: a prospective study. *J Am Coll Cardiol*. 2006;48:708–714. doi: 10.1016/j.jacc.2006.04.081
5. Weingärtner O, Lütjohann D, Meyer S, Fuhrmann A, Cremers B, Seiler-Mußler S, Schött HF, Kerksiek A, Friedrichs S, Ulbricht U, et al. Low serum lathosterol levels associate with fatal cardiovascular disease and excess all-cause mortality: a prospective cohort study. *Clin Res Cardiol*. 2019;108:1381-1385. doi: 10.1007/s00392-019-01474-2