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Review article

Statin therapy for the primary prevention of cardiovascular disease: Cons

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ABSTRACT

While recent decades have seen substantial reductions in cardiovascular mortality, heart disease remains the number one cause of death both in the United States and globally. This has led many to advocate for prescribing statins even more widely, including to patients with low risk of cardiovascular disease, based on the hypothesis that any reduction in lipid levels will eventually translate to a reduction in the development of atherosclerosis and thus to subsequent mortality. However, empirical evidence to date has not substantiated the hoped for benefits of this strategy. When healthy patients without cardiovascular disease are prescribed statins they do not live longer, and they have only a marginal reduction in the risk of ischemic events. Furthermore, statins cause numerous side effects which substantially limit their net benefit. These tradeoffs are even more lopsided in elderly patients treated for primary prevention, in whom statin therapy does not lead to a reduction in mortality or ischemic events and has the potential for significant harms. Strategies to reduce the risk of cardiovascular disease should therefore avoid a focus on cholesterol levels and subsequent pharmacological therapy and should instead redouble efforts to improve the lifestyle factors that are far more consequential to the development of cardiovascular disease and overall good health.

1. The difficulty of achieving net benefit with medications prescribed for primary prevention

The decision to start a medication must be made only if the reasonably expected benefits outweigh the reasonably expected risks in the individual patient being treated. When medications are given for primary prevention this is a difficult bar to clear, as by definition the drugs are prescribed to healthy patients who feel well. Thus, these drugs cannot make these persons feel better and indeed will make many feel worse, and most will never experience the disease of concern even without medication. All patients are therefore subjected to possible harms from the medication, but only a much smaller number will receive any benefits. Despite this unfavorable risk/benefit profile, guidelines have continued to expand the pool of healthy patients that are advised to take statins for primary prevention. There remains a paucity of evidence that these patients will experience any improved outcomes. As we will discuss, the benefits of statin therapy in patients without cardiovascular disease (CVD) are minor to none, and the harms are real and often downplayed, although common. Thus, the decision to prescribe statins for primary prevention is seldom if ever in a patient's best interest, and especially not when compared to the many other effective lifestyle options available to help them prevent CVD.

2. Statins have only marginal benefits in primary prevention

The vast majority of randomized controlled trials (RCTs) of statins in primary prevention have failed to find statistically significant reductions in overall mortality [1–8]. For example, of the 19 trials pooled in the recent US Preventive Services Task Force (USPSTF) meta-analysis [9] only two demonstrated such a reduction, and both trials have features that raise concerns about the generalizability of their conclusions. The first, ACAPS [10], excluded the majority of patients screened for enrollment as they did not have ultrasound detectable carotid atherosclerosis, and therefore likely studied a population with significant pre-existing CVD. The other, JUPITER [11], was stopped early for supposedly overwhelming mortality benefit in the statin arm despite not having met the prespecified threshold for interim analysis and consideration of early termination [12]. Trials stopped prematurely are known to exaggerate the effects of the treatment arm [13]. The original publication of this RCT also omitted the results for cardiovascular mortality [11], and when these were later released there turned out to be no statistically significant reduction in cardiovascular deaths in the statin arm [14]. This unanticipated result suggests that the reduced mortality seen with statins that led investigators to terminate this trial early was driven more by a reduction in non-cardiovascular deaths, which was

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contrary to the hypothesis being tested. It is therefore possible that the trial was stopped at a point when by chance there were fewer deaths in the statin arm, and if completed as originally intended this may have "regressed to the mean" and this trial like almost all others would have failed to demonstrate a reduction in mortality [15].

Meta-analyses that have pooled RCTs have claimed that statin therapy for primary prevention leads to small statistically significant reductions in overall mortality [9,16–18]. However, these analyses have knowingly included trials where a portion of patients had pre-existing CVD and were enrolled for secondary prevention, which likely influenced the pooled results. Though investigators repeated their analyses after excluding some of these trials and claimed equivalent reductions in mortality, even these more limited analyses have continued to include RCTs such as WOSCOPS where a significant number of patients had baseline angina or claudication suggestive of pre-existing CVD [2,9,16]. In contrast, a meta-analysis that extracted individual patient-level data from RCTs to specifically analyze only the pure primary prevention population of patients without CVD found no statistically significant reduction in overall mortality with statin use [19]. Multiple evaluations of another meta-analysis that subdivided patients by baseline risk found that those with an ASCVD risk <20%, which encompasses most patients without CVD, had no significant reduction in mortality with statin therapy [18,20]. Thus, the most rigorous analyses available suggest that patients without CVD are unlikely to live longer if started on a statin for primary prevention.

Both individual RCTs and meta-analyses have more consistently found a reduction in the incidence of myocardial infarctions (MIs) and ischemic strokes with statin therapy in patients without CVD [1–6,8,9,16–18]. But while these studies have often proclaimed large relative risk reductions, the absolute risk reductions have consistently been quite small. For example, the USPSTF meta-analysis found an absolute risk reduction of 0.81% for MIs and 0.38% for ischemic strokes [9]. This suggests that more than 100 patients would need to be treated with statins for multiple years to prevent a single ischemic event, and none would live longer. For many this minor benefit may still sound favorable, and if statins had these benefits without side effects then perhaps the decision to start them is understandable. But statins have numerous adverse effects that significantly impact the risk-benefit calculation.

3. The risks of statins are underappreciated and counterbalance their minor benefits

Cohort studies [21,22], individual RCTs [11], and meta-analyses [23,24] have all found that statin therapy increases the risk of developing diabetes. The absolute risk increase for diabetes after four years of statin therapy is 0.39%, which is similar to the absolute risk reduction for MIs and strokes [23]. This suggests that for every patient in whom an ischemic event is prevented by statins another is likely to be diagnosed with diabetes.

RCTs have also found that statins significantly increase self-reported fatigue [25] and reduce performance on neurocognitive testing [26,27]. Observational studies have also linked them to peripheral neuropathy [28,29]. Beyond these neurological effects, statins are also known to negatively impact liver function [30] and kidney function [31].

Finally, perhaps the most widely recognized and yet downplayed side effect of statins is muscle damage. Myopathy occurs in ~0.5% of patients and rhabdomyolysis in ~0.01% [32,33], which are small but not negligible risks. As there are objective laboratory findings for these conditions their incidence is widely accepted, whereas the incidence of statin-induced myalgias is far more contentious.

Observational studies have found that at least 10–20% of patients on statins report muscle pain [34,35]. Myalgias are the most common reason patients cite for discontinuing statins, and they contribute to the overall high level of dropout from statin therapy [36,37]. Meta-analyses, however, have concluded that there is no difference in the incidence of myalgias between statins and placebo in RCTs [38–40]. Some have attributed this difference between observational and experimental studies to the nocebo effect [41], where patients experience side effects that they are expecting. But another possible explanation for this discrepancy may be that only one of the 44 trials included in meta-analyses actually queried for myalgias [32]. Additionally, industry-sponsored trials, as almost all statin trials have been, are known to underreport side effects [42]. The data from these RCTs are also held privately by the Cholesterol Treatment Trialists' Collaboration, and despite numerous requests over many years, are kept secret and unavailable for independent review and validation [43]. Finally, statin trials have often excluded patients with a history of muscle problems, which may be the population most at risk for myalgias when statins are prescribed in actual clinical practice [44].

Additional studies have attempted to resolve this conflict between observational and experimental data. The STOMP trial randomized patients to placebo or statin and specifically asked about muscle symptoms biweekly [45]. It found a 4.7% absolute increase in muscle pain among patients taking statins, though this finding just missed statistical significance. Other trials have rechallenged statin intolerant patients to determine what proportion have myalgias that can be causally attributed to their medications [35,46]. These have concluded that between 1/3 and 1/2 of patients consistently report muscle pain on statins but not placebo.

All of this data has been used to suggest that fewer than half of patients who experience side effects on statins can truly attribute them to their medications, and thus that it is worth urging patients to disregard these adverse effects and continue therapy. Regardless of whether these side effects are attributable to the medications or to the nocebo effect, in our experience patients feel quite debilitated and discouraged by them and are understandably reluctant to continue or restart their statins. If these medications could reliably lengthen their lifespans or alleviate some symptoms then perhaps the effort to convince them would be advisable, but is it truly worthwhile to spend valuable time during an appointment arguing with patients to continue these drugs when they will have no net benefit? Or would that time be better spent on other interventions to prevent CVD such as reinforcing a healthy diet and exercise?

Before addressing these questions, consider several other effects of statins that directly impact the answers. First, patients on statin therapy have been found to increase their calorie intake more than those that are not [47]. While this was an observational study and the exact mechanism could not be ascertained, it is plausible either that statins impact satiety or more worryingly that patients on statins believe these drugs will adequately protect them from CVD and so they disregard other elements of a healthy lifestyle. Statins have also been shown to blunt the improvement in cardiorespiratory fitness normally achieved by aerobic exercise [48]. Furthermore, exercise exacerbates statin-induced myalgias to the extent that more than 80% of professional athletes with familial hypercholesterolemia discontinue statin therapy [49]. The worsened myalgias may lead other patients to instead make the opposite choice and reduce their level of exercise, a choice that would be quite detrimental to their overall health.

Now consider again whether a patient with side effects on statin therapy should be convinced to continue the medication. Though there may be less than a 50% chance the statin is causing their symptoms, taking it will not lead them to live longer, will have a less than 1% chance of preventing an ischemic event, will have a roughly equal chance of causing a complication such as diabetes, and will potentially lead them to eat worse and derive less benefit from exercise. Would it not be better to instead spend this time counseling patients on how to improve their diets and achieve adequate exercise, both of which will reliably reduce their risk of CVD [50–52]? Especially when this will also have positive effects on their mental health and overall wellbeing [53–55]? To us the answer is obvious.

4. Statins have no benefits in elderly patients treated for primary prevention and have the potential for considerable harm

While the risks associated with statins are at least accompanied by a small reduction in ischemic events in middle-aged adults, these same benefits have not been demonstrated in elderly patients and thus the risk-benefit calculation shifts decidedly towards risk. Individual trials have without exception failed to demonstrate an improvement in overall survival in elderly patients treated with statins for primary prevention, with RCTs such as ALLHAT-LLA actually demonstrating a trend towards increased mortality in patients over the age of 75[56,57]. Meta-analyses have likewise failed to find a mortality reduction in elderly patients treated with statins for primary prevention [58–60]. However, perhaps even more importantly, a meta-analysis that stratified patients by age even failed to demonstrate a reduction in major vascular events in patients over the age of 70 without pre-existing CVD [59]. This suggests that the minor reductions in MIs and ischemic strokes seen in middle aged adults cannot be expected in elderly patients, exposing them to all the harms of statins without any benefits. Some trials such as PROSPER have even found that elderly patients treated with statins have an increased incidence of cancer [57]. Meta-analyses have so far found only a non-significant trend towards increased cancer incidence in the elderly, though the overall number of patients pooled is quite low [60]. Trials are currently ongoing that may help elucidate this association more definitively (NCT02099123, NCT04262206). At this time, however, the available evidence suggests that prescribing statins to elderly patients without CVD will not lead them to live longer, will not even reduce their risk of MIs or strokes, and may make them more likely to develop cancer on top of the other side effects of statins. Statins should therefore unquestionably be avoided for primary prevention in elderly patients.

5. Conclusions

As stated earlier, a medication must only be started when its benefits are reasonably expected to outweigh its risks in the specific patient being treated. In both middle-aged and elderly patients without CVD, we believe that statins clearly fail this test. The insistence on prescribing statins is especially perplexing given the multitude of options available to physicians seeking to prevent CVD in their patients. Counseling interventions as short as 10 min delivered by trained physicians can reduce cardiovascular risk factors in patients [61], with more intensive behavioral counseling showing even more effective results [62]. Such interventions can help patients commit to a healthy diet and exercise which are far more important, both for preventing CVD and for improving overall well-being. A better appreciation by both physicians and patients for the relative benefit of such behaviors compared to medications would go a long way towards avoiding unnecessary interventions and improving the true underlying drivers of health.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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References

[1] J.R. Downs, M. Clearfield, S. Weis, et al., Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS, JAMA 279 (20) (1998) 1615, https://doi.org/10.1001/jama.279.20.1615.

[2] J. Shepherd, S.M. Cobbe, I. Ford, et al., Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia, N. Engl. J. Med. 333 (20) (1995) 1301–1308, https://doi.org/10.1056/NEJM199511163332001.

[3] P.S. Sever, B. Dahlöf, N.R. Poulter, et al., Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial, Lancet 361 (9364) (2003) 1149–1158, https://doi.org/10.1016/S0140-6736(03)12948-0.

[4] R.H. Knopp, M. d'Emden, J.G. Smilde, S.J. Pocock, On behalf of the ASPEN study group. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes, Diabetes Care 29 (7) (2006) 1478–1485, https://doi.org/10.2337/dc05-2415.

[5] H.M. Colhoun, D.J. Betteridge, P.N. Durrington, et al., Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial, Lancet 364 (9435) (2004) 685–696, https://doi.org/10.1016/S0140-6736(04)16895-5.

[6] S. Yusuf, J. Bosch, G. Dagenais, et al., Cholesterol lowering in intermediate-risk persons without cardiovascular disease, N. Engl. J. Med. 374 (21) (2016) 2021–2031, https://doi.org/10.1056/NEJMoa1600176.

[7] C. Wanner, V. Krane, W. März, et al., Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis, N. Engl. J. Med. 353 (3) (2005) 238–248, https://doi.org/10.1056/NEJMoa043545.

[8] H. Nakamura, K. Arakawa, H. Itakura, et al., Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial, Lancet 368 (9542) (2006) 1155–1163, https://doi.org/10.1016/S0140-6736(06)69472-5.

[9] R. Chou, T. Dana, I. Blazina, M. Daeges, T.L. Jeanne, Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US preventive Services Task Force, JAMA 316 (19) (2016) 2008, https://doi.org/10.1001/jama.2015.15629.

[10] C.D. Furberg, H.P. Adams, W.B. Applegate, et al., Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic carotid artery progression study (ACAPS) research group, Circulation 90 (4) (1994) 1679–1687, https://doi.org/10.1161/01.CIR.90.4.1679.

[11] P.M. Ridker, E. Danielson, F.A.H. Fonseca, et al., Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein, N. Engl. J. Med. 359 (21) (2008) 2195–2207, https://doi.org/10.1056/NEJMoa0807646.

[12] R.P. Morrissey, G.A. Diamond, S. Kaul, The JUPITER trial: myth or reality? Curr. Atherosclerosis Rep. 13 (5) (2011) 413–421, https://doi.org/10.1007/s11883-011-0197-9.

[13] D. Bassler, Stopping randomized trials early for benefit and estimation of treatment EffectsSystematic review and meta-regression analysis, JAMA 303 (12) (2010) 1180, https://doi.org/10.1001/jama.2010.310.

[14] Rosuvastatin in patients with elevated C-reactive protein, N. Engl. J. Med. 360 (10) (2009) 1038–1042, https://doi.org/10.1056/NEJMc082574.

[15] S. Kaul, R.P. Morrissey, G.A. Diamond, By jove! What is a clinician to make of JUPITER? Arch. Intern. Med. 170 (12) (2010) 1073, https://doi.org/10.1001/archinternmed.2010.189.

[16] F. Taylor, M.D. Huffman, A.F. Macedo, et al., Statins for the primary prevention of cardiovascular disease, in: Cochrane Database Syst Rev, 2021, Cochrane Heart Group, 2013, https://doi.org/10.1002/14651858.CD004816.pub5, 9.

[17] J.J. Brugts, T. Yetgin, S.E. Hoeks, et al., The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials (jun30 1, BMJ 338 (2009) b2376, https://doi.org/10.1136/bmj.b2376. b2376.

[18] Cholesterol Treatment Trialists' (CTT) Collaborators, The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials, Lancet 380 (9841) (2012) 581–590, https://doi.org/10.1016/S0140-6736(12)60367-5.

[19] K.K. Ray, S.R.K. Seshasai, S. Erqou, et al., Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65 229 participants, Arch. Intern. Med. 170 (12) (2010) 1024, https://doi.org/10.1001/archinternmed.2010.182.

[20] J.D. Abramson, H.G. Rosenberg, N. Jewell, J.M. Wright, Should people at low risk of cardiovascular disease take a statin?, oct22 3, BMJ 347 (2013) f6123, https://doi.org/10.1136/bmj.f6123. f6123.

[21] A.L. Culver, I.S. Ockene, R. Balasubramanian, et al., Statin use and risk of diabetes mellitus in postmenopausal women in the women's health initiative, Arch. Intern. Med. 172 (2) (2012) 144, https://doi.org/10.1001/archinternmed.2011.625.

[22] I. Mansi, C.R. Frei, C.P. Wang, E.M. Mortensen, Statins and new-onset diabetes mellitus and diabetic complications: a retrospective cohort study of us healthy adults, J. Gen. Intern. Med. 30 (11) (2015) 1599–1610, https://doi.org/10.1007/s11606-015-3335-1.

[23] N. Sattar, D. Preiss, H.M. Murray, et al., Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials, Lancet 375 (9716) (2010) 735–742, https://doi.org/10.1016/S0140-6736(09)61965-6.

[24] D. Preiss, S.R.K. Seshasai, P. Welsh, et al., Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis, JAMA 305 (24) (2011) 2556, https://doi.org/10.1001/jama.2011.860.

[25] B.A. Golomb, M.A. Evans, J.E. Dimsdale, H.L. White, Effects of statins on energy and fatigue with exertion: results from a randomized controlled trial, Arch. Intern. Med. 172 (15) (2012), https://doi.org/10.1001/archinternmed.2012.2171.

[26] M.F. Muldoon, S.D. Barger, C.M. Ryan, et al., Effects of lovastatin on cognitive function and psychological well-being**Access the "Journal Club" discussion of,

Am. J. Med. 108 (7) (2000) 538–546, https://doi.org/10.1016/S0002-9343(00)00353-3, this paper at, http://www.elsevier.com/locate/ajmselect/.

[27] M.F. Muldoon, C.M. Ryan, S.M. Sereika, J.D. Flory, S.B. Manuck, Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults, Am. J. Med. 117 (11) (2004) 823–829, https://doi.org/10.1016/j.amjmed.2004.07.041.

[28] D. Gaist, U. Jeppesen, M. Andersen, L.A. Garcia Rodriguez, J. Hallas, S.H. Sindrup, Statins and risk of polyneuropathy: a case-control study, Neurology 58 (9) (2002) 1333–1337, https://doi.org/10.1212/WNL.58.9.1333.

[29] G. Corrao, A. Zambon, L. Bertu, E. Botteri, O. Leoni, P. Contiero, Lipid lowering drugs prescription and the risk of peripheral neuropathy: an exploratory case-control study using automated databases, J. Epidemiol. Community Health 58 (12) (2004) 1047–1051, https://doi.org/10.1136/jech.2003.013409.

[30] S de Denus, S.A. Spinler, K. Miller, A.M. Peterson, Statins and liver toxicity: a meta-analysis, Pharmacotherapy 24 (5) (2004) 584–591, https://doi.org/10.1592/phco.24.6.584.34738.

[31] C.R. Dormuth, B.R. Hemmelgarn, J.M. Paterson, et al., Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases, mar18 3, BMJ 346 (2013) f880, https://doi.org/10.1136/bmj.f880. f880.

[32] H.V. Ganga, H.B. Slim, P.D. Thompson, A systematic review of statin-induced muscle problems in clinical trials, Am. Heart J. 168 (1) (2014) 6–15, https://doi.org/10.1016/j.ahj.2014.03.019.

[33] Cholesterol Treatment Trialists' (CTT) Collaboration, Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials, Lancet 376 (9753) (2010) 1670–1681, https://doi.org/10.1016/S0140-6736(10)61350-5.

[34] E. Bruckert, G. Hayem, S. Dejager, C. Yau, B. Bégaud, Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients —the PRIMO study, Cardiovasc. Drugs Ther. 19 (6) (2005) 403–414, https://doi.org/10.1007/s10557-005-5686-z.

[35] P.D. Thompson, G. Panza, A. Zaleski, B. Taylor, Statin-associated side effects, J. Am. Coll. Cardiol. 67 (20) (2016) 2395–2410, https://doi.org/10.1016/j.jacc.2016.02.071.

[36] J.D. Cohen, E.A. Brinton, M.K. Ito, T.A. Jacobson, Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users, J. Clin. Lipidol. 6 (3) (2012) 208–215, https://doi.org/10.1016/j.jacl.2012.03.003.

[37] C.A. Jackevicius, M. Mamdani, J.V. Tu, Adherence with statin therapy in elderly patients with and without acute coronary syndromes, JAMA 288 (4) (2002) 462, https://doi.org/10.1001/jama.288.4.462.

[38] R. Collins, C. Reith, J. Emberson, et al., Interpretation of the evidence for the efficacy and safety of statin therapy, Lancet 388 (10059) (2016) 2532–2561, https://doi.org/10.1016/S0140-6736(16)31357-5.

[39] A. Kashani, C.O. Phillips, J.M. Foody, et al., Risks associated with statin therapy: a systematic overview of randomized clinical trials, Circulation 114 (25) (2006) 2788–2797, https://doi.org/10.1161/CIRCULATIONAHA.106.624890.

[40] J.A. Finegold, C.H. Manisty, B. Goldacre, A.J. Barron, D.P. Francis, 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. 21 (4) (2014) 464–474, https://doi.org/10.1177/2047487314525531.

[41] J.A. Tobert, C.B. Newman, The nocebo effect in the context of statin intolerance, J. Clin. Lipidol. 10 (4) (2016) 739–747, https://doi.org/10.1016/j.jacl.2016.05.002.

[42] Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. The Cochrane Collaboration, ed. Cochrane Database Syst Rev. Published online December 12, 2012:MR000033.pub2. doi:10.1002/14651858.MR000033.pub2.

[43] R.F. Redberg, M.H. Katz, Statins for primary prevention: the debate is intense, but the data are weak, JAMA 316 (19) (2016) 1979, https://doi.org/10.1001/jama.2016.15085.

[44] G. Fernandez, E.S. Spatz, C. Jablecki, P.S. Phillips, Statin myopathy: a common dilemma not reflected in clinical trials, Cleve. Clin. J. Med. 78 (6) (2011) 393–403, https://doi.org/10.3949/ccjm.78a.10073.

[45] B.A. Parker, J.A. Capizzi, A.S. Grimaldi, et al., Effect of statins on skeletal muscle function, Circulation 127 (1) (2013) 96–103, https://doi.org/10.1161/CIRCULATIONAHA.112.136101.

[46] B.A. Taylor, L. Lorson, C.M. White, P.D. Thompson, A randomized trial of coenzyme Q10 in patients with confirmed Statin Myopathy, Atherosclerosis 238 (2) (2015) 329–335, https://doi.org/10.1016/j.atherosclerosis.2014.12.016.

[47] T. Sugiyama, Y. Tsugawa, C.H. Tseng, Y. Kobayashi, M.F. Shapiro, Different time trends of caloric and fat intake between statin users and nonusers among US adults: gluttony in the time of statins? JAMA Intern. Med. 174 (7) (2014) 1038, https://doi.org/10.1001/jamainternmed.2014.1927.

[48] C.R. Mikus, L.J. Boyle, S.J. Borengasser, et al., Simvastatin impairs exercise training adaptations, J. Am. Coll. Cardiol. 62 (8) (2013) 709–714, https://doi.org/10.1016/j.jacc.2013.02.074.

[49] H. Sinzinger, J. O'Grady, Professional athletes suffering from familial hypercholesterolaemia rarely tolerate statin treatment because of muscular problems, Br. J. Clin. Pharmacol. 57 (4) (2004) 525–528, https://doi.org/10.1111/j.1365-2125.2003.02044.x.

[50] R. Estruch, E. Ros, J. Salas-Salvadó, et al., Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts, N. Engl. J. Med. 378 (25) (2018) e34, https://doi.org/10.1056/NEJMoa1800389.

[51] S.N. Blair, Changes in physical fitness and all-cause mortality: a prospective study of healthy and unhealthy men, JAMA 273 (14) (1995) 1093, https://doi.org/10.1001/jama.1995.03520380029031.

[52] R.S. Paffenbarger, R.T. Hyde, A.L. Wing, I.M. Lee, D.L. Jung, J.B. Kampert, The association of changes in physical-activity level and other lifestyle characteristics with mortality among men, N. Engl. J. Med. 328 (8) (1993) 538–545, https://doi.org/10.1056/NEJM199302253280804.

[53] U.M. Kujala, Evidence on the effects of exercise therapy in the treatment of chronic disease, Br. J. Sports Med. 43 (8) (2009) 550–555, https://doi.org/10.1136/bjsm.2009.059808.

[54] Cooney GM, Dwan K, Greig CA, et al. Exercise for depression. Cochrane Common Mental Disorders Group, ed. Cochrane Database Syst Rev. Published online September 12, 2013. doi:10.1002/14651858.CD004366.pub6.

[55] M. Pahor, J.M. Guralnik, W.T. Ambrosius, et al., Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial, JAMA 311 (23) (2014) 2387, https://doi.org/10.1001/jama.2014.5616.

[56] B.H. Han, D. Sutin, J.D. Williamson, et al., Effect of statin treatment vs usual care on primary cardiovascular prevention among older adults: the ALLHAT-LLT randomized clinical trial, JAMA Intern. Med. 177 (7) (2017) 955, https://doi.org/10.1001/jamainternmed.2017.1442.

[57] J. Shepherd, G.J. Blauw, M.B. Murphy, et al., Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial, Lancet 360 (9346) (2002) 1623–1630, https://doi.org/10.1016/S0140-6736(02)11600-X.

[58] G. Savarese, A.M. Gotto, S. Paolillo, et al., Benefits of statins in elderly subjects without established cardiovascular disease, J. Am. Coll. Cardiol. 62 (22) (2013) 2090–2099, https://doi.org/10.1016/j.jacc.2013.07.069.

[59] J. Armitage, C. Baigent, E. Barnes, et al., Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials, Lancet 393 (10170) (2019) 407–415, https://doi.org/10.1016/S0140-6736(18)31942-1.

[60] B. Gencer, N.A. Marston, K. Im, et al., Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials, Lancet 396 (10263) (2020) 1637–1643, https://doi.org/10.1016/S0140-6736(20)32332-1.

[61] I.S. Ockene, J.R. Hebert, J.K. Ockene, et al., Effect of physician-delivered nutrition counseling training and an office-support program on saturated fat intake, weight, and serum lipid measurements in a hyperlipidemic population: worcester area trial for counseling in hyperlipidemia (WATCH), Arch. Intern. Med. 159 (7) (1999) 725, https://doi.org/10.1001/archinte.159.7.725.

[62] M.L. LeFevre, Behavioral counseling to promote a healthful diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: U.S. Preventive Services Task Force recommendation statement, Ann. Intern. Med. 161 (8) (2014) 587, https://doi.org/10.7326/M14-1796.