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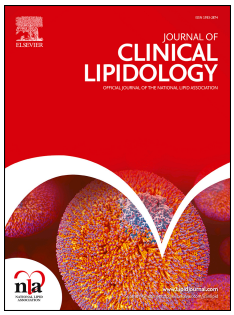

Effects of Morning Versus Evening Statin Administration on Lipid Profile: A Systematic Review and Meta-Analysis

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EFFECTS OF MORNING VERSUS EVENING STATIN ADMINISTRATION ON LIPID PROFILE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Kamal Awad[1,2,*], Maria-Corina Serban[3], Peter Penson[4], Dimitri P. Mikhailidis[5], Peter P. Toth[6,7], Steven R. Jones[7], Manfredi Rizzo[8], George Howard[9], Gregory Y.H. Lip[10], Maciej Banach[11,12]

Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group

[1]Faculty of Medicine, Zagazig University, Egypt; [2]Student Research Unit, Zagazig University, Egypt; [3]Department of Functional Sciences, Discipline of Pathophysiology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania; [4]School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK; [5]Department of Clinical Biochemistry, Royal Free Campus, University College London Medical School, University College London (UCL), London, UK; [6]Preventive Cardiology, CGH Medical Center, Sterling, IL, USA; [7]The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD, USA; [8]Biomedical Department of Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy; [9]Department of Biostatistics, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, USA; [10]University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, UK; [11]Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Poland; [12]Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland.

***Correspondence to**: Kamal Awad, Faculty of Medicine, Zagazig University and Student Research Unit, Zagazig University, Egypt; **Institutional address**: Zagazig, El-Sharkia, Egypt (Postal code: 44519); **Email**: kamal225244@medicine.zu.edu.eg **Phone**: +20 1004092741

Running title: Morning versus evening statins for lipid profile.

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ABSTRACT:

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

OBJECTIVE: To synthesize evidence about effects of morning versus evening statin administration on lipid profile.

METHODS: We searched PubMed, SCOPUS, Web of Science and Embase databases (**from inception up to July 24th, 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 versus evening administration of statins on plasma total cholesterol (TC) (p=0.10), high density lipoprotein cholesterol (HDL-C) (p=0.90) and triglycerides (TG) (p=0.45) 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=0.002). 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=0.003, and 2.53 mg/dl, 95%CI: 0.41, 4.64, p=0.02, respectively), and also for TC reduction in case of short half-life statins only (p=0.0005).

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.

Keywords: Cholesterol, LDL, Hydroxymethylglutaryl-CoA Reductase Inhibitors, Half-Life, Lipids.

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INTRODUCTION

Coronary heart disease (CHD) is the leading cause of mortality and morbidity worldwide [1,2]. It is now unequivocal that elevated levels of total (TC) and low density lipoprotein cholesterol (LDL-C) are major risk factors for the development of atherosclerosis and CHD, 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 (HMG-CoA) reductase inhibitors (statins) are very effective drugs for reducing the elevated levels of plasma cholesterol [2,12]. **Statins reduce both LDL-C and triglycerides (TG) 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 (CAD) 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 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 in order 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 (PRISMA) 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).

Search strategy

We searched PubMed, SCOPUS, Web of Science and Embase from inception until July 24th, 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 (ESC), the American Heart Association (AHA), American College of Cardiology (ACC), European Society of Atherosclerosis (EAS) and National Lipid Association (NLA). 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 in humans.

After removal of duplicates by Endnote X7 (Thompson Reuter, CA, USA), two independent authors (K.A. and P.P.) screened the retrieved citations in two 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: (I) prospective or retrospective clinical controlled studies (with randomized or non-randomized design), (II) 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, (III) reporting sufficient information on blood lipid levels at baseline and at the end of study in both groups, or reporting the net change scores or the mean difference between the change scores of the two groups.

Exclusion criteria were: (I) non-clinical studies, (II) studies that contained false statements or which had been retracted by the journal, (III) studies whose full-texts were not available, and, (IV) studies which provided insufficient data for analysis.

Data extraction

Eligible studies were reviewed and the following data were extracted: (1) first author's name, (2) year of publication, (3) study location, (4) study design, (5) interventions doses, time and duration; (6) study population characteristics, (7) study results, and, (8) concentrations of TC, LDL-C, HDL-C and TG.

Data extraction was performed independently by 2 reviewers (K.A. and P.P.); disagreements were resolved by a third reviewer (M.B.).

Outcomes of interest

The primary outcome was the mean difference between the change scores of the two groups in one of the following lipid parameters: TC, LDL-C, HDL-C and TG. Additionally, the secondary outcome was the compliance of patients with statin regimens.

Quantitative data synthesis

Lipid concentrations were collated in mg/dl using the following site to convert mmol/L to mg/dl: (http://www.onlineconversion.com/cholesterol.htm). Change scores in the lipid levels were calculated as follows: (measure at end of follow-up) – (measure at baseline). Standard deviations (SD) of the change scores were calculated using the following formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\ treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5 [35–37]. If the outcome measures were reported as median and range, mean and SD values were estimated using the method described by Hozo *et al.* [38] and if reported as mean and standard error [SE] (or confidence interval [CI]), mean and SD values were estimated using the method described by Altman *et al.* [39] Mean difference (MD) between the change scores of the morning and evening groups were calculated as follows: (change score of morning group) – (change score of evening group) and its SE was calculated using the following formula: SE = square root $\{[(SD_{treatment\ group})^2 \div n_{traetment\ group}] + [(SD_{control\ group})^2 \div n_{control\ group}]\}$, where (n) was the sample size. If any study reported the MD between the change scores of the morning and evening groups directly with 95% CI, SE was calculated using the following formula: SE = [(upper confidence limit – lower confidence limit) ÷ 3.92], where 3.92 was changed to 3.29 if a 90% CI was given rather than a 95% CI.

MDs between the change scores of the morning and evening groups were pooled in a meta-analysis model with a 95% CI. We used RevMan version 5.3 (The Cochrane Collaboration, Oxford, UK) to conduct this analysis.

Subgroup analysis

Data were divided into two subgroups according to the design of the studies as follows: (I) RCTs, and (II) non-randomized studies. To investigate the impact of statin half-lives on the results, data were separately divided into subgroups as follows: (I) short half-lives below 7 hours (lovastatin, simvastatin, pravastatin and fluvastatin), and (II) long half-lives above 7 hours (atorvastatin, rosuvastatin, controlled-release simvastatin and extended-release fluvastatin) [12,40–42].

Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of the forest plots and was measured by *I*-squared and *Chi*-squared tests. We interpreted heterogeneity according to the recommendations of the Cochrane Handbook of Systematic Reviews and Meta-analysis in which an alpha level (for *Chi*-squared test) below 0.1 is considered to be a significant heterogeneity, and *I*-squared test is interpreted as follows: (0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity). In the case of significant heterogeneity, the random effect model was used. Otherwise, the fixed effect model was employed in meta-analysis.

Sensitivity analysis

Sensitivity analysis was conducted using leave-one-out method, i.e. removing one study each time and repeating the analysis to determine whether exclusion of any one of

the included studies altered the results, particularly when substantial heterogeneity was noted between trials.

Quality assessment

We used the Cochrane Collaboration tool for assessing the risk of bias in included RCTs. This tool includes the following domains: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The authors' judgment is classified as 'Low risk', 'High risk' or 'Unclear risk' of bias.

We used the Newcastle-Ottawa Scale for assessing the risk of bias in non-randomized studies [43]. This scale uses a star system to judge three general domains: selection of study groups, comparability of groups and exposure.

Risk-of-bias assessment was performed independently by 2 reviewers (K.A. and P.P.); disagreements were resolved by a third reviewer (M.B.).

Publication bias

For assessment of publication bias, the pooled effect estimate was plotted against its SE in a funnel plot generated by RevMan software and potential publication bias was explored by visual inspection of Begg's funnel plot asymmetry, and also we used Egger's

weighted regression test to confirm it statistically [44]. We used Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) to perform Egger`s test.

RESULTS

Flow and characteristics of included studies

Our search discovered 549 articles. Following removal of duplicates and detailed screening, only 11 articles (12 treatment arms)[45–55] met our inclusion criteria and were eligible for the meta-analysis (*see PRISMA flow diagram;* **Figure 1**).

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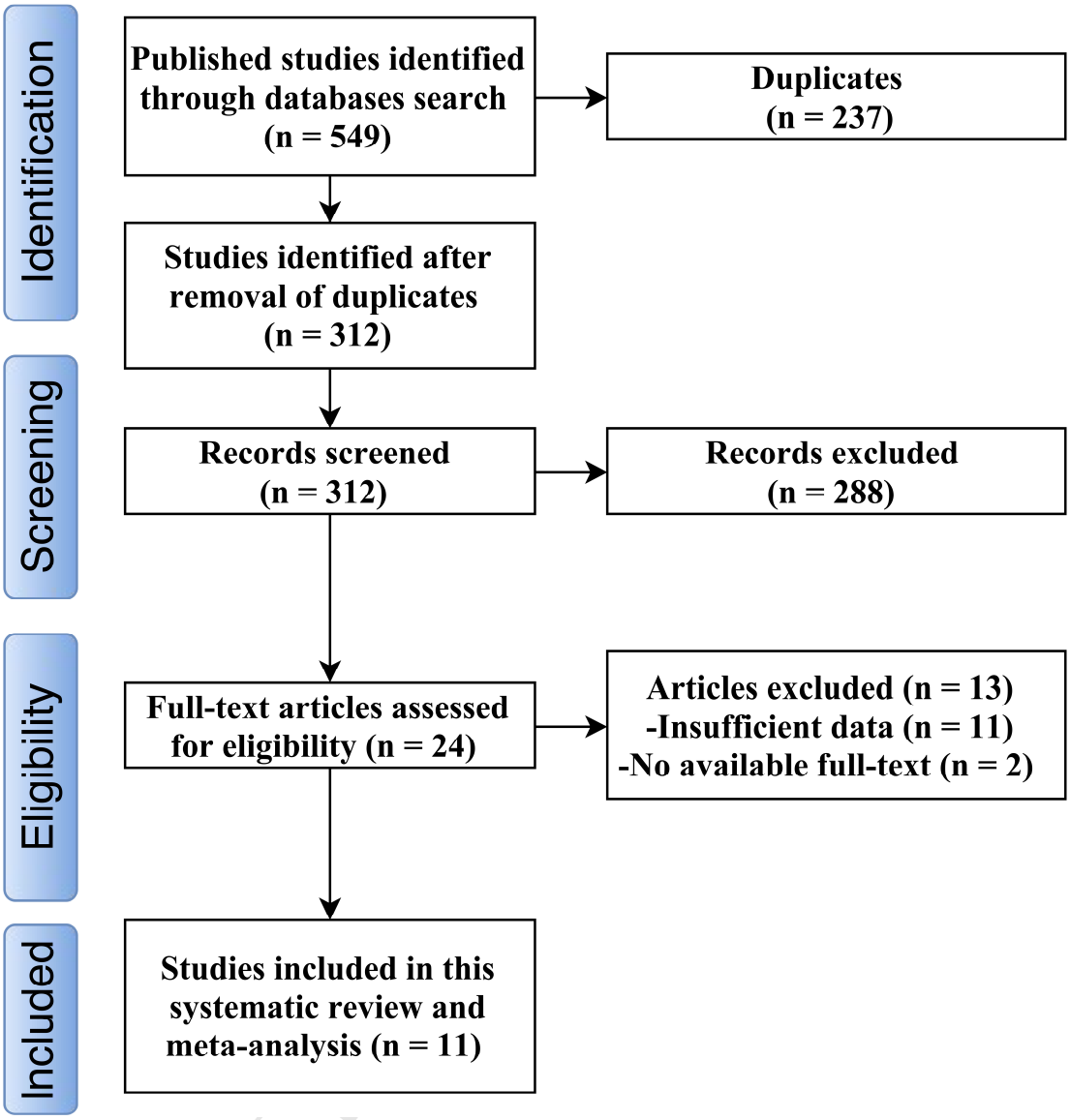

Figure 1: Shows the PRISMA flow diagram of studies' screening and selection.

In total, 1034 participants were included in our analysis. The number of participants in these studies ranged from 12 to 229. Studies included in the meta-analysis were published between 1986 and 2014, and were conducted in USA (n = 4), Germany (n = 2), Korea (n = 2), Turkey, Japan, UK. The following statin doses were administrated in the included studies: 40 mg/day atorvastatin, 2.5-20 mg/day simvastatin, 10 mg/day rosuvastatin, 20 mg/day lovastatin, 40 mg/day pravastatin and 80 mg/day fluvastatin. The duration of the included studies ranged between 4 weeks and 12 weeks. Nine of the included studies were RCTs and one was non-RCT and the other one was a retrospective cohort study. The summary of the included studies and their main results are shown in **Table 1**, and the baseline characteristics of their populations are shown in **Table 2**.

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Table 1: Summary of the included studies.

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Study	Year	Location	Design	Duration	Statin used	Population	Result
Hurminghake et al	1990	USA	Randomized, double-blind, placebo-controlled, parallel trial	8 weeks	pravastatin (40 mg)	Patients with primary hypercholesterolemia who were between the ages of 20 and 72 years.	Pravastatin was well tolerated and was associated with a low incidence of adverse events.
Illingworth et al	1986	USA	Non-randomized, controlled, trial	9 weeks	mevinolin	Patients with severe type II hypercholesterolemia (persistent primary hypercholesterolemia greater than 350 mg/dl)	Once-daily administration of mevinolin, particularly in the evening, is an effective hypocholesterolemic regimen in patients with familial hypercholesterolemia.
Kim et al	2013	Korea	Randomized, double-blind, controlled, parallel trial	8 weeks	controlled-release simvastatin (20 mg)	Patients with LDL-C levels between 100 and 220 mg/dL and triglyceride levels o400 mg/dL	Although controlled-release simvastatin significantly reduces LDL-C levels with good tolerability in Korean adults with dyslipidemia, the time of administration does not affect its efficacy
Kruse et al	1993	Germany	Randomized, single-blind, controlled, parallel trial	4 weeks	lovastatin (20 mg)	Patients with familial hypercholesterolemia	The present study adds further evidence that drug use seems to be more regular in the morning than in the evening.
Martin et al	2002	USA	Randomized, open-label, controlled, crossover trial	8 weeks	rosuvastatin (10 mg)	Healthy adult volunteers, ranging in age from 19 to 61 years and weighing 57–100 kg	The therapeutic benefit of rosuvastatin is not dose-time dependent, and that morning or evening administration is equally effective in regulating lipid levels
Ozaydin et al	2006	Turkey	Randomized, controlled, parallel trial	6 months	atorvastatin (40 mg)	Patients with single-vessel coronary disease who underwent first elective percutaneous coronary intervention (PCI)	Compared with the intake of atorvastatin in the morning, intake in the evening before PCI was associated with a more pronounced decrease in total cholesterol, LDL cholesterol, and triglyceride values, and an increase in HDL cholesterol levels

Plakogiannis et al	2005	USA	Retrospective cohort	4 weeks	atorvastatin (40 mg)	Hyperlipidemic patients at the New York Harbor Healthcare System (NYHHS)	Changes in the levels of total cholesterol, LDL cholesterol, triglycerides, and HDL cholesterol were similar among hyperlipidemic patients receiving atorvastatin calcium 40 mg daily, regardless of the time of day the drug was administered
Saito et al	1991	Japan	Double-blind, placebo-controlled, parallel trial	12 weeks	Simvastatin (2.5 or 5 mg)	Patients diagnosed as having hyperlipidemia (a serum cholesterol value of at least 220 mg/dl , including patients with familial hypercholesterolemia)	When simvastatin was administered orally once per day in the evening, it reduced cholesterol levels to a significantly greater degree than when it was given in the morning
Scharnagl et al	2006	Germany	Randomized, double-blind, controlled, parallel trial	8 weeks	Fluvastatin Extended Release (80 mg)	Patients aged 35–80 years and have type IIa/b hypercholesterolemia (Frederickson), and LDL-C ≥ 160 mg/dl and triglycerides (TG) < 400 mg/dl in the absence of lipid-lowering treatment	The efficacy and safety profiles of fluvastatin Extended Release are equivalent for morning and evening administration
Wallace et al	2003	UK	Randomized, controlled, parallel trial	8 weeks	simvastatin (10 or 20 mg)	Adults stable on 10 or 20 mg of simvastatin at night for primary or secondary prevention of coronary heart disease, stroke, or peripheral vascular disease	Simvastatin is probably best taken at night because concentrations of total cholesterol and of low density lipoprotein are significantly greater when it is taken in the morning
Yi et al	2014	Korea	Randomized, double-blind, controlled, parallel trial	8 weeks	simvastatin (20 mg)	Patients, 20 to 75 years of age, with CKD stage 3, 4, or 5 (predialysis) were enrolled if their serum LDL-C levels were between 100 and 220 mg/dL and their serum triglyceride (TG) levels were < 400 mg/dL	The efficacy of morning administration of CR simvastatin was non-inferior to evening administration of IR simvastatin in patients with CKD. Morning administration of CR simvastatin is expected to increase patient compliance and therefore better control of dyslipidemia in CKD patients

Abbreviations: LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CR: controlled release; IR: immediate release; CKD: chronic kidney disease

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Table 2: Baseline characteristics of the included studies.

Study	Year	Group (# of Patients)	Age (years)	Weight (kg)	Gender (m/f)	Total cholesterol (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	Triglycerides (mg/dl)
Hurminghake et al	1990	Pravastatin qam (n = 48)	53.3	79.1	36/12	320.2 (69.7)	245.6 (67)	44.5 (10.7)	127.5 (49)
		Pravastatin qpm (n = 43)	54.0	76.4	30/13	320.6 (73.5)	244.8 (73.5)	44.5 (12.7)	126.7 (69.7)
Illingworth et al	1986	Mevinolin qam *versus* Mevinolin qpm (n = 12)	54 (13.9)	67 (10.4)	4/8	440 (48.5)	357 (48.5)	54 (17.3)	147 (45)
			54 (13.9)	67 (10.4)	4/8	440 (48.5)	357 (48.5)	54 (17.3)	147 (45)
Kim et al	2013	Simvastatin qam (n = 61)	58.7 (8.3)	66.1 (11.0)	26/35	236.0 (28.9)	155.0 (22.3)	48.6 (9.7)	157.1 (65.2)
		Simvastatin qpm (n = 62)	58.5 (9.5)	66.6 (9.5)	29/33	238.4 (31.1)	160.6 (25.0)	50.3 (11.3)	147.3 (63.1)
Kruse et al	1993	Lovastatin qam (n = 12)	48.4 (11.4)	74.7 (5.2)	9/3	424.6 (129.9)	338.7 (111.2)	36.3 (10.7)	178.9 (92)
		Lovastatin qpm (n = 12)	45 (9.7)	74.3 (11.8)	8/4	450.9 (87.1)	379.7 (80.4)	40.2 (8)	130.2 (52)
Martin et al	2002	rosuvastatin qam (n = 21)	NS	NS	NS	191	120.7	49.5	105.4
		rosuvastatin qpm (n = 21)	NS	NS	NS	189.5	119.5	47.6	112.5
Ozaydin et al	2006	Atorvastatin qam (n = 73)	59 (6)	NS	59/14	211 (26)	140 (14)	35 (3)	175 (27)
		Atorvastatin qpm (n = 79)	58 (5)	NS	59/20	206 (18)	138 (13)	37 (4)	170 (21)
Plakogiannis et al	2005	Atorvastatin qam (n = 32)	58.5 (7.8)	NS	32/0	321.4 (28.0)	188.3 (13.0)	46.4 (8.9)	434.0 (87.2)
		Atorvastatin qpm (n = 32)	57.8 (7.8)	NS	32/0	329.2 (23.3)	195.0 (10.4)	40.8 (5.5)	468.5 (93.0)
Saito et al	1991	Simvastatin 2.5 mg qam (n = 30)	NS	NS	8/22	273.0 (39.6)	182.7 (46.8)	54.38 (24.26)	179.6 (105.3)
		Simvastatin 2.5 mg qpm (n = 28)	NS	NS	6/22	274.9 (37.2)	195.9 (36.7)	46.95 (15.00)	160.3 (72.3)

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		Simvastatin 5 mg qam (n = 32)	NS	NS	8/24	277.4 (49.8)	194.2 (48.1)	52.71 (17.94)	152.5 (77.4)
		Simvastatin 5 mg qpm (n = 29)	NS	NS	4/25	288.8 (46.9)	204.3 (52.2)	53.15 (12.97)	156.3 (68.9)
Scharnagl et al	2006	Fluvastatin qam (n = 109)	60.1	NS	38/71	282.3 (32.6)	189.9 (27.6)	58 (16.5)	176 (80.7)
		Fluvastatin qpm (n = 120)	60.6	NS	49/71	282.5 (35.4)	188.5 (32.9)	59.4 (16.3)	176.4 (74.4)
Wallace et al	2003	Simvastatin qam *versus* simvastatin qpm (n = 60)	66	NS	27/33	170.1 (30.9)	92.8 (23)	50 (11.6)	141.7 (70.9)
Yi et al	2014	CR simvastatin qam (n = 59)	56.9 (10.5)	64.3 (11.1)	28/31	228.7 (36.8)	143.9 (28.1)	46.9 (14.5)	190.3 (73.0)
		IR simvastatin qpm (n = 59)	57.0 (12.1)	63.7 (10.4)	29/30	220.0 (36.4)	137.0 (28.4)	48.8 (13.5)	167.6 (70.7)

Continuous variables are described as Mean or Mean (SD) and categorical variables are described as N. Abbreviations: NS: not stated; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; m: male; f: female; qam: every morning; qpm: every evening; CR: controlled release; IR: immediate release

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Quality of the included studies

According to Cochrane Collaboration tool and Newcastle-Ottawa Scale, the quality of the included studies ranged from low to high quality. The summary of quality assessment domains of included studies is shown in **Tables 3 & 4.**

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Table 3: Assessment of risk of bias in the included randomized controlled trials using Cochrane criteria.

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Hurminghake (1990)	**U**	**U**	**L**	**U**	**L**	**U**	**L**
Kim (2013)	**L**	**L**	**L**	**U**	**L**	**U**	**L**
Kruse (1993)	**U**	**U**	**L**	**H**	**L**	**U**	**L**
Martin (2002)	**U**	**U**	**H**	**H**	**L**	**U**	**L**
Ozaydin (2006)	**U**	**U**	**H**	**L**	**L**	**U**	**H***
Saito (1991)	**U**	**U**	**L**	**U**	**L**	**U**	**L**
Scharnagl (2006)	**U**	**U**	**L**	**U**	**L**	**U**	**L**
Wallace (2003)	**U**	**U**	**H**	**H**	**L**	**U**	**L**
Yi (2014)	**U**	**U**	**L**	**U**	**L**	**U**	**H****

L: low risk of bias; H: high risk of bias; U: unclear risk of bias.

*Differences in baseline characteristics
** Different formulation used: controlled release in the morning and immediate release in the evening groups.

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Table 4: Assessment of the Quality of non-randomized studies using the Newcastle-Ottawa Scale

Domain and Topic (max. 10 stars)										
		Selection (max. 5 stars)				**Comparability (max. 2 stars)**	**Outcome (max. 3 stars)**			
Author	**Year**	**Representativeness of the sample**	**Selection of the non exposed cohort #**	**Ascertainment of the exposure**	**Demonstration that outcome of interest was not present at start of study ##**	**Subjects in different outcome groups are comparable**	**Assessment of Outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	**Total**
Illingworth	1986	*	*	*	*	*	*	*	*	8
Plakogiannis	2005	*	*	*	*	*	*	*	*	8

Comparability of selection of baseline day and night groups

Reporting of baseline plasma lipid values

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Efficacy analysis

The overall pooled analysis of 11 studies (12 treatment arms) comparing effects of morning versus evening administration of statins on plasma TC (MD: 1.68 mg/dl, 95%CI: -0.33, 3.69, p=0.10, **Figure 2**), HDL-C (MD: 0.05 mg/dl, 95%CI: -0.77, 0.87, p=0.90, **Figure 3**) and TG (MD: 1.66 mg/dl, 95%CI: -2.68, 5.99, p=0.45, **Figure 4**) was not statistically significant. However, it favored evening-dose over morning-dose with respect to the effect of statins on plasma LDL-C (MD: 3.24 mg/dl, 95%CI: 1.23, 5.25, p=0.002, **Figure 5**). No significant heterogeneity was noted for any of the outcomes (*Chi* square p>0.1)

The pooled analysis of the short half-life statins subgroup did not reveal any significant difference between the morning-dose and evening-dose groups in terms of HDL-C (MD: 0.28 mg/dl, 95%CI: -1.49, 2.06, p=0.75, **Figure 3**) and TG (MD: 0.97 mg/dl, 95%CI: -13.54, 15.48, p=0.90, **Figure 4**). However, it favored evening-dose over morning-dose in terms of TC (MD: 12.10 mg/dl, 95%CI: 5.25, 18.95, p=0.0005, **Figure 2**) and LDL-C (MD: 9.68 mg/dl, 95%CI: 3.32, 16.03, p=0.003, **Figure 5**). For all outcomes there was no significant heterogeneity (*Chi* square p>0.1).

The pooled analysis of the long half-life statins subgroup did not show any significant difference for TC (MD: 0.70 mg/dl, 95%CI: -1.40, 2.80, p=0.51, **Figure 2**), HDL-C (MD: -0.01 mg/dl, 95%CI: -0.94, 0.92, p=0.98, **Figure 3**) and TG (MD: 1.72 mg/dl, 95%CI: -2.82, 6.27, p=0.46, **Figure 4).** However, it favored evening-dose over morning-dose in term of LDL-C (MD: 2.53 mg/dl, 95%CI: 0.41, 4.64, p=0.02, **Figure 5**). No significant heterogeneity was noted for any of the outcomes (*Chi* square p>0.1).

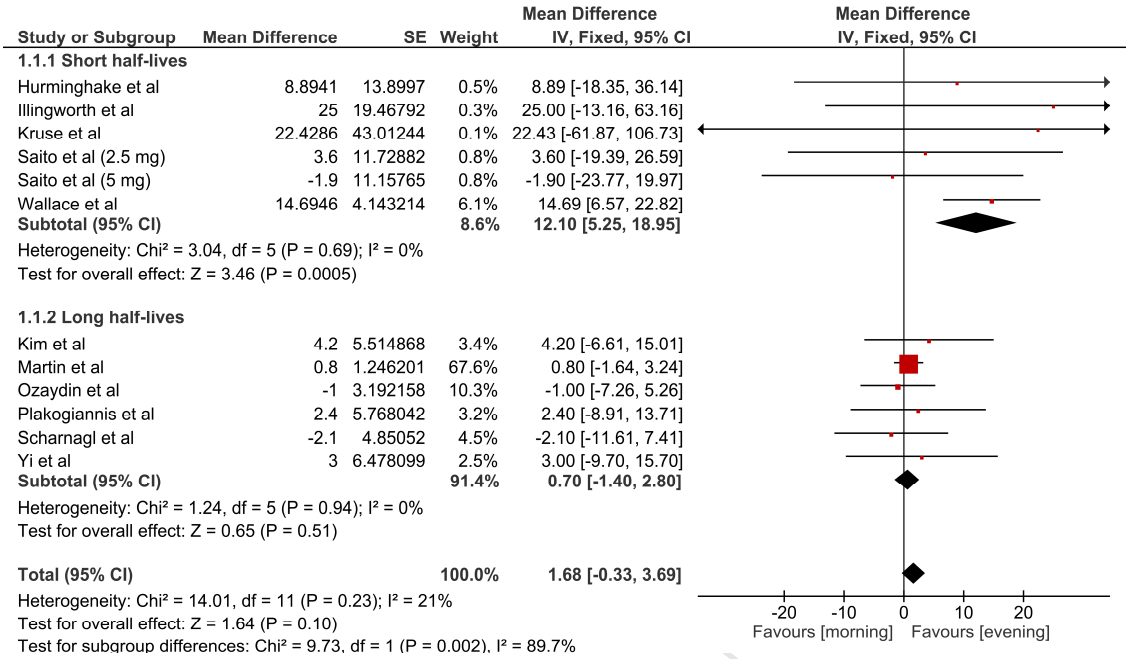

Figure 2: Forest plot displaying the results of the meta-analysis of morning vs evening statins on total cholesterol with subgrouping according to half-lives of statins. CI, confidence interval; df, degrees of freedom; SE, standard error.

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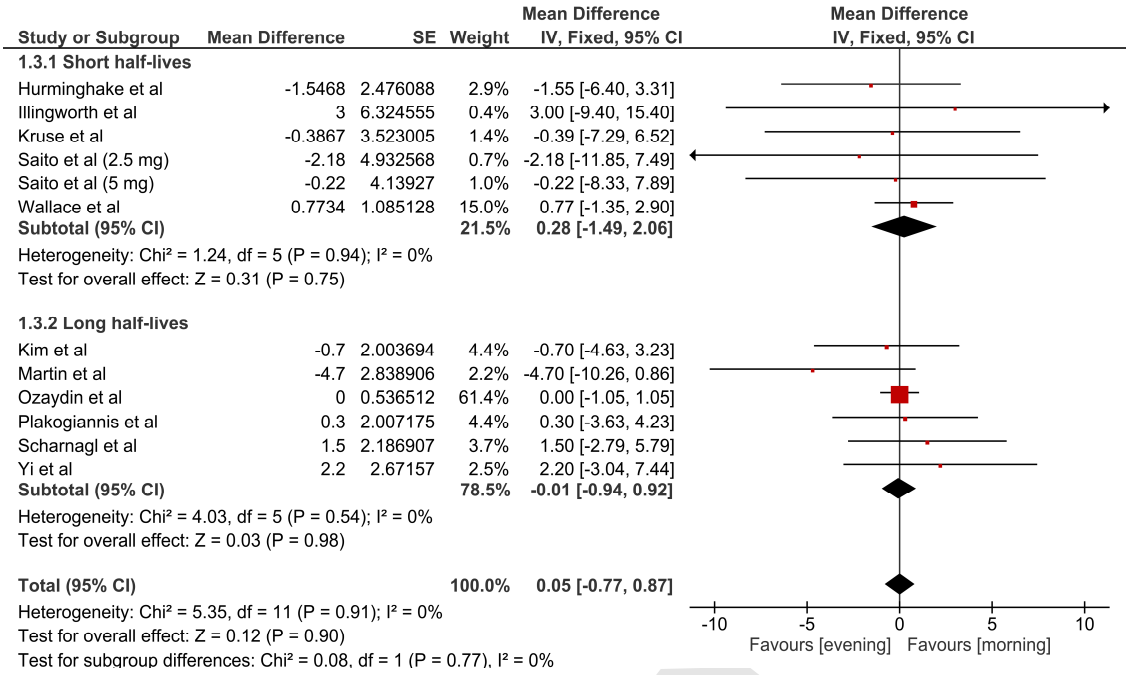

Figure 3: Forest plot displaying the results of the meta-analysis of morning vs evening statins on high density lipoprotein cholesterol with subgrouping according to half-lives of statins. CI, confidence interval; df, degrees of freedom; SE, standard error.

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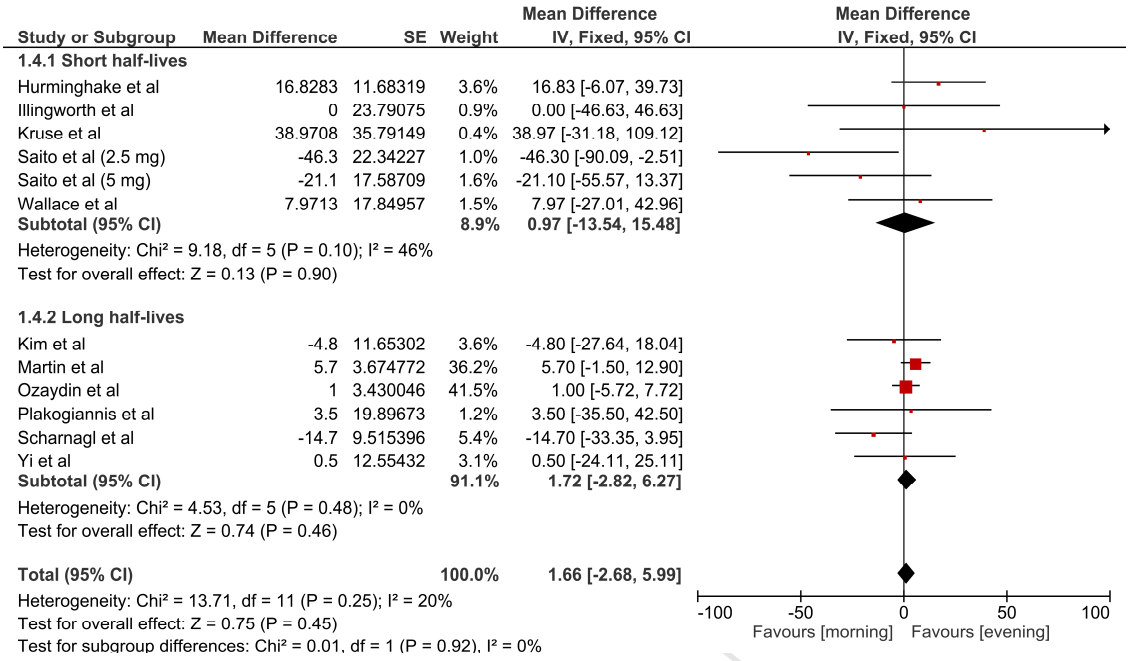

Figure 4: Forest plot displaying the results of the meta-analysis of morning vs evening statins on triglycerides with subgrouping according to half-lives of statins. CI, confidence interval; df, degrees of freedom; SE, standard error.

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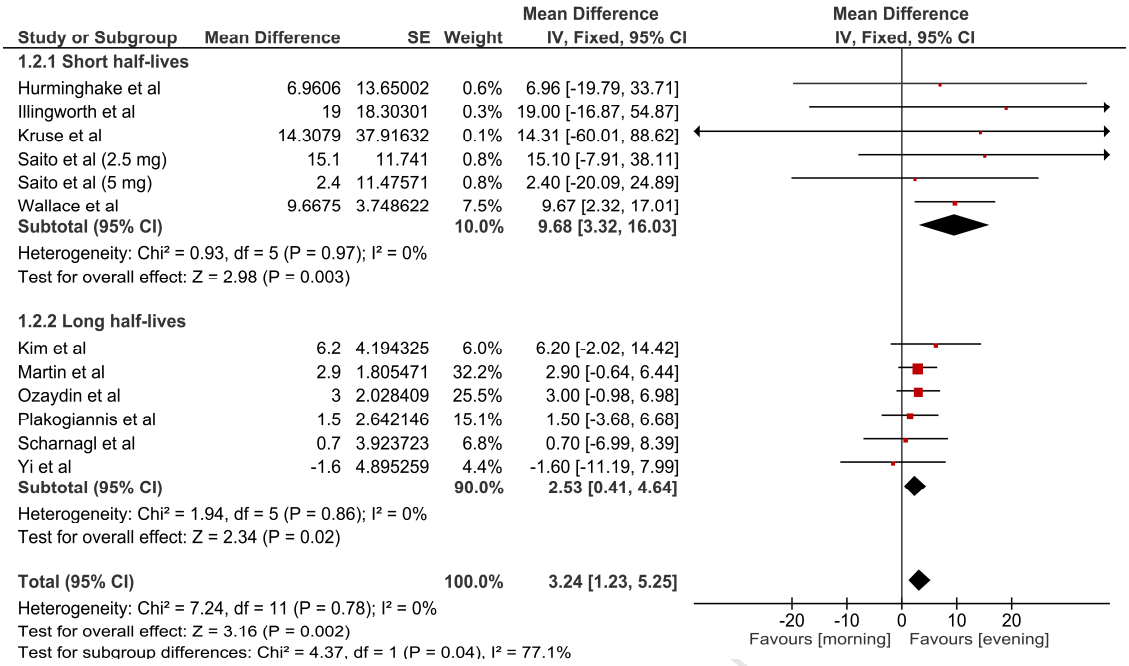

Figure 5: Forest plot displaying the results of the meta-analysis of morning vs evening statins on low density lipoprotein cholesterol with subgrouping according to half-lives of statins. CI, confidence interval; df, degrees of freedom; SE, standard error.

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The pooled analysis of RCTs subgroup did not reveal any significant difference between the two groups concerning their effects on plasma TC (MD: 1.59 mg/dl, 95%CI: -0.45, 3.63, p=0.13, **Supplementary File 2: Figure S1**), HDL-C (MD: 0.03 mg/dl, 95%CI: -0.82, 0.87, p=0.95, **Supplementary File 2: Figure S2**) and TG (MD: 1.65 mg/dl, 95%CI: -2.73, 6.03, p=0.46, **Supplementary File 2: Figure S3**). However, it favored evening-dose over morning-dose with respect to the effect of statins on plasma LDL-C (MD: 3.49 mg/dl, 95%CI: 1.31, 5.68, p=0.002, **Supplementary File 2: Figure S4).** No significant heterogeneity was noted for any outcomes (*Chi* square p>0.1). The combined analysis of non-randomized studies did not reveal any significant difference between the morning-dose and evening-dose groups on any of the investigated outcomes: plasma TC (MD: 4.22 mg/dl, 95%CI: -6.62, 15.06, p=0.45, **Supplementary File 2: Figure S1**), HDL-C (MD: 0.55 mg/dl, 95%CI: -3.2, 4.3, p=0.77, **Supplementary File 2: Figure S2**), TG (MD: 2.06 mg/dl, 95%CI: -27.85, 31.97, p=0.89, **Supplementary File 2: Figure S3**) and LDL-C (MD: 1.86 mg/dl, 95%CI: -3.27, 6.98, p=0.48, **Supplementary File 2: Figure S4**). No significant heterogeneity was noted for any outcomes (*Chi* square p>0.1).

Compliance with both regimens

Only three studies [46,47,52] of the 11 included in this meta-analysis reported the rates of compliance with both statin regimens. Two of them [46,52] revealed no significant difference between the two regimens, and one study [47] indicated that drug compliance was better when the drug was taken in the morning than in the evening. Compared with morning-dosing, evening-dosing of lovastatin was

associated with a 7% reduction in the number of prescribed doses, which were taken by the patient. [47].

Sensitivity analysis

For all efficacy outcomes, the overall pooled effect size was robust and the statistical significance or non-significance of the differences between groups was not altered in the leave-one-out sensitivity analysis. This means that none of the included studies individually changed the overall result. However, the pooled analyses of effects of morning-dose versus evening-dose of short half-life statins on LDL-C and TC were sensitive to the study by Wallace *et al.* [52], because of the substantial weight of this study, i.e. removing this study from the analysis led to no significant difference being detectable between the groups. In long half-life statins, the pooled effect on LDL-C was sensitive to the studies by Martin *et al.* [48] and Ozaydin *et al.* [49] because of the substantial weights of these studies. Summary of the leave-one-out sensitivity analysis is shown in **(Supplementary File 3: Table S2).**

Publication bias

Visual inspection of the funnel plots suggested a potential publication bias for the effects of morning-dose versus evening-dose of statin on plasma TC and LDL-C (Supplementary File 2: Figures S5 & S6). However, the funnel plots were symmetric in the case of the effects of statins on TG and HDL-C (Supplementary File 2:

Figures S7 & S8). In contrast, the Egger`s test statistically excluded the presence of publication bias for all outcomes (two-tailed p>0.05).

DISCUSSION

To our knowledge, this meta-analysis is the first to compare the effects of morning and evening doses of statin therapy on lipid profiles. Data from 11 studies showed that the LDL-C–lowering effect of the drugs was significantly greater when statins were taken in the evening than when they were taken in the morning. This effect was independent of the half-live of the drugs used. In the case of short half-life statins, evening-dosing resulted in a larger TC-lowering effect. The evening-dosing and morning-dosing regimens were equivalent with respect to the effects of statins on HDL-C and TG.

The US Food and Drug Administration (FDA) recommends evening administration of lovastatin,[56] simvastatin,[57]and fluvastatin[58]. This is based on their short half-lives (2-3, 2-3 and 0.5-2.3 hours respectively) and the fact that peak cholesterol biosynthesis occurs during the night [12,25,40,59]. It is advised that atorvastatin,[60] rosuvastatin,[61]and extended-release fluvastatin[42,58] can be given at any time of day due to their long half-lives (15-30, 30 and 7.3-10.5 hours respectively). The results of this meta-analysis are in line with these recommendations. However, the FDA advises that pravastatin can be taken at any time of the day despite its short half-life (1.3-2.8 hours) [12,40,62]. This might be because the systemic bioavailability of pravastatin is decreased by 60% when administrated in the evening compared with that following the morning dose [63]. However, the

evening dose of pravastatin was found to be marginally more effective than the morning dose. Our finding that LDL-C lowering was greater when statins with long half-lives were administered in the evening, than when they were taken in the morning is somewhat unexpected. However, it should be noted that the difference between the groups is small and might be not clinically relevant. However, under the assumption that a 1 mmol/l (38.7 mg/dl) reduction in LDL-C is associated with a 20-25% reduction in CVD mortality,[11] this difference might have been associated with a 0.3-3% reduction in CVD mortality at the population-level.

Adherence to statin treatment remains problematic, and affects the clinical effectiveness of these drugs [64,65]. There are many factors that affect statin adherence such as adverse effects (statin associated muscle symptoms / statin intolerance), complex drug regimens, drug-drug interactions, patient preference (rather than provider preference), cost, age and gender [66–70]. Good adherence to statin has been associated with a 15-20% lower risk of CVD events [71]. Some other studies have reported a much greater reduction that may reach up to 40% [72–77]. **Regimens requiring evening doses of cardiovascular drugs have been associated with a 5-25% drop in compliance when compared with administration in the morning [78–80]. One of the studies included in this meta-analysis reported a 7% reduction in the number of the prescribed doses of lovastatin, which were taken when the drug was directed to be taken in the evening, compared with morning doses [47]**. One important factor that may help to improve adherence is to allow patients to decide at which time of the day they prefer to take their statin (e.g. with other medication in the morning) [31,80]. This selected time should be the one most likely to result in an uninterrupted intake of the medicine [31]. However, some prescribers may insist on

patients taking statins in the evening because they are under the impression that these drugs are substantially more effective when taken at night. Based on the results of this meta-analysis, evening dosing appears to be important for short-acting statins, but in the case of statins with long half-lives, prescribing instructions should allow more patient-based choice. In addition, it should be emphasized that taking the statin at the same time every day (e.g. developing a morning routine) might result in better adherence [31,80].

Patients treated with statins often receive multiple concomitant drugs [30]. Polypharmacy and complex drug regimens have been associated with decreased adherence [29]. Taking multiple medications at the same time or in the form of a 'polypill' has been proposed a possible solution to the complexity of drug regimens, and has been associated with increased adherence[81,82]. However, many of the drugs, which might be administered concomitantly with statins are usually administrated in the morning (e.g. antihypertensive drugs and aspirin) [83]. The results of our analysis are important because they clearly confirm that administration of long-acting statins in the morning is as efficacious as administration in the evening. Therefore, the efficacy of long-acting statins will not be altered when administrated, in a polypill, with these concomitant medications in the morning.

This meta-analysis has several limitations: most importantly, the sample size of each individual study was relatively small (12 to 229 participants), and the follow-up was relatively short (4-12 weeks). Secondly, some of the included studies did not have a well-defined exclusion criteria [48,52,54]. Thirdly, the difference in effects of morning-dose versus evening-dose of statins was a secondary finding in some of included studies [45,47,49,54]. Fourthly, the patient population in the included studies was heterogeneous with respect to

various factors including health, hyperlipidemia and chronic kidney disease (CKD). **Fifthly, most of the included studies did not report the results of patients' compliance with statin regimens**.

Bearing in mind the limitations of the current evidence, further well-designed, large-scale RCTs are required to confirm our results and to investigate long-term compliance with morning and evening regimens of statins. In 2011, Wright *et al.* investigated the effect of the timing of simvastatin on its efficacy in a pharmacokinetic–pharmacodynamics model [80]. They found no clinically important difference between morning and evening doses. They explained this result by the relativity slow turnover of the cholesterol in the plasma (3-4 days) and, in turn, the delayed peak effect of simvastatin on LDL-C reduction [84,85]. Therefore, the chronobiologic effects of short-acting statins should be further established in large-scale RCTs.

In conclusion, the current meta-analysis shows that LDL-C and TC lowering were significantly greater in the evening-dose than in the morning-dose in case of short-acting statins. However, apart from a small but statistically significant effect on LDL-C, the efficacy of long-acting statins was equivalent for morning and evening administration. Therefore, it would be appropriate to consider choosing the time of administration of long-acting statins based upon what will best aid compliance. On the other hand, short-acting statins should be taken in evening. Future well-designed, large-scale, prospective RCTs are recommended, especially on short-acting statins, to confirm our findings.

Conflict of Interest Disclosures

None.

Contributors

Kamal Awad: protocol writing, literature search, screening, data extraction, data analysis and manuscript writing. Maria-Corina Serban: protocol writing, literature search, data analysis, manuscript writing and revision. Peter Penson: screening, data extraction, manuscript writing and revision. Dimitri P. Mikhailidis, Peter P. Toth, Steven R. Jones, Manfredi Rizzo, George Howard and Gregory Y.H. Lip: manuscript writing and revision Maciej Banach: study design, supervision, coordination and preparation of the revision. All authors have approved the final article.

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- LDL-C lowering was greater in the evening-dose of short and long half-life statins.
- TC lowering was greater in the evening-dose of short half-life statins only.
- Morning-dose was equivalent to evening-dose in terms of HDL-C and TG.

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