Journal of Clinical Lipidology (2017) ■, ■–■

Journal of Clinical Lipidology

Original Article

Effects of morning vs evening statin administration on lipid profile: An systematic review and meta-analysis

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KEYWORDS:
Cholesterol;
LDL;
Hydroxymethylglutaryl-CoA reductase inhibitors;
Half-life;
Lipids

BACKGROUND: Evidence about the optimal time of day at which to administer statins is lacking.

OBJECTIVE: The objective of this study is to synthesize evidence about effects of morning vs evening statin administration on lipid profile.

METHODS: We searched PubMed, SCOPUS, Web of Science, and Embase databases (from inception up to July 24, 2016) to identify the relevant studies. Mean differences (MDs) between the change scores in lipid parameters were pooled using a fixed-effect model.

RESULTS: Eleven articles with 1034 participants were eligible for the analysis. The pooled analysis comparing effects of morning vs evening administration of statins on plasma total cholesterol (TC; $P = .10$), high-density lipoprotein cholesterol ($P = .90$), and triglycerides ($P = .45$) was not statistically significant. Low-density lipoprotein cholesterol (LDL-C) lowering was statistically greater in the evening-dose group (MD: 3.24 mg/dL, 95% CI: 1.23–5.25, $P = .002$). Subgroup analysis according to statin half-lives showed that evening dose of statins was significantly superior to morning dose for lowering LDL-C in case of both short and long half-life statins (MD: 9.68 mg/dL, 95% CI: 3.32–16.03, $P = .003$ and MD: 2.53 mg/dL, 95% CI: 0.41–4.64, $P = .02$, respectively) and also for TC reduction in case of short half-life statins only ($P = .0005$).

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Submitted November 16, 2016. Accepted for publication June 2, 2017.

http://dx.doi.org/10.1016/j.jacl.2017.06.001

CONCLUSIONS: LDL-C and TC lowering were significantly greater in the evening dose than in the morning dose in case of short-acting statins. Besides slight but significant effect on LDL-C, the efficacy of long-acting statins was equivalent for both regimens. Therefore, long-acting statins should be given at a time that will best aid compliance. Short-acting statins should be given in the evening.

Introduction

Coronary heart disease is the leading cause of mortality and morbidity world wide.[1,2] It is now unequivocal that elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are major risk factors for the development of atherosclerosis and coronary heart disease and that lowering these values diminishes the incidence of these diseases.[3–10] Previous meta-analyses showed that for every 1.0 mmol/L (38.7 mg/dL) reduction in LDL-C, there is a corresponding 20%–25% reduction in cardiovascular disease (CVD) mortality.[11]

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are very effective drugs for reducing the elevated levels of plasma cholesterol.[2,12] Statins reduce both LDL-C and triglycerides (TGs) by up to 50% and 20%, respectively.[2,13] Moreover, they increase high-density lipoprotein cholesterol (HDL-C) by up to 10%.[14,15] It is now well established that statins are beneficial for primary and secondary prevention of CVD.[7–10,16–20] In a meta-analysis of 170,000 participants, which included data from 26 randomized controlled trials (RCTs) with statins, all-cause mortality was reduced by 10%, coronary artery disease death by 20%, risk of major coronary events by 23%, and risk of stroke by 17% per 1 mmol/L (38.7 mg/dL) reduction in LDL-C.[21] Statins are considered to be the standard therapy for many types of dyslipidemia due to their ability to inhibit the endogenous biosynthesis of cholesterol and to increase the hepatic uptake of LDL-C by stimulating the expression of LDL-C receptors in the liver.[11,12,22] This is important because more than 75% of cholesterol found in the body is synthesized endogenously and two-thirds of it is synthesized in the liver alone.[12]

Statins are usually administrated in the evening because cholesterol biosynthesis peaks during the night and also because most of them (simvastatin, pravastatin, fluvastatin, and lovastatin) have short half-lives.[12,23–25] The timing of drug administration can alter patient compliance and adherence to the treatment.[26–28] Patients treated with statins often receive multiple concomitant medications and this leads to more complex drug regimens, which have the potential to reduce compliance and adherence to therapy.[29,30] Allowing flexibility in choosing the time, at which statins are administrated, according to the patient's preference, is likely to improve patient compliance and decrease drug discontinuation.[31] This will enable more patients to achieve their target lipid levels.[32,33]

Therefore, we performed this systematic review and meta-analysis to synthesize evidence about the different effects of morning and evening statin administration on lipid profiles to discover the dosing regimen, which led to the highest therapeutic efficacy.

Material and methods

We followed Preferred Reporting Items for Systematic Reviews and Meta-analyses statement guidelines during the preparation of this meta-analysis (Supplementary File 1: Table S1).[34] This meta-analysis was registered in PROSPERO, University of York (CRD42016043480). Q6

Search strategy

We searched PubMed, SCOPUS, Web of Science, and Embase from inception until July 24, 2016, using the following query: (atorvastatin OR fluvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin OR cerivastatin OR mevinolin OR statin OR statins) AND (morning) AND (evening). Additional searches for potential trials included the references of review articles on that issue and the abstracts from selected congresses: scientific sessions of the European Society of Cardiology, the American Heart Association, American College of Cardiology, European Society of Atherosclerosis, and National Lipid Association. The wild-card term "*" was used to increase the sensitivity of the search strategy. The literature search was limited to articles published in English and to studies on humans.

After removal of duplicates by Endnote X7 (Thompson Reuter, CA), 2 independent authors (K.A. and P.P.) screened the retrieved citations in 2 steps; the first step was to screen the titles and abstracts for eligibility and the second step was to screen the full texts of the eligible abstracts according to the inclusion and exclusion criteria. Disagreement was resolved by the opinion of a third author (M.B.)

Study selection

Original studies were included if they met the following criteria: (1) prospective or retrospective clinical controlled studies (with randomized or nonrandomized design); (2) comparing the effects of morning administration against evening administration of statin therapy on one of the following lipid profile parameters: TC, LDL-C, HDL-C, or TG; and (3) reporting sufficient information on blood lipid levels at baseline and at the end of study in