EDITORIAL

Journal of Cachexia, Sarcopenia and Muscle (2016)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12109

Discussion around statin discontinuation in older adults and patients with wasting diseases

Maciej Banach[1]* Maria-Corina Serban[2,3]

[1]*Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Lodz, Poland;* [2]*Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA;* [3]*Department of Functional Sciences, Discipline of Pathophysiology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania*

Received: 26 January 2016; Accepted: 28 January 2016
**Correspondence to: Maciej Banach, Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113, 90-549 Lodz, Poland: Fax: +48 42 639 37 71, Email: maciejbanach@aol.co.uk*

Statins—where are we now?

Statins are usually selected as the first-line therapy to lower plasma levels of low-density lipoprotein cholesterol (LDL-C) and cardiovascular disease (CVD) morbidity and mortality.[1] They reduce the risk of myocardial infarction, stroke and CVD mortality by about 25–30%.[2] That is one of the reasons why all current clinical guidelines 'virtually mandate' lifetime use of statins once they are started, thus becoming a challenge for the patients due to their possible side effects.[3] Furthermore, there has been recently a tendency towards maximizing the strength of statin treatment, sometimes with greater doses or potent forms.[3,4] The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial showed that the combination with ezetimibe/simvastatin 10 mg/40 mg let to an absolute 2.0% reduction (relative risk reduction: 6.4%) of the risk of CV events in contrast to simvastatin 40 mg alone.[4,5] The trial also demonstrated that the patients with obtained very low LDL-C levels $<$30 mg/dL experienced no discrepancies in adverse effects than those with higher LDL-C levels.[5] ODYSSEY LONG-TERM and the Open-Label Study of Long-term Evaluation against LDL-C trials with proprotein convertase subtilisin/kexin type 9 inhibitors also supported the hypothesis 'the lower the better' for LDL-C levels, generating more arguments for lower LDL-C targets $<$50 mg/dL (1.3 mmol/L), in contrast with the current targets $<$70 mg/dL (1.8 mmol/L) for patients at the highest risk.[6] These results are in line with the 2013 American College of Cardiology/American Heart Association guidelines, which advise the use of high-intensity statin therapy and extend its use to more categories susceptible to CVD.[7] Taking into account still poor to moderate statin therapy control in the high-risk and highest-risk patients (even 50% of patients are non-adherent to therapy after 2 years), as well as the aforementioned data, more intense targets seem to be very important; however, on the other hand, high-intensity statin therapy might also increase the risk of statin-related side effects and statin discontinuation rate due to this fact.[6]

Statin discontinuation—a problem to be solved

Statin discontinuation may concern the patients with complete statin intolerance,[8] as well as patients with cancer, palliative care patients, patients with cachexia,[9] but also elderly patients, and primary CV prevention individuals, in which the risk of statin-related side effects (mainly associated with new-onset diabetes) might exceed the benefits (especially with subjects with risk factors of diabetes well adhered to non-pharmacological therapy).[10]

Statin discontinuation (as well as essential dose reduction) has been associated with higher risk for CVD events and death in patients with coronary artery disease (CAD), and especially in patients after acute coronary syndrome, in which the instability of atheroma plaque might appear.[3,11] However, research on the causes of discontinuation of statins in routine practice is still very limited.[3,8] In the retrospective cohort study, the authors investigated the reasons for statin discontinuation and the role of statin-related side effects in 134 263 statin users from the Brigham and Women's Hospital and Massachusetts General Hospital.[12] Of these, 53.1% patients reported statin discontinuation at least once, and 17.4% reported statin-related events. More than half of the patients who stopped taking a statin because of a statin-related event were successfully restarted with a statin.[12] Another survey, conducted in the group of 1074 French subjects treated with low doses of rosuvastatin, atorvastatin or simvastatin, reported statin discontinuation in 30% of the symptomatic patients due to muscular symptoms.[13] Approximately 38% of them reported that their symptoms prevented even moderate exertion during everyday activities,

while 42% of patients suffered major disruption to their everyday life.[13] In the Understanding Statin Use in America and Gaps in Education survey carried out on 10 138 US adults, the causes of discontinuation were muscle side effects (60%), cost (16%) and perceived lack of efficacy (13%).[14] However, in randomized placebo-controlled trials (RCTs), it has been shown that statins do not increase minor or serious symptomatic adverse events.[15] A meta-analysis involving more than 80 000 patients from 29 RCTs found that only a small minority of side effects was attributable to statins.[16] On the other hand, the misinterpretation of trial facts about statin side effects might cause harm to patients,[17] and it needs to be emphasized that most patients with any side effects to statin therapy as well as statin therapy nonadherence were excluded from RCTs at baseline.[6] Data so far also support the possibility of unnecessary statin discontinuation in patients who like to report side effects (so-called *nocebo effect*), thereby placing them at increased risk of CVD.[18] Statins have an acceptable margin of safety, when used in properly selected individuals who are appropriately monitored. What is more, despite the fact that we do not have any sensitive biomarkers of statin intolerance (it is difficult to treat creatine kinase as such), it is crucial to try to predict the side effects of statins, based on the well-known risk factors and conditions that might increase this risk.[19]

Statin discontinuation—elderly patients

Along with their primary lipid-lowering effects, statins have many ancillary actions that may be relevant for body wasting.[8] There is the suitable number of available reports that suggests that low body mass index is one of the risk factors of statin intolerance.[8,20] Cardiac cachexia and sarcopenia occurrence is also associated with age, and in this aspect, the available data have suggested that statin-related sided effects may more often affect elderly patients, reducing their quality of life (QOL).[21] Available data and guidelines suggest that statin therapy may be suitable for older adults with CVD.[21] However, elderly patients, particularly those over the age of 75 years (or 80+), have not been properly investigated in RCTs evaluating lipid-lowering therapy.[21,22] Therefore, the available data on the efficacy and safety of statin therapy in elderly patients (especially without diagnosed CAD) are still very limited. Especially in the group of very elderly patients (80+), the levels of LDL-C and total cholesterol are usually lower than in the younger subjects.[21,22] Some authors also reported a *lipid paradox* in this group, suggesting that low levels of total cholesterol might be associated with the worsen prognosis.[21–23]

Ageing causes changes in drug pharmacokinetics and pharmacodynamics, which may increase drug concentration, increasing the risk of side effects.[8,22] Physiologic changes with ageing include absorption, distribution, metabolism and excretion; there is also a decrease in lean body mass and in total body water, causing a reduction in volume of distribution of hydrophilic drugs, as well as lipophilic drugs but mainly due to increased proportion of body fat.[8,24] Reduced liver mass, hepatic blood flow and hepatic metabolic capacity observed in the elderly causing accumulation of metabolized drugs and decreased glomerular filtration rate, renal tubular function and renal blood flow is a reason of accumulation of drugs cleared by the kidney.[8,24] Reduced chemoreceptor and baroreceptor sensitivity, reduced beta-receptor sensitivity, impaired haemostasis, and comorbidities and multiple medications are other important factors that might be the reason of statin-related side effects in older adults.[8,24] Statin metabolism differences may also essentially influence potential drug interactions.[21,24]

Taking all the aforementioned data into account, elderly patients are at the high risk of statin intolerance.[8] A prospective community-based cohort with 4137 men aged >65 years followed for about 7 years showed that elderly patients on statins were less physically active compared with those who did not use cholesterol-lowering medications, independent of cardiac medication or medical history.[25] The possible reasons for lower physical activity levels in statin users may be general muscle pain caused by statins, exercise-induced myopathy or muscular fatigue.[25] What is more, taking into account numerous concomitant diseases (as well as life expectancy, time to benefit, functional status, polypharmacy and adherence to treatment), with the absence of CAD, and taking into account the risk of side effects, the question is whether statins should be really considered as the first-line therapy for these patients. According to the International Lipid Expert Panel Position Paper,[8] there are very detailed recommendations on how to use statins in elderly patients in order to be the most effective in case of CV prevention as well as to reduce the risk of statin-related side effects: (i) statin therapy should be started when clinically appropriate, especially if the benefits on CVD prevention outweigh potential risks; (ii) discontinuation of statin therapy should be recommended in case of severe illness, major surgery or major trauma until the person recovers. Any such decision should be balanced with the risk of discontinuing statins; and (iii) hydrophilic statins at moderate-intensity doses should be first considered in elderly patients with CVD.

Statin discontinuation—terminally ill patients

Statin discontinuation in terminally ill patients might be harmless, saves money, spares patients from taking medication and from the symptoms connected with statins and is usually well received by patients.[26–28] In the recent study

DOI: 10.1002/jcsm.12109

by Kutner *et al*.,[26] the authors evaluated the safety, clinical and cost impact of discontinuing statin medications for patients in the palliative care setting. A total of 381 patients were enrolled, of which 189 were randomized to discontinue statin therapy and 192 to continue the therapy. Mean age was 74.1 years, 22.0% of the participants were cognitively impaired and 48.8% had cancer. The proportion of participants in the discontinuation vs. continuation groups who died within 60 days was not significantly different (23.8 vs. 20.3%; $P = 0.36$) and did not meet the non-inferiority end point. Total QOL was better for the group discontinuing statin therapy (mean McGill QOL score, 7.11 vs. 6.85; $P = 0.04$). Few participants experienced CV events (13 in the discontinuation group vs. 11 in the continuation group). Mean cost savings were $3.37 per day and $716 per patient.[26] Based on these results, the authors suggest that stopping statin medication therapy is safe and may be associated with benefits including improved QOL, use of fewer non-statin medications and a corresponding reduction in medication costs.[26] However, they also emphasized that further studies in different clinical settings (chronic diseases, including older adults, patients with chronic heart failure and/or cardiac cachexia/sarcopenia) are warranted to finally answer the question on the risks/benefits associated with statin therapy discontinuation.[8,26]

Despite widely discussed limitations on the aforementioned study, including lack of meeting of the primary outcome and study design,[26–28] the authors provided strong arguments for the safety and QOL improvement after statin discontinuation in palliative patients. However, available studies offer insufficient details regarding the patient's needs in the different stages of terminal diseases. There are also single studies investigating the impact of statin discontinuation on the reduced risk of drug-related side effects and QOL improvement, especially in patients with cancer with the limited life expectancy.[26–28] Therefore, it needs to be emphasized that the available data are not sufficient to draw any direct conclusions or recommendations, and any reduction in the statin dose or discontinuation should be balanced with the increased risk of CV events.[8,29] In the recent study by Nielsen *et al*.[30] in the group of 674 900 individuals aged 40 years or older on statin therapy, the authors showed that the prevalence of statin discontinuation was 18% at the end of the study and was associated with increased risk of myocardial infarction (odds ratio 1.26, 95% confidence interval: 1.21–1.30) and CVD death (odds ratio 1.18, 95% confidence interval: 1.14–1.23).

Acknowledgement

The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle.[31]

Conflict of interest

None declared.

References

1. Stepien M, Banach M, Mikhailidis DP, Gluba A, Kjeldsen SE, Rysz J. Role and significance of statins in the treatment of hypertensive patients. *Curr Med Res Opin* 2009;**25**:1995–2005.
2. Hobbs FD, Banach M, Mikhailidis DP, Malhotra A, Capewell S. Is statin-modified reduction in lipids the most important preventive therapy for cardiovascular disease? A pro/con debate. *BMC Med* 2016;**14**:4.
3. Grundy SM. Statin discontinuation and intolerance: the challenge of lifelong therapy. *Ann Intern Med* 2013;**158**:562–563.
4. Serban MC, Banach M, Mikhailidis DP. Clinical implications of the IMPROVE-IT trial in the light of current and future lipid-lowering treatment options. *Expert Opin Pharmacother* 2016; doi:10.1517/14656566.2016.1118055.
5. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, *et al*. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387–2397.
6. Banach M, Aronow WS, Serban MC, Rysz J, Voroneanu L, Covic A. Lipids, blood pressure and kidney update 2015. *Lipids Health Dis* 2015;**14**:167.
7. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, *et al*. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;**63**:2889–2934.
8. Banach M, Rizzo M, Toth PP, Farnier M, Davidson MH, Al-Rasadi K, *et al*. Statin intolerance—an attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Arch Med Sci* 2015;**11**:1–23.
9. Anker MS, von Haehling S, Springer J, Banach M, Anker SD. Highlights of the mechanistic and therapeutic cachexia and sarcopenia research 2010 to 2012 and their relevance for cardiology. *Int J Cardiol* 2013;**162**:73–76.
10. Banach M, Malodobra-Mazur M, Gluba A, Katsiki N, Rysz J, Dobrzyn A. Statin therapy and new-onset diabetes: molecular mechanisms and clinical relevance. *Curr Pharm Des* 2013;**19**:4904–4912.
11. Banach M, Serban C, Sahebkar A, Mikhailidis DP, Ursoniu S, Ray KK, *et al*. Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Impact of statin therapy on coronary plaque composition: a systematic review and meta-analysis of virtual histology intravascular ultrasound studies. *BMC Med* 2015;**13**:229.
12. Zhang H, Plutzky J, Skentzos S, Morrison F, Mar P, Shubina M, *et al*. Discontinuation of statins in routine care settings: a cohort study. *Ann Intern Med* 2013;**158**:526–534.
13. Rosenbaum D, Dallongeville J, Sabouret P, Bruckert E. Discontinuation of statin therapy due to muscular side effects: a survey in real life. *Nutr Metabol Cardiovasc Dis* 2013;**23**:871–875.
14. Wei MY, Ito MK, Cohen JD, Brinton EA, Jacobson TA. Predictors of statin adherence, switching, and discontinuation in the USAGE survey: understanding the use of statins in America and gaps in patient education. *J Clin Lipidol* 2013;**7**:472–483.
15. Club AJ. Statins do not increase minor or serious symptomatic adverse events in

placebo-controlled trials. *Ann Intern Med* 2014;**161**:JC3.
16. Finegold JA, Manisty CH, Goldacre B, Barron AJ, Francis DP. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. *Eur J Prev Cardiol* 2014;**21**:464–474.
17. Golomb BA. Misinterpretation of trial evidence on statin adverse effects may harm patients. *Eur J Prev Cardiol* 2015;**22**:492–493.
18. Zhang H, Plutzky J, Skentzos S. Statins often tolerated after supposed statin-related event. *Ann Intern Med* 2013;**158**:526–534.
19. Banach M, Serban C, Sahebkar A, Ursoniu S, Rysz J, Muntner P, *et al*. Lipid and Blood Pressure Meta-analysis Collaboration Group. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. *Mayo Clin Proc* 2015;**90**:24–34.
20. Banach M, Aronow WS, Serban C, Sahabkar A, Rysz J, Voroneanu L, *et al*. Lipids, blood pressure and kidney update 2014. *Pharmacol Res* 2015;**95–96**:111–125.
21. Aronow WS. Lipid-lowering therapy in older persons. *Arch Med Sci* 2015;**11**:43–56.
22. Szadkowska I, Stanczyk A, Aronow WS, Kowalski J, Pawlicki L, Ahmed A, *et al*. Statin therapy in the elderly: a review. *Arch Gerontol Geriatr* 2010;**50**:114–118.
23. Petersen LK, Christensen K, Kragstrup J. Lipid-lowering treatment to the end? A review of observational studies and RCTs on cholesterol and mortality in 80+-year olds. *Age Ageing* 2010;**39**:674–680.
24. Frishman WH, Aronow WS, Cheng-Lai A. Cardiovascular drug therapy in the elderly. In Aronow WS, Fleg J, Rich MW, eds. Tresch and Aronow's Cardiovascular Disease in the Elderly, 5th ed. Boca Raton: London, New York, CRC press; 2013. p67–103.
25. Lee DS, Markwardt S, Goeres L, Lee CG, Eckstrom E, Williams C, *et al*. Statins and physical activity in older men: the osteoporotic fractures in men study. *JAMA Intern Med* 2014;**174**:1263–1270.
26. Kutner JS, Blatchford PJ, Taylor DH Jr, Ritchie CS, Bull JH, Fairclough DL, *et al*. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA Intern Med* 2015;**175**:691–700.
27. Geijteman ECT, Tiemeier H, van Gelder T. Selecting the optimal design for drug discontinuation trials in a setting of advanced, life-limiting illness. *JAMA Intern Med* 2015;**175**:1724–1725.
28. Mody P, Nguyen OK. Selecting the optimal design for drug discontinuation trials in a setting of advanced, life-limiting illness. *JAMA Intern Med* 2015;**175**:1725.
29. Colantonio LD, Bittner V, Reynolds K, Levitan EB, Rosenson RS, Banach M, *et al*. Association of serum lipids and coronary heart disease in contemporary observational studies. *Circulation* 2016;**133**:256–264.
30. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. *Eur Heart J* 2016;doi:10.1093/eurheartj/ehv641.
31. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015. *J Cachexia Sarcopenia Muscle* 2015;**4**:315–316.