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REVIEW ARTICLE

Efficacy and Safety of Alternate-Day Versus Daily Dosing of Statins: a Systematic Review and Meta-Analysis

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Abstract

Purpose We conducted a meta-analysis of randomized controlled trials (RCTs) and quasi-RCTs to synthesize evidence about the efficacy and safety of alternate-day vs daily dosing of statins.

Methods We searched selected databases through January 2, 2017 to identify relevant RCTs and quasi-RCTs. The primary outcome was change in low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG), while secondary outcomes included adverse events and adherence.

Results Twelve RCTs and 1 quasi-RCT (n = 1023 patients) were included in the analysis. Pooled analysis revealed no statistically significant difference between alternate-day and daily regimens of atorvastatin and rosuvastatin in terms of change in LDL-C (mean difference [MD] 6.79 mg/dL, 95% confidence interval [CI] −1.59, 15.17, $p = 0.11$, and 10.51 mg/dL, 95%CI −0.23, 21.26, $p = 0.06$, respectively) and TG ($p > 0.05$). Daily regimens of atorvastatin and rosuvastatin were superior to alternate-day regimes in term of change in TC (MD 12.45 mg/L, 95%CI 8.14, 16.76, $p < 0.00001$, and 15.80 mg/dL, 95%CI 5.66, 25.95, $p = 0.002$, respectively). For all outcomes, there was no statistically significant difference between alternate-day and daily regimens for both fluvastatin and pravastatin ($p > 0.05$). Both regimens of statins were generally well tolerated with good adherence.

Conclusions Alternate-day dosing of individual statins (especially atorvastatin and rosuvastatin) is as efficacious as daily dosing on LDL-C and TG.

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Introduction

Statins are some of the most widely prescribed medications worldwide [1–3]. Statins are effective in lowering low-density lipoprotein cholesterol (LDL-C) by up to 52% and triglycerides (TG) by up to 44% [4, 5]. Additionally, they increase high-density lipoprotein cholesterol (HDL-C) by up to 10% [6–8]. For every 1.0 mmol/L (38.7 mg/dL) reduction in LDL-C, there is a corresponding 20–25% drop in cardiovascular (CV) disease (CVD) mortality [9]. Therefore, their key role in primary and secondary prevention of CVD is now well established [10–15].

In general, statins have a favorable safety profile [16–19]. However, adverse events (AEs) are considered the most common cause for statin therapy discontinuation [20–23]. The most common AEs associated with statin therapy are muscle-related [24–27]. Statin-associated adverse muscle symptoms (SAMSs) may affect 10–15% of patients receiving statins [25, 28, 29]. Fortunately, statin-associated fatal rhabdomyolysis is a rare event that develops in only about 2–3 cases per 100,000 patients treated per year [30, 31]. Alternate-day dosing of statins has been proposed for patients who experience side effects with daily dosing [27]. Therefore, several studies investigated the effectiveness of this approach compared with daily dosing of statins [32–36]. However, most of these studies are limited by small sample size. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) and quasi-RCTs to provide more definitive evidence about the efficacy and safety of alternate-day dosing of statins compared with daily dosing.

Methods

We followed preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement guidelines for the preparation of this meta-analysis (Supplementary File 1: Table S1) [37]. All steps were conducted in accordance with the "*Cochrane handbook for systematic reviews of interventions*." This study was prospectively registered in PROSPERO, University of York (CRD42017054519).

Literature Search Strategy

We performed a computerized literature search of PubMed, SCOPUS, Web of Science, and Embase from inception until January 2, 2017 using the following keywords: (atorvastatin OR fluvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin OR cerivastatin OR mevinolin OR statin OR statins) and (alternate day OR alternate-day OR every other day OR every-other-day OR non-every day OR non-daily OR twice a week OR twice-weekly OR twice weekly OR once a week OR once-weekly OR once weekly). To ensure that no relevant studies were missed, we conducted manual searches for potential trials that were included in the reference lists of review articles on that topic 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 restricted to articles published in English and conducted on human subjects.

After removal of duplicate articles by Endnote X7 (Thompson Reuter, CA, USA), two independent authors screened the retrieved articles in two steps: the first step was to screen the titles and abstracts for eligibility, and the second step was to screen the full text of the eligible abstracts according to the inclusion and exclusion criteria. Disagreement was resolved by the opinion of a third author (MB).

Study Selection

Original studies were included if they met the following criteria: (i) a RCT or a quasi-RCT (i.e., the method of allocation is known but is not considered strictly random); (ii) comparison of the efficacy of alternate-day dosing of statin therapy vs daily dosing on one or more of the following lipid profile parameters: total cholesterol (TC), LDL-C, or TG for a duration ≥6 weeks; and (iii) reporting complete data on serum lipid concentrations after treatment.

Exclusion criteria included (i) non-randomized trials, observational studies, experimental studies, reviews, book chapters, and theses; (ii) studies whose full texts were not available; (iii) studies that contained fabricated data or were retracted by the journal; and (iv) studies whose data were not reliable for extraction (e.g., reported graphically only). Exclusion of an article for the last reason was applied only after contacting the authors for details and not receiving a response.

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 and durations; (6) study population characteristics; (7) concentrations of TC, LDL-C, and TG; and (8) incidence of adverse events.

If there were multiple groups with different treatment doses of any or both regimens (alternate-day and daily), we extracted the data of the group with the same dose as the comparator

group. Moreover, if there were multiple follow-up time points, we extracted the data from the last time point. Data extraction was performed independently by two reviewers. Disagreements were resolved by a third reviewer (MB).

Outcomes of Interest

The primary outcome was the mean change in one of the following lipid parameters: TC, LDL-C, and TG. Secondary outcomes included the incidence of AEs and the adherence of patients with statin therapy.

Quantitative Data Synthesis

Lipid concentrations were collated in mg/dL in an Excel spreadsheet. To convert from mmol/L to mg/dL, cholesterol (TC and LDL-C) levels were multiplied by 38.67, and TG levels were multiplied by 88.57. If the changes in lipid levels during the trial were not directly reported, they were calculated as follows: (measure at end of follow-up) − (measure at baseline). Standard deviations (SDs) of the change scores were calculated using the following formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\ treatment})^2 - (2R \times SD_{pre\ treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5 [38–40]. If the outcome measures were reported as median and range, mean and SD values were estimated using the method described by Hozo et al. [41] 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. [42].

The change scores in lipid concentrations between randomization groups (i.e., alternate day vs daily dosing) were pooled as mean differences (MDs) with a 95% CI in a meta-analysis model. RevMan version 5.3 (The Cochrane Collaboration, Oxford, UK) was used to conduct this analysis.

Subgroup Analysis

To investigate the effect of each type of statin on the lipid concentrations, data were presented into four subgroups as follows: (i) atorvastatin, (ii) rosuvastatin, (iii) fluvastatin, and (iv) pravastatin.

Assessment of Heterogeneity

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

Sensitivity Analysis

In order to evaluate the effect of each study on the combined effect estimate, we performed a sensitivity analysis using the "leave-one-out approach," i.e., removing one study each time and repeating the analysis. Also, the same approach was conducted to resolve the presence of any significant heterogeneity. Moreover, we conducted an additional sensitivity analysis that excluded studies that compared the same overall doses in both alternate-day and daily groups (e.g., 10 mg daily vs 20 mg every other day).

Meta-Regression

We conducted a random-effect meta-regression using the unrestricted maximum likelihood method to evaluate the association between the changes in the lipid parameters and the duration of statin therapy.

Quality Assessment

We used "*The Cochrane Collaboration tool*" for assessing the risk of bias in the included trials. 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. This assessment was performed independently by two reviewers. Disagreements were resolved by a third reviewer (MB).

Publication Bias

Potential publication bias was evaluated by visual inception of Begg's funnel plot asymmetry and was statistically confirmed by Egger's weighted regression test [43]. Additionally, the "trim-and-fill" approach was conducted to correct the funnel plot asymmetry resulting from the publication bias by imputing the potentially missing number of studies [44]. We used Comprehensive Meta-Analysis (CMA) version 2 (Biostat, NJ, USA) to conduct the publication bias analyses.

Results

Flow and Characteristics of Included Studies

Our search resulted in 2398 citations. Following removal of duplicates and title/abstract screening, only 19 articles were eligible for full-text screening. Of these 19 articles, 6 were excluded for the following reasons: non-randomized trials ($n = 3$), observational study ($n = 1$), insufficient data for analysis ($n = 1$), and daily dosing was compared with three-times-weekly dosing not with alternate-day dosing ($n = 1$). Finally, 12 RCTs [33–35, 45–53] and 1 quasi-RCT [32] met our inclusion criteria and were included in our analysis (see *PRISMA flow diagram*; Fig. 1).

In total, 1023 patients were included in our analysis. Of these patients, 505 received alternate-day dosing of statin therapy and 518 received daily dosing. The sample size of the included trials ranged from 37 to 284 patients. Only 3 trials used the same overall doses of statins in both alternate-day and daily groups (e.g., 10 mg daily vs 20 mg every other day), while the remaining trials used different overall doses of statins but with the same doses given per day (e.g., 10 mg daily vs 10 mg every other day). Included trials were published between 1998 and 2014, and they were conducted in the USA ($n = 3$), India ($n = 3$), Iran ($n = 2$), Egypt, China, Turkey, Canada, and Thailand. The duration of the treatment ranged from 6 to 24 weeks. The summary of the included studies and their main results are shown in Table 1; the baseline characteristics of their populations are shown in Table 2.

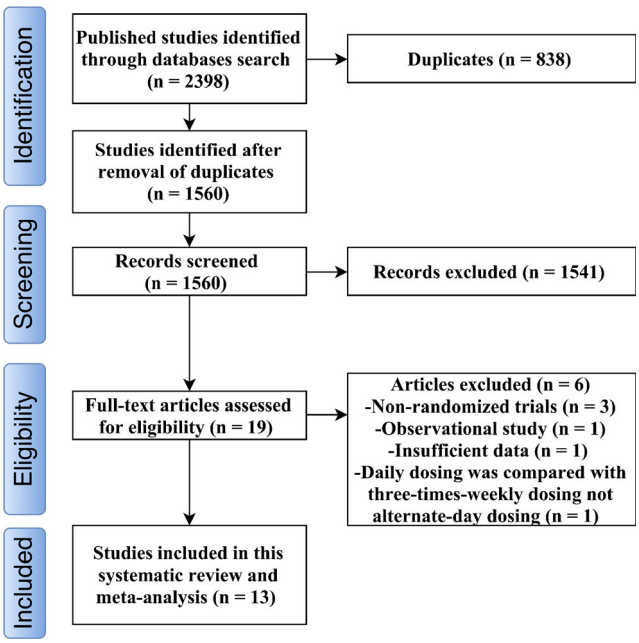

Fig. 1 PRISMA flow diagram of study screening and selection

Quality of the Included Studies

According to *The Cochrane Collaboration tool*, the included trials ranged from low to moderate quality. The summary of quality assessment domains of the included studies is shown in Fig. 2.

Efficacy Analysis (Primary Outcome)

Overall Pooled Analysis

The overall pooled analysis of 13 RCTs comparing the impact of alternate-day dosing vs daily dosing of statin therapy on TG (MD 6.56 mg/dL, 95%CI −1.76, 14.88, $p = 0.12$, Fig. 3) was not statistically significant. However, TC and LDL-C lowering was significantly greater in the daily dosing group (MD 12.08 mg/dL, 95%CI 8.58, 15.58, $p < 0.00001$ (Fig. 4) and 7.95 mg/dL, 95%CI 2.62, 13.29, $p = 0.003$ (Fig. 5), respectively). A statistically significant heterogeneity was present for LDL-C (Chi^2 $p < 0.0001$ and TG (Chi^2 $p = 0.01$). This was resolved by sensitivity analysis that excluded the study by Rifaie et al. [51] (Chi^2 $p = 0.31$) for TG. However, sensitivity analysis failed to resolve the heterogeneity for LDL-C. For TC, no heterogeneity was present (Chi^2 $p = 0.24$).

Subgroup Analysis

Subgroup pooled analysis of 8 RCTs compared the impact of alternate-day dosing vs daily dosing of atorvastatin on LDL-C (MD 6.79 mg/dL, 95%CI −1.59, 15.17, $p = 0.11$, Fig. 5) and TG (MD: 6.43 mg/dL, 95%CI −5.75, 18.61, $p = 0.30$, Fig. 3) was not statistically significant. The lowering effect of atorvastatin on TC was statistically greater in the daily dosing group (MD 12.45 mg/dL, 95%CI 8.14, 16.76, $p < 0.00001$, Fig. 4). A statistically significant heterogeneity was present for LDL-C (Chi^2 $p < 0.00001$) and TG (Chi^2 $p = 0.002$). This was resolved by sensitivity analysis that excluded the study by Rifaie et al. [51] (Chi^2 $p = 0.11$) for TG. However, sensitivity analysis failed to resolve the heterogeneity for LDL-C. In case of TC, no heterogeneity was present (Chi^2 $p = 0.27$).

Subgroup pooled analysis of 3 trials compared the impact of alternate-day dosing vs daily dosing of rosuvastatin on LDL-C (MD 10.51 mg/dL, 95%CI −0.23, 21.26, $p = 0.06$, Fig. 5) and TG (MD 9.20 mg/dL, 95%CI −2.78, 21.19, $p = 0.13$, Fig. 3) was not statistically significant. However, TC lowering was statistically greater in the daily dosing group (MD 15.80 mg/dL, 95%CI 5.66, 25.95, $p = 0.002$, Fig. 4). No statistically significant heterogeneity was observed for all outcomes (Chi^2 $p > 0.1$) except for LDL-C, and it was best resolved by sensitivity analysis that excluded the study by Wongwiwatthananukit et al. [53] (Chi^2 $p = 0.24$).

Table 1 Summary of the included studies

Study	Year	Location	Design	Duration	Statin used (doses)	Population
Aghasadeghi et al.	2008	Iran	Randomized, blinded, controlled, parallel trial	6 weeks	Atorvastatin (20 mg QOD vs 20 mg QD)	Patients with hypercholesterolemia
Dulay et al.	2009	Canada	Quasi-randomized, open-label, controlled, crossover trial	6 weeks then 4 weeks washout period and another 6 weeks	Rosuvastatin (20 mg QOD vs 10 mg QD)	Patients with hypercholesterolemia
Ghia et al.	2014	India	Randomized, open-label, controlled, parallel trial	3 months	Atorvastatin (10 mg QOD vs 10 mg QD)	Naïve patients of dyslipidemia
Graham et al.	2002	USA	Randomized, open-label, controlled, parallel trial	4 months	Pravastatin (same dose QOD vs half dose as before QD)	Patients who were receiving pravastatin daily and had maintained their NCEP-defined LDL-C goal for at least 3 months
Hadjibabaie et al.	2007	Iran	Randomized, open-label, controlled, parallel trial	8 weeks	Atorvastatin (10 mg QOD vs 10 mg QD)	Patients with type 2 DM with hypercholesterolemia
Jafari et al.	2003	USA	Randomized, open-label, controlled, parallel trial	6 weeks	Atorvastatin (10 mg QOD vs 10 mg QD)	Patients with LDL-C of 100 to 200 mg/dL
Keles et al.	2008	Turkey	Randomized, controlled, parallel trial	3 months	Atorvastatin (20 mg QOD vs 20 mg QD)	Patients with serum TC levels >200 mg/dL and LDL-C levels >130 mg/dL
Li et al.	2012	China	Randomized, controlled, parallel trial	6 weeks	Rosuvastatin (10 mg QOD vs 10 mg QD)	Patients with LDL-C ≥160 mg/dL and/or TG ≥200 mg/dL
Pattanaik et al.	2012	India	Randomized, open-label, controlled, parallel trial	12 weeks	Atorvastatin (same dose as before QOD vs same dose as before QD)	Patients who were receiving atorvastatin for at least 6 months and had met their NCEP-defined LDL-C goal
Pramanik et al.	2012	India	Randomized, open-label, controlled, crossover trial	12 weeks then 4 weeks washout period and another 12 weeks	Atorvastatin (20 mg QOD vs 20 mg QD)	Patients with hypercholesterolemia
Rifaie et al.	2012	Egypt	Randomized, single-blinded, controlled, parallel trial	6 weeks	Atorvastatin (10 mg QOD vs 10 mg QD)	Patients with CAD
Rindone et al.	1998	USA	Randomized, open-label, controlled, crossover trial	6 weeks for each regime	Fluvastatin (40 mg QOD vs 20 mg QD)	Patients with a LDL-C level >160 mg/dL despite at least 3 months of a low-fat diet
Wongwiwatthananukit et al.	2006	Thailand	Randomized, open-label, controlled, parallel trial	8 weeks	Rosuvastatin (10 mg QOD vs 10 mg QD)	Patients with hypercholesterolemia

LDL-C *low-density lipoprotein cholesterol,* NCEP *National Cholesterol Education Program,* ATP *Adult Treatment Panel,* DM *diabetes mellitus,* TC *total cholesterol,* TG *triglycerides,* CAD *coronary artery disease,* QD *every day,* QOD *every other day,* vs *versus*

Table 2 Baseline characteristics of the included studies

Study	Year	Group (no. of patients)	Age (years)	Weight (kg)	Gender		TC (mg/dL)	LDL-C (mg/dL)	TG (mg/dL)
					M	F			
Aghasadeghi et al.	2008	Atorvastatin QOD [*n* = 20]	61 (11)	70 (8)	11	9	228 (31)	152 (31)	189 (46)
		Atorvastatin QD [*n* = 20]	55 (12)	72 (13)	10	10	226 (55)	152 (50)	176 (85)
Dulay et al.	2009	Rosuvastatin QOD [*n* = 39] Rosuvastatin QD [*n* = 39]	68.2 (12.3)	NS	24	15	232 (34.8)	147 (31)	151 (80)
Ghia et al.	2014	Atorvastatin QOD [*n* = 39]	48.13 (9.671)	62.9744 (8.7494)	18	21	246.15 (37.89)	176.05 (35.12)	135.25 (62.51)
		Atorvastatin QD [*n* = 46]	48 (8)	66.02 (8.277)	22	24	258.48 (30.86)	190.19 (27.48)	141.15 (29.65)
Graham et al.	2002	Pravastatin QOD [*n* = 53]	63 (10)	93 (21)	53	0	172 (25)	96 (18)	178 (82)
		Pravastatin QD [*n* = 51]	68 (8)	92 (19.5)	51	0	170 (24)	92 (20)	162 (76)
Hadjibabaie et al.	2007	Atorvastatin QOD [*n* = 20]	55.45 (1.74)†	NS	11	9	239.1 (5.95)†	149.45 (4.62)†	185.2 (14.4)†
		Atorvastatin QD [*n* = 20]	53.45 (2.11)†	NS	12	8	252.2 (8.79)†	153.7 (6.95)†	239.2 (19.4)†
Jafari et al.	2003	Atorvastatin QOD [*n* = 18]	56 (11)	NS	NS	NS	240 (44)	153 (30)	179 (108)
		Atorvastatin QD [*n* = 19]	56 (10)	NS	NS	NS	228 (44)	139 (29)	178 (106)
Keles et al.	2008	Atorvastatin QOD [*n* = 30]	53 (13)	NS	18	12	244 (26)	166 (25)	163 (64)
		Atorvastatin QD [*n* = 31]	57 (11)	NS	21	10	242 (29)	162 (23)	159 (55)
Li et al.	2012	Rosuvastatin QOD [*n* = 19]	48 (6)	NS	13	6	247 (15.3)	158 (9.70	137 (25.5)
		Rosuvastatin QD [*n* = 18]	50 (8)	NS	11	7	251 (16)	160 (10.1)	141 (28.4)
Pattanaik et al.	2012	Atorvastatin QOD [*n* = 141]	50.8 (7.0)	NS	90	51	145.49 (21.75)	77.68 (17.34)	126.83 (42.85)
		Atorvastatin QD [*n* = 143]	50.3 (6.9)	NS	85	58	157.45 (31.37)	80.06 (25.14)	141.25 (52.01)
Pramanik et al.	2012	Atorvastatin QOD [*n* = 38]	52.89 (1.549)[a]	61.47 (1.783)[a]	25	13	221.4 (3.696)†	150.0 (2.616)†	152.5 (8.134)†
		Atorvastatin QD [*n* = 38]					223.2 (3.266)†	149.5 (2.837)†	160.9 (6.521)†
Rifaie et al.	2012	Atorvastatin QOD [*n* = 30]	53.9 (6.4)	NS	20	10	144 (26)	79 (19)	142 (25)
		Atorvastatin QD [*n* = 30]	55 (8.9)	NS	22	8	153 (21)	87 (16)	157 (28)
Rindone et al.	1998	Fluvastatin QOD [*n* = 23] Fluvastatin QD [*n* = 23]	64 (8)	NS	22	1	269 (22)	182 (24)	244 (62)
Wongwiwatthananukit et al.	2006	Rosuvastatin QOD [*n* = 40]	62.10 (1.57)	NS	15	25	241.52 (34.04)	170.33 (28.22)	151.30 (74.41)
		Rosuvastatin QD [*n* = 40]	57.18 (1.48)	NS	17	23	256.20 (35.47)	181.73 (34.65)	155.27 (79.44)

Continuous variables are described as mean (standard deviation) and categorical variables are described as N

NS not stated, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglycerides, *M* male, *F* female, *QD* every day, *QOD* every other day

[a] Data are described as mean (standard error)

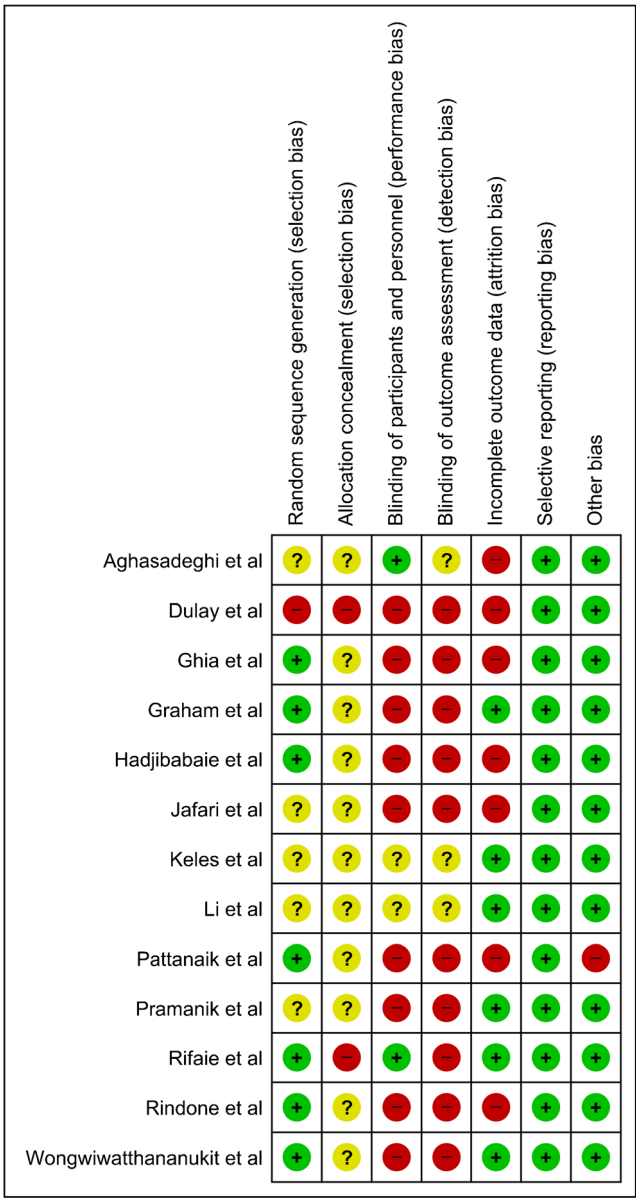

Fig. 2 Risk of bias summary according to Cochrane Risk of Bias assessment tool

For all outcomes, subgroup analysis showed insignificant difference between alternate-day dosing vs. daily dosing of both fluvastatin and pravastatin ($p > 0.05$, Figs. 3, 4, and 5).

Secondary Outcomes

Adverse Events

Most of the included studies did not report the incidence of AEs in each group separately. Therefore, we could not pool the AEs in a meta-analysis model. However, both regimens were generally well tolerated. The descriptive summary of incidence of AEs in the included studies is shown in Table 3.

Compliance with Both Regimens

Of the 13 trials that were included in this meta-analysis, 7 trials [32, 35, 47, 48, 50–52] did not report adherence in any of the treatment groups, 5 trials [33, 45, 46, 49, 53] reported no difference in adherence between both groups, and 1 trial [34] suggested that the alternate-day regimen resulted in a worse adherence when compared with the daily dosing.

Sensitivity Analysis

The leave-one-out sensitivity analysis revealed that the overall combined analyses were robust for all outcomes except for TG, which was sensitive to the study by Rifaie et al. [51] ($p = 0.002$). As for the "atorvastatin" subgroup, the combined effect estimate on TC was robust. However, the combined effect estimates on LDL-C and TG were sensitive to the studies by Aghasadeghi et al. [45] ($p = 0.01$) and Rifaie et al. [51] ($p = 0.02$), respectively. In case of the "rosuvastatin" subgroup, the combined effect estimate on TG was robust. However, the combined effect estimates on TC and LDL-C were sensitive to the studies by Dulay et al. [32] ($p = 0.06$) and Li et al. [48] ($p = 0.006$), respectively. Removing any of the mentioned studies from the analysis resulted in favoring the daily dosing over the alternate-day dosing except for the study by Dulay et al. [32], which caused an insignificant difference between the two groups. The summary of leave-one-out sensitivity analyses is shown in Supplementary File 2: Tables S2a–c. The overall combined effect estimates on TC, LDL-C, and TG were robust in case of sensitivity analysis that excluded the three trials that used the same overall doses of statins in both regimens (e.g., 10 mg daily vs 20 mg every other day).

Meta-Regression

The random-effect meta-regression using the unrestricted maximum likelihood method did not indicate any statistically significant association between the changes in any of the lipid parameters and the duration of statin therapy (LDL-C [slope −0.1961; 95% CI −1.218 to 0.8257; $p = 0.7068$]; TC [slope −0.4631; 95% CI −1.0548 to 0.1286; $p = 0.125$]; TG [slope 1.2882; 95% CI −0.1099 to 2.6863; $p = 0.0709$]). Meta-regression scatter plots are shown in Supplementary File 3: Figs. S1–S3.

Publication Bias

Visual inception of funnel plots suggested a potential publication bias for TG. The trim and fill approach corrected the asymmetry of the funnel plot of TG by imputing 4 studies (corrected MD 0.28354 mg/dL, 95%CI −8.51685, 9.08393, Supplementary File 3: Fig. S4). However, the funnel plots

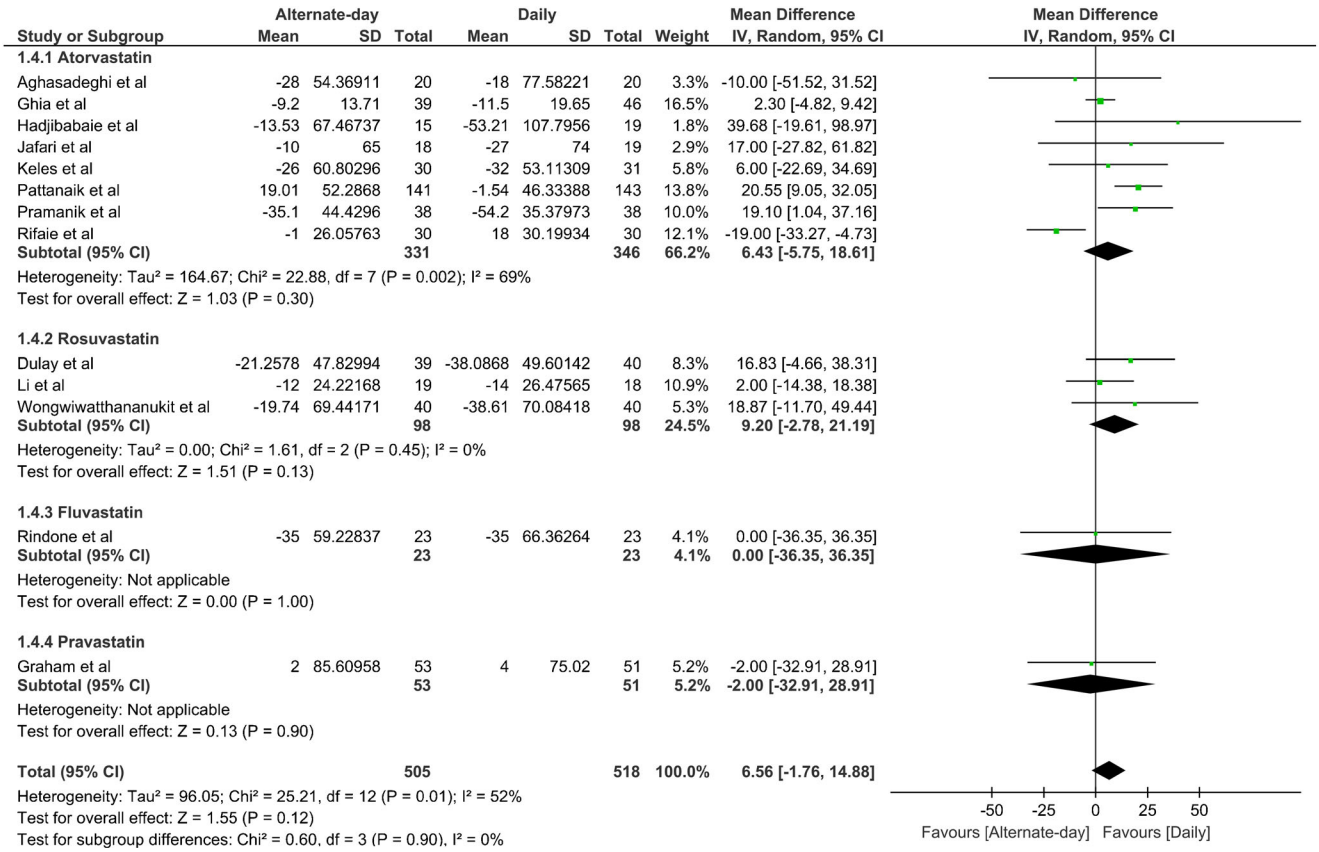

Fig. 3 `Forest plot displaying the results of the meta-analysis of alternate-day dosing versus daily dosing of statin therapy on triglycerides (TGs) with subgrouping according to individual statins. *CI* confidence interval, *df* degrees of freedom, *SD* standard deviation

were symmetric for TC and LDL-C (Supplementary File 3: Fig. S5, S6). Egger's test excluded the presence of publication bias in all outcomes (two-tailed $p > 0.05$).

Discussion

To our knowledge, this is the first meta-analysis to evaluate the efficacy and safety of alternate-day dosing of statin therapy compared with daily dosing. The results of this meta-analysis suggest that there was no statistically significant difference between alternate-day and daily regimens of atorvastatin and rosuvastatin in terms of LDL-C and TG. However, the effect of daily regimens of atorvastatin and rosuvastatin were superior to alternate-day regimes on TC.

Atorvastatin and rosuvastatin are considered high-potency statins [54]. Besides the long half-life of atorvastatin which is about 14 h, its long-lasting active metabolites prolong its inhibiting effect on HMG-CoA reductase up to 20–30 h [54–57]. The half-life of rosuvastatin is 19 h [58]. This prolonged action of both atorvastatin and rosuvastatin could explain the effectiveness of their alternate-day dosing on LDL-C compared with daily dosing. In contrast, our meta-analysis did not show any difference between alternate-day dosing of either fluvastatin or pravastatin versus daily dosing for all outcomes despite the short half-lives of these agents (1.2 and 1.8 h, respectively) [16]. The effectiveness of the alternate-day dosing with fluvastatin and pravastatin is more dependent upon their prolonged action at the cellular level than plasma half-life [52].

Statin intolerance has become a critical challenge to the widespread use of guideline-directed LDL-C lowering therapy [59]. Among myocardial infarction survivors who experience statin intolerance, the risk of recurrent myocardial infarction, CV events, and hospitalizations for CV events is 50% higher than patients who adhere to high-intensity statin therapy [60]. Several factors improve adherence to high-intensity statin therapy; these include interaction with the prescriber, participation in cardiac rehabilitation, and elimination of economic barriers [31]. A change in statin agent and/or dosage is a recommended approach by many consensus documents and the practice of lipid specialists worldwide [61, 62]. Some patients can tolerate alternate-day statins but not daily dose statins. In this meta-analysis, the use of alternate-day dosing of statins (particularly the long-acting statins, atorvastatin, and rosuvastatin) is a reasonable treatment option in patients who are intolerant to more than one statin.

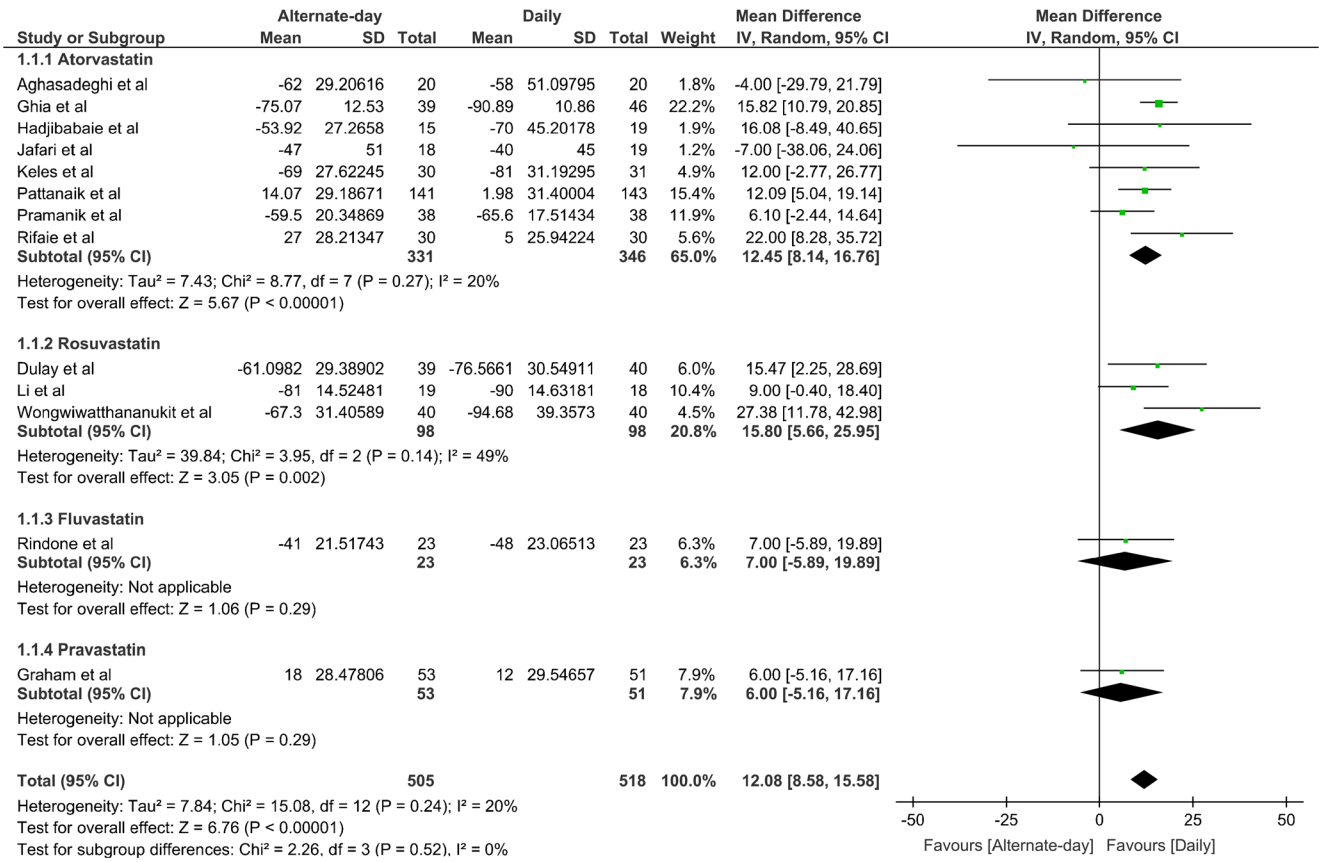

Fig. 4 Forest plot displaying the results of the meta-analysis of alternate-day dosing versus daily dosing of statin therapy on total cholesterol (TC) with subgrouping according to individual statins. *CI* confidence interval, *df* degrees of freedom, *SD* standard deviation

The issue of compliance with the alternate-day dosing has been a limitation to this regimen [52]. According to the current meta-analysis, only 1 RCT reported poor compliance with alternate-day regimen [34]. However, the durations of most of the included trials were relatively short; therefore, long-term compliance with alternate-day regimen compared with daily regimen has not been established.

It has been suggested in many large studies that statins are associated with an increase in the risk of new-onset diabetes mellitus (NODM) [63, 64]. Moreover, Preiss et al. concluded, in a large meta-analysis of RCTs, that high-dose statins are associated with a larger risk of NODM compared with moderate-dose statins [65]. From this, we could say that, theoretically, alternate-day statins may have a reduced risk of NODM. However, this hypothesis needs to be tested in large RCTs.

This meta-analysis has several limitations: (1) the sample size of most of included trials was relatively small [33, 45, 47, 48, 52]; (2) heterogeneity was observed between studies especially in term of change in LDL-C. This heterogeneity may result from many factors including the population characteristics, hypersynthesis vs decreased catabolism of LDL (with possibly different half-lives of LDL particles), and statin doses or the duration of treatment. However, this significant heterogeneity was addressed by using a random-effect model in the analysis. It was also explored by subgroup analysis and meta-regression; (3) we excluded an important RCT because the data were insufficient for analysis [36]; (4) alternate-day regimens with fluvastatin and pravastatin were investigated in only 1 RCT for each statin [46, 52]; (5) most of the included trials were of short duration [33, 45, 48, 51]; (6) the included studies did not use a standardized tool to assess SAMS [66]; (7) we could not pool the AEs of both groups in a meta-analysis model because most of the included studies did not report the AEs in each group separately [32, 46, 49, 50, 52, 53]; and (8) none of the included studies reported any data on non-HDL-C, a secondary target of therapy in several recent lipid guideline documents [67, 68].

Based on the results of this meta-analysis, further large-scale RCTs with long-term treatment are recommended to confirm these findings and investigate the effects of alternate-day dosing of statins vs daily dosing on patient compliance particularly in patients with SAMS, risk of NODM and CV events. More RCTs are needed to investigate the efficacy of other statin regimens (e.g., twice or once weekly) compared with daily and alternate-day regimens. Also, there is a need to investigate the effectiveness of combining other statin regimens (e.g., twice or once weekly) with other lipid-

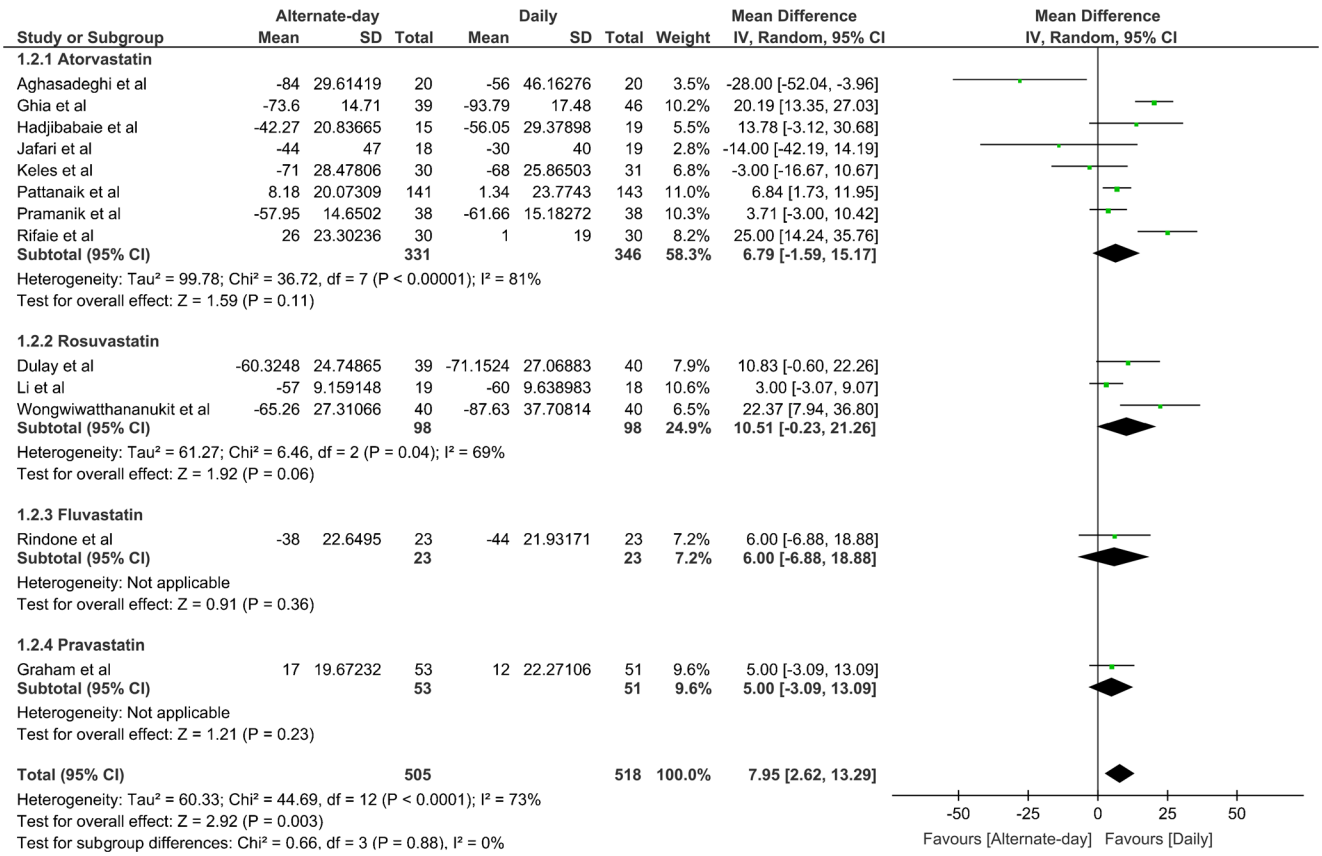

Fig. 5 Forest plot displaying the results of the meta-analysis of alternate-day dosing versus daily dosing of statin therapy on low-density lipoprotein cholesterol (LDL-C) with subgrouping according to individual statins. *CI* confidence interval, *df* degrees of freedom, *SD* standard deviation

Table 3 Summary of adverse events in the included studies

Study	Adverse events (AEs)
Aghasadeghi et al.	No AEs
Dulay et al.	One patient experienced myalgia without a rise in CK, which resolved with time. Gastrointestinal upset was the most common complaint
Ghia et al.	- *Daily dosing group*: 1 headache, 1 asthenia, 2 dizziness, 3 parasthesia, 1 depression, 1 myalgia and 1 elevated liver enzymes
	- *Alternate-day dosing group*: 1 headache, 1 dyspepsia, 1 dizziness and 1 parasthesia
Graham et al.	One complained of heartburn and myalgia at the 4-month visit
Hadjibabaie et al.	No AEs
Jafari et al.	No AEs
Keles et al.	No AEs
Li et al.	Not reported
Pattanaik et al.	One patient experienced myalgia without a rise in CK
Pramanik et al.	One patient experienced myalgia in daily dosing group
Rifaie et al.	No AEs
Rindone et al.	Two patients experienced gastrointestinal upset and one patients experienced urinary retention
Wongwiwatthananukit et al.	Two patients in the daily dosing group experienced malaise and myalgia and one patient in the alternate-day dosing group developed headache

CK *creatine kinase*

lowering agents, especially since some of these options have demonstrated favorable results in a few small studies [69–71].

In conclusion, this meta-analysis shows that alternate-day dosing of individual statins (especially atorvastatin and rosuvastatin) is as efficacious as daily dosing on LDL-C and TG. Moreover, this regimen is well-tolerated with good adherence. Therefore, alternate-day dosing is a reasonable treatment option in patients with statin intolerance. Further large-scale RCTs are recommended to confirm and extend these findings.

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Compliance with Ethical Standards

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Conflict of Interest *Dimitri P. Mikhailidis* has given talks and attended conferences sponsored by MSD, AstraZeneca and Libytec; *Peter P. Toth* consults for Abbvie, Amarin, AstraZeneca, Amgen, Gemphire, Kowa, Merck, Regeneron, and Sanofi and serves on the Speakers Bureau for Amarin, Amgen, Kowa, Merck, Regeneron, and Sanofi; *Patrick Moriarty* has research funding from Regeneron, Sanofi-Aventis, Pfizer, Novartis, Amgen, Ionis, and Catabasis, and he serves as a consultant for Genzyme, Kowa, Duke Clinical Research Institute, Eliaz Therapeutics, Aegerion, Alexion, and Esperion; *Paul Muntner* received grant support and honoraria from Amgen; *Alberico L. Catapano* has received research grants to his institution from Amgen, Astra-Zeneca, Merck, Regeneron/Sanofi, and Sigma Tau and honoraria for lectures, advisory boards, or as a steering committee member from Aegerion, Akcea, Amgen, Sanofi-Regeneron, Pfizer, AstraZeneca, ISIS Pharma, Kowa, Lilly, Boehringer Ingelheim, MSD,Sigma Tau, Recordati; *Michael J. Pencina* declares research grants from Sanofi-Regeneron; *Robert S. Rosenson* declares research funding to his institution from Akcea, Amgen, Astra Zeneca, Eli Lilly, Esperion, Medicines Company, Regneron, and Sanofi; advisory board fees from Akcea, Amgen, Easy Vitals, Eli Lilly, Regneron and Sanofi; honoraria from Kowa; royalties from UpToDate, Inc.; and stock holdings in MediMergent LLC; *Maciej Banach* declares advisory boards fees from Abbott Vascular, Amgen, Daichi Sankyo, Esperion, Lilly, MSD, Resverlogix, Sanofi-Aventis, Speakers Bureau from Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Sanofi-Aventis, and Valeant and grants from Valeant, Sanofi-Aventis.

Ethical Approval This article does not include any studies with human participants or animals performed by any of the authors.

Informed Consent Not applicable.

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