A discussion on Statins use at the light of new 2022 recomendations

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The U.S. Preventive Services Task Force (USPSTF) recently published its Recommendation Statement for Statin Use for the Primary Prevention of Cardiovascular Disease in Adults. Also the American College of Cardiology (ACC) Expert Consensus have introduced some new considerations on statins and non-statins therapeutic drugs use. Although both recommendations are slightly different, they share the idea that pursuing the precise patients with statins is key to gaining the most benefit.

For half a century, great efforts have been made in understanding the pathophysiology of atherosclerosis and cardiovascular disease (CVD). Many studies have linked a high level of total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) as a major cause of atherosclerosis and CVD, and as so it has been extending statin treatment for cardiovascular prevention (Ravnskov et al., 2018). Results from several statin treatment trials indicated that the benefits for facing against CVD are proportional to the relevance of LDL-C reduction. Epidemiological and genetic studies have emphasized cardioprotective effects of low lifetime atherogenic cholesterol exposure and supported the pursuing of LDL-C reduction, but without establishing a threshold at which this reduction becomes non-beneficial (Soran et al., 2017). Actually, it is well established that attaining a rigorous control of LDL-C levels represents one of the most effective strategies for preventing CVD and CVD-related mortality. For example, results of a recent published meta-analysis showed that reductions in LDL-C by statin treatments consistently decrease the incidence of major vascular events (Perrone et al., 2022). Indeed, Agabiti et al (2016) described that several trials have clearly demonstrated that lowering LDL-C, especially when treated with statins, reduces major cardiovascular events and mortality. All commercially available statins are recognized as inhibitors of the enzyme HMG-CoA reductase activity which is the rate-limiting enzyme of mevalonate pathway. The net result is the lowering endogenous production and circulating LDL cholesterol levels. Statins are generally well tolerated; however, several statin trials and large meta-analyses have revealed an increase incidence of a plenty of adverse effects. Ravnskov et al. (2018) gathered evidence in case-control and cross-sectional studies that statin use is

significantly frequently associated with some events in patients such as cataract, hearing loss, suicidal ideation, peripheral neuropathy, depression, Parkinson's disease, interstitial cystitis, shingles, sexual impotence, cognitive impairments, and diabetes. An association has been found between discontinuation of treatment and disappearance of symptoms, as well as worsening of symptoms with reintroduction of statins. Collins et al. (2016) have described, however, that the most serious adverse events that have been shown to be caused by long-term statin therapy are myopathy, new-onset diabetes mellitus, and, probably, haemorrhagic stroke. Concerning type-2 diabetes (T2D), Authors have estimated that treatment of 10.000 patients for 5 years with a standard statin regimen would cause about 50-100 new cases of T2D (Figure 1). Besides, it caused about 5 cases of myopathy, and 5–10 haemorrhagic strokes (only 0.01% of individuals treated per year). An analysis of this finding has found that in most statin trials, myopathy was only recorded if creatine kinase level is more than 10 times higher than normal level. This criticism was also supported by Garcia (2019), citing withdrawal of cerivastatin from the market because of several deaths caused by renal glomerular obstruction resulting from proteins released as a result of muscle damage. Thus, Authors have concluded that the adverse effects of statins are shown to be relevant when considering their current clinical use in millions of patients. Albeit, Authors have stated that "placebo-controlled randomised trials have shown definitively that almost all of the symptomatic adverse events that are attributed to statin therapy in routine practice are not actually caused by it (they represent misattribution)".

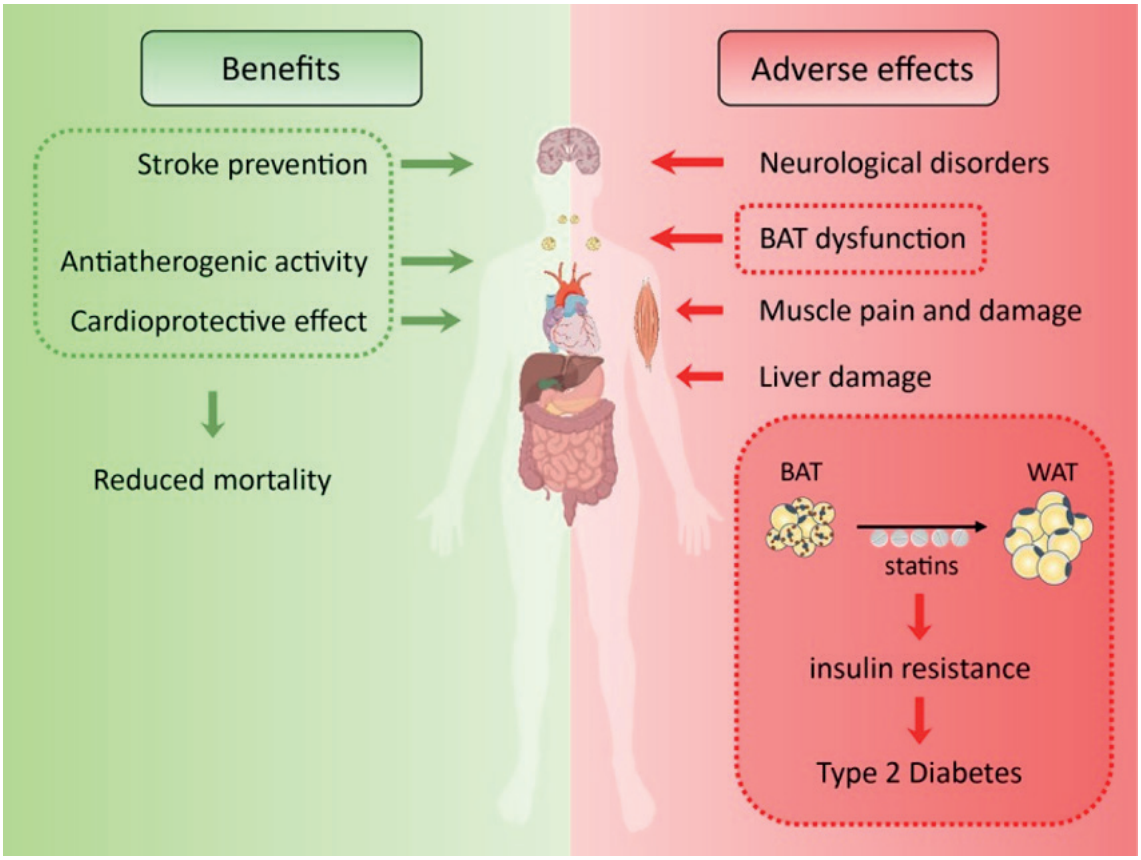

Figure 1. Statin benefits and adverse effects. Statin therapy shows cardioprotective and antiatherogenic effect, thereby reducing mortality. However, statins show also adverse effects, particularly on brown adipose tissue (BAT), liver and muscle function. We suggest that BAT dysfunction might be the mediator of statin induced insulin resistance and type 2 diabetes. (Extract from "Statins: benefits and risks revisited"; Miroslav Balaz and Christian Wolfrum, Aging (Albany NY). 2019 Jul 15; 11(13): 4300–4302. Published online 2019 Jul 14. doi: 10.18632/aging.102056).

Recently, the relationship of several other risk factors for atherosclerosis and CVD has been raised. By contrast, some studies have showed that statin treatment may have little or no health benefits. Consequently, it has been suggested that factors such as hypertension, diabetes, smoking, obesity, sedentary lifestyle, family history, and psychosocial stress factors may also play a key role in the pathogenesis of CVD. Thus, it is important to evaluate the role of statins in the treatment of atherosclerosis and CVD, and particularly, as primary cardiovascular prevention. In order to further explore this growing discussion, Ravnskov et al (2018) evaluated three major reviews on statins use (Collins et al., 2016; Silverman et al., 2016; Ference et al., 2017), raising questions about contradictory results, possible errors and falsifications.

Much has already been discussed about whether elevated TC causes atherosclerosis. In Ravnskov et al (2018) investigation, some studies have pointed out that people with low TC were as atherosclerotic as people with high TC. The studies that found a weak association between TC and the degree of atherosclerosis, however, were performed with patients from only one hospital, and therefore may have included patients with familial hypercholesterolemia (FH), creating a bias in the research. Of 16 angiographic studies of cholesterol lowering, the correlation between TC and atherosclerosis was present in only one. Authors have suggested that TC elevation is probably not the only main cause of the disease. Indeed, they have described that in two additional reviews supporting the cholesterol hypothesis, about half of the contrary articles were ignored. Statistically non-significant findings in favor of the cholesterol hypothesis were overestimated, and results that did not provide support were cited as if they were encouraging. Only one of the six randomized cholesterol-lowering studies with a negative result was cited, and only in one of the reviews. Regarding CVD, the hypothesis that elevated TC causes disturbs was generated from the publication of the Framingham Heart Study (1987). The 30-year follow-up of the research, which began in 1960, concluded that “for every 1 mg/dl drop in TC per year, there was an eleven percent increase in coronary and total mortality”. Indeed García (2019) published an opinion article supporting the arguments made in Ravnskov et al investigation. It was pointed out that cholesterol hypothesis was kept alive for decades perhaps because the review authors used dubious statistical criteria. García (2019) drew a parallel of statin treatment for CVD, with the treatment of chronic myeloid leukemia (CML), with tyrosine kinase inhibitors imatinib, dasatinib, nilotinib, and ponatinib, with regard to treatment time. The treatment has turned CML, a short-term fatal disease, into a chronic disease. He considered that the question of stopping the medication and bearing in mind the patient cured of CML has been raised since some studies have shown that at least 30% of patients did not relapse when the medication was stopped. This practice certainly positively influenced the quality of life of patients with reduced adverse effects and of course, to the currencies saving generated by the suppression of a drug as expensive as imatinib.

Therefore, considering a plenty of studies that have pointed out the growing idea that TC is not the only one accurate predictor for CVD, combined with many reported side effects in a significant percentage of patients who do not tolerate statin treatment, researchers have focused their attention on novel LDL-C lowering agents that act through mechanisms distinct from those of statins (Agabiti et al., 2016).

The American College of Cardiology (ACC) Expert Consensus works towards complementing clinical practice guidelines. Since the publication of the cholesterol guidelines in 2013, several newer non-statin agents such as bempedoic acid, evinacumab, and inclisiran have demonstrated efficacy in LDL-C reduction and received FDA approval, being now commercially available for the treatment of at-risk patients. In 2018,

the ACC reaffirmed the clinical benefits of statin therapy, emphasizing the importance of appropriate intensity of statin therapy and the role of physician-patient discussion and shared decision making. But it made an important recommendation: the use of an LDL-C threshold of ≥70 mg/dL (1.8 mmol/L) to consider the addition of non-statin therapy for maximally tolerated statin therapy in patients with stable atherosclerotic cardiovascular disease (ASCVD). In this regard, in 2022 the ACC laid out other elements to consider when adding non-statin therapy for further ASCVD risk reduction, namely checking the percentage of LDL-C reduction achieved with evidence-based statin therapy (if <50% and not on maximal statin use, one should first increase statin therapy and reinforce lifestyle modifications) and whether the patient is above the LDL-C threshold for consideration of non-statin therapies (ACC, 2022).

The likelihood that patients will benefit from statin use depends on their absolute risk of having a future cardiovascular event. It is forecasted that the higher the 10-year risk of a cardiovascular event, the greater the chance of benefit from preventive statin treatment according to the US Preventive Services Task Force (USPSTF). In a recent review of the evidence on the benefits and harms of statins for reducing CVD-related morbidity or mortality or all-cause mortality, the Task 22 studies that reported the benefits of statin use for primary prevention. In pooled analyses, statin therapy was associated with decreased risk of all-cause mortality (18 trials; n = 85,816; relative risk [RR], 0.92 [95% CI, 0.87 to 0.98], fatal or nonfatal stroke (15 trials; n = 76. 610; RR, 0.78 [95% CI, 0.68 to 0.90], Fatal or nonfatal myocardial infarction (12 trials; n = 76 498; RR, 0.67 [95% CI, 0.60 to 0.75]. The primary prevention endpoints of the 2002 PROSPER trial, on the other hand, found no decrease in all-cause mortality, stroke risk, or a composite cardiovascular endpoint among people taking a statin compared with placebo. In analyzing the benefit of statin use by the primary prevention population, the ALLHAT-LLT study (2002), concluded that statin therapy was associated with higher risk of cardiovascular and all-cause mortality in people aged 75 years and older than in those aged 65 to 74 years. However several limitations were noted in the study, including its open-ended design, high loss to follow-up, and high crossover from usual care treatment group (USPSTF, 2022). Nevertheless, the Task Force recommended that the presence of CVD risk factors (i.e., dyslipidemia, diabetes, hypertension, or smoking) and the estimated 10-year CVD risk be assessed to determine which people should initiate statin use (USPSTF, 2022).

In determining harms of preventive statin treatment, the USPSTF reviewed 19 studies (n = 75,005) and 3 observational studies (n = 417,523) that reported the harms of statin therapy in adults without a history of cardiovascular event. Although the results of the observational studies found an association between statin use and muscle pain, a pooled analysis of 9 studies (n = 46,388) found no increased risk of myalgia with statin therapy compared with placebo. Furthermore, these trials did not prove an association between statin therapy and the adverse events myopathy or rhabdomyolysis . According to twelve studies (n = 55,358) investigated by the USPSTF, there was no difference between statin therapy and placebo with respect to the risk of elevated aminotransferase levels. Added to this, pooled analyses of 13 studies (n = 71,733) found no difference between statin therapy and placebo or no statin on the risk of any cancer. In the primary preventive use setting, six studies (n = 59,083) and three observational studies (n = 417,523) reported the risk of recent onset diabetes with statin therapy. In contrast, a pooled analysis of 6 trials showed no difference between statins and placebo or no statin in the risk of diabetes. The JUPITER trial (2008), which used high-intensity statin therapy, reported an increased risk of diabetes with statin use, but this risk was found to be limited to the participants with one or more risk factors for diabetes (USPSTF, 2022).

The USPSTF recommended that further studies are required with possible aiming: the prediction of CVD risk in all racial, ethnic, and socioeconomic groups; the balance between benefit and harm of initiating statin use for primary prevention in adults aged 76 years and older; the efficacy and safety of prolonged statin treatment in adults younger than 40 years; and eventually the effects of early versus late initiation, especially in people at high risk of CVD.

Taken together, all of the studies brought in this article clearly casted a plenty of certainties - and also uncertainties - on the statins therapeutic use and cardiovascular diseases.

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