JOURNAL OF DRUG ASSESSMENT, 2016
VOL. 5, NO. 1, 4–5
http://dx.doi.org/10.3109/21556660.2016.1168302
Article XX-0000.X0/1168302

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

Off target effects of statins shape total mortality?

Re: Kazerooni R, Lim J. Predictors of long-term mortality in new start statin users. J Drug Assess 2015;4:7-11

Dear Editor,

Kazerooni and Lim[1] report several independent predictors of mortality in new start statin users after long-term follow-up [age, race, number of medications, comorbidities, and body mass index (BMI)]; however, differences in lipid groups and adherence to statin treatment after 1 year were not predictive of long-term mortality in the veteran population studied[1]. This may be due to the low adherence rates to statin therapy[1]. This interpretation would fit in well with polypharmacy being more common in the mortality group[2]. In turn, the latter observation suggests the need to decrease the number of administered drugs by prescription reviews and use of combination formulations[2].

In this context, it should be mentioned that specific statin treatment (atorvastatin) improves renal function and ameliorates chronic kidney disease (CKD) with an independent beneficial effect on morbidity and mortality[3,4]. Also, treatment with atorvastatin lowers the levels of serum uric acid (SUA)[5,6], which may be an independent cardiovascular disease (CVD) risk factor[7,8]; this translated into a benefit in morbidity and mortality rates[4]. Furthermore, resolution of non-alcoholic fatty liver disease (NAFLD)-non alcoholic steatohepatitis (NASH), by atorvastatin[9,10] or rosuvastatin[11], was associated with an independent reduction in vascular events at a level almost double that in those with normal liver function on the same dose[9,10]. In this context, do the authors have any information on the effect of CKD, SUA, or NAFLD/NASH on vascular events in their population? Also, did any of these factors improve on statin treatment?

Is there any evidence of a role for metabolic syndrome (MetS)? Two diagnostic characteristics of MetS, high density lipoprotein cholesterol (HDL-C) and hypertension[12], were significantly lower and higher, respectively, in the mortality group in the Kazerooni and Lim[1] study. Triglyceride levels, another MetS diagnostic characteristic[12], were higher in the mortality group, but this did not achieve significance. BMI, which reflects waist circumference, a key MetS diagnostic characteristic[12], was lower in the mortality group. Obesity followed the same pattern as BMI. There are no glucose (the 5th and final MetS diagnostic characteristic) levels. Is there an explanation for the possible BMI/obesity paradox?[13] Was there a greater number of patients in the mortality group who were so ill that they had some degree of "cachexia"?[14]

The high tobacco consumption in both studied groups (survival and mortality) is of interest and may explain why this strong predictor, second after abnormal lipids, accounting for most of the risk of vascular events worldwide[15], did not differ significantly between these groups.

Transparency

Declaration of funding

This letter was written independently; no company or institution supported the authors financially or by providing a professional writer.

Declaration of financial/other interests

There are no conflicts of interest. VGA has given talks, attended conferences, and participated in trials sponsored by MSD, Sanofi, and Amgen; NK for MSD, Novartis, Amgen, Sanofi, Novo Nordisk, and Libytec; AK for Amgen and Pfizer.

References

1. Kazerooni R, Lim J. Predictors of long-term mortality in new start statin users. J Drug Assess 2016;4:7-11
2. Düsing R. The case for single pill combinations. Curr Med Res Opin 2014;30:2423-4
3. Athyros VG, Mikhailidis DP, Papageorgiou AA, et al. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. J Clin Pathol 2004;57:728-34
4. Shepherd J, Breazna A, Deedwania PC, et al.; Treating to New Targets Steering Committee and Investigators. Relation between change in renal function and cardiovascular outcomes in atorvastatin-treated patients (from the Treating to New Targets [TNT] Study). Am J Cardiol 2016 pii: S0002-9149(16)30136-9
5. Athyros VG, Elisaf M, Papageorgiou AA, et al.; GREACE Study Collaborative Group. Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: a subgroup analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Am J Kidney Dis 2004;43:589-99
6. Daskalopoulou SS, Athyros VG, Elisaf M, et al. Uric acid levels and vascular disease. Curr Med Res Opin 2004;20:951-4
7. Saito Y, Nakayama T, Sugimoto K, et al. Relation of lipid content of coronary plaque to level of serum uric acid. Am J Cardiol 2015;116:1346-50
8. Karagiannis A, Mikhailidis DP, Tziomalos K, et al. Serum uric acid as an independent predictor of early death after acute stroke. Circ J 2007;71:1120-7
9. Athyros VG, Tziomalos K, Gossios TD, et al. GREACE Study Collaborative Group Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: A post-hoc analysis. Lancet 2010;376:1916-22

10. Athyros VG, Katsiki N, Karagiannis A, et al. Are statins 'IDEAL' for non-alcoholic fatty liver disease? Curr Med Res Opin 2014;30:229-31
11. Kargiotis K, Athyros VG, Giouleme O, et al. Resolution of non-alcoholic steatohepatitis by rosuvastatin monotherapy in patients with metabolic syndrome. World J Gastroenterol 2015;21:7860-8
12. Athyros VG, Ganotakis ES, Bathianaki M, et al. Awareness, treatment and control of the metabolic syndrome and its components: A multicentre Greek study. Hellenic J Cardiol 2005;46:380-6
13. Habbu A, Lakkis NM, Dokainish H. The obesity paradox: Fact or fiction? Am J Cardiol 2006;98:944-8
14. Jiménez Jiménez FJ, Cervera Montes M, Blesa Malpica AL; Metabolism and Nutrition Working Group of the Spanish Society of Intensive Care Medicine and Coronary units. Guidelines for specialized nutritional and metabolic support in the critically-ill patient: Update. Consensus SEMICYUC-SENPE: Cardiac patient. Nutr Hosp 2011;26(2 Suppl):76-80
15. Yusuf S1, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. Lancet 2004;364:937-52

Vasilios G. Athyros, Niki Katsiki and Asterios Karagiannis
Second Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, Hippocration Hospital, Thessaloniki, Greece
vathyros@gmail.com

Received 16 March 2016; accepted 16 March 2016