Alternate-day versus daily atorvastatin in coronary artery disease: a randomized study

Koroner arter hastalığında atorvastatinin günlük kullanıma karşın-gün aşırı kullanımı: Randomize bir çalışma

Osama Rifaie, Ahmed Zahran, Wail Nammas

From Department of Cardiology, Faculty of Medicine, Ain Shams University, Cairo-*Egypt*

ABSTRACT

Objective: We sought to compare the effect of alternate-day versus daily atorvastatin 10 mg, on serum low-density lipoprotein cholesterol (LDL-C) and high-sensitivity C-reactive protein (hs-CRP) in patients with coronary artery disease (CAD) and controlled serum LDL-C by daily atorvastatin.
Methods: The study was prospective, randomized, single-blinded, two-armed. Randomization was performed by a computer-generated randomization list. We randomized 60 patients with CAD and controlled serum LDL-C to receive either atorvastatin in the standard-dose of 10 mg daily (Group A=30 patients), or the same medication every other day (Group B=30 patients). Primary efficacy criterion included changes in serum LDL-C and hs-CRP from the initial to the 6-week follow-up values.
Results: The mean age was 54.5±7.7 years, (70% males). LDL-C was significantly lower in Group A as compared with group B at 6-week follow-up (88±21 versus 105±26 mg/dl, respectively, p=0.008). Similarly, the mean percent increase of LDL-C from baseline to final assessment was significantly lower in Group A as compared with Group B (1.5±0.2 versus 32.8±6.2%, respectively, p<0.0001). However, the mean percent change of hs-CRP value was statistically similar between the two groups (p=0.108). Patients reported no side effects attributable to the medication.
Conclusion: The current pilot study demonstrated that in patients with CAD who have achieved target LDL-C level, maintenance on alternate-day atorvastatin 10 mg was inferior to daily atorvastatin in keeping LDL-C below the target level; however, it produced a similar effect on hs-CRP.
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Key words: Low-density lipoprotein cholesterol, statins, coronary artery disease

ÖZET

Amaç: Koroner arter hastalığı (KAH) olan hastalarda, serum düşük dansiteli lipoprotein kolestrol (LDL-K) ve yüksek duyarlılıklı C-reaktif protein (hs-CRP) üzerine günlük atorvastatin 10 mg'a karşılık gün aşırının etkisini karşılaştırmayı amaçladık ve LDL-K'yı günlük atorvastatinle kontrol ettik.
Yöntemler: Prospektif, randomize, tek kör ve çift kollu bir çalışmadır. Randomizasyon bir bilgisayar tarafından randomizasyon listesi ile yapıldı. Koroner arter hastalığı olan 60 hastayı randomize ettik, günlük standart doz 10 mg atorvastatin alan (Grup A=30 hasta) ya da aynı tıbbi tedaviyi her gün alanların kontrollü serum LDL-K'ını kontrol ettik (Grup B=30 hasta). Primer etkinlik kriteri, başlangıçtan itibaren 6 haftalık takip değerlerindeki serum LDL-K ve hs-CRP seviyelerinin değişikliklerini içermektedir.
Bulgular: Ortalama yaş 54.5±7.7 yıldır (%70 erkek). Altı haftalık takipte, LDL-K değeri, Grup A Grup B ile karşılaştırıldığında, önemli derece düşüktü (88±21 karşın 105±26 md/dl, sırasıyla, p=0.008). Benzer şekilde, başlangıçtan son değerlendirmeye ortalama LDL-K artış yüzdesi Grup A' dakilerle Grup AB'dekilerle karşılaştırıldığında önemli derecede düşüktü (1.5±0.2 karşın %32.8±6.2, sırasıyla, p<0.0001). Ancak, hs-CRP ortalama yüzde değişim değeri iki grup arasında istatistiksel olarak benzerdi (p=0.108). Hastalar ilaca dair yan etki bildirmediler.
Sonuç: Mevcut pilot çalışma ile hedef LDL-K seviyesi sağlanan KAH'larında gün aşırı 10 mg atorvastatinde kalınması LDL-K'nin hedef seviyesinin altında tutulabilmesi açısından günlük atorvastatinin gerisinde kalmıştır; bununla beraber, hs-CRP üzerinde benzer etki yarattı.
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Anahtar kelimeler: Düşük-dansiteli lipoprotein kolesterol, statinler, koroner arter hastalığı

Address for Correspondence/Yazışma Adresi: Wail Nammas M.D, Department of Cardiology, Ain Shams University Hospitals, Faculty of Medicine, Ain Shams University, Abbassia, Cairo-*Egypt* Phone: +2 02 24063718 Fax: +2 02 24820416 E-mail: wnammas@hotmail.com
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Introduction

Since their early introduction, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have become among the most effective and widely used medications for reducing cardiovascular risk. The value of statins in primary and secondary prevention has been established in a broad spectrum of clinical scenarios; at one end of the spectrum are those without known vascular disease (1); at the other end are patients admitted with acute coronary syndrome (2). Yet, this observed benefit is well beyond their cholesterol-lowering effect; indeed, the benefit appears even before any effect on cholesterol becomes manifest. This has led to the wide acknowledgement of the anti-inflammatory effects of statins that was demonstrated, thereafter, in several randomized clinical trials (2-5). In this regard, a mechanism involving reduction of high-sensitivity C-reactive protein (hs-CRP) may play a pivotal role in exerting the anti-inflammatory and anti-atherosclerotic effects of statins (6).

Unfortunately, however, only half of all patients who have been prescribed a statin ultimately adhere to this indispensable medication (7). Not surprisingly, non-adherence is a chief reason why many patients do not achieve the recommended low-density lipoprotein cholesterol (LDL-C) goals and patients who are non-adherent have a worse clinical outcome (8). The reasons for non-adherence are highly variable from one patient to another. Above all, intolerance is a frequent and rational cause of statin discontinuation. Moreover, many patients underestimate the importance of statins, given the asymptomatic nature of hypercholesterolemia, especially when burdened with the polypharmacological regimens needed by most patients with vascular disease. Undisputable, for many patients, cost is a substantial barrier to appropriate medication use (9).

In a prospective randomized pilot study design, we sought to compare the effect of a reduced-dose alternate-day regimen of atorvastatin 10 mg versus the standard-dose conventional daily regimen, on serum LDL-C and hs-CRP in patients with coronary artery disease who have already achieved the recommended LDL-C target level of less than 100 mg/dl by the conventional daily regimen. A cost-effectiveness analysis was intended for the two regimens.

Methods

Patient selection and study design

Prospectively, we enrolled 60 patients with documented coronary artery disease referred to our outpatient clinic during the period from May 2009 to November 2009, for routine follow-up. Patients were considered eligible for inclusion if they were already on the conventional regimen of atorvastatin 10 mg daily orally, and have their LDL-C level already brought to the target level of less than 100 mg/dl, as recommended by the US National Cholesterol Education Program Adult Treatment Panel III (10). We excluded patients with acute myocardial infarction, coronary bypass surgery or angioplasty within 6 months of study entry; unstable angina pectoris; history of unstable or severe peripheral arterial disease within 3 months of study entry; congestive heart failure (defined as New York Heart Association class III or IV heart failure); uncontrolled cardiac arrhythmias; uncontrolled or newly diagnosed (within 1 month of study entry) diabetes mellitus; uncontrolled endocrine or metabolic diseases known to influence serum lipids or lipoproteins; active or chronic hepatic or hepatobiliary disease; known prior myositis associated with statin therapy; and current infection or inflammatory disease that might influence serum CRP levels. Before inclusion, an informed written consent was obtained from each patient after full explanation of the study protocol, and the study protocol was reviewed and approved by our Local Institutional Human Research committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2002. The study was totally funded by our institution, with no other external sources of funding.

Study design

The current pilot study was prospective, randomized, single-blinded, with two parallel treatment arms (Fig. 1). Patients were evaluated chiefly at 3 time points: an initial screening visit for enrollment of eligible patients, a second visit for baseline data collection and randomization, and a final follow-up visit after 6 weeks of the assigned treatment. Patient assessment for eligibility, enrollment of participants and assignment for a particular study group were performed by attendant doctors in the outpatient clinic who were not blinded to patient allocation. Simple randomization was performed by an independent statistician who has drawn a computer-generated randomization list, and provided it to the outpatient clinic. Qualifying patients were randomly assigned (in a 1:1 ratio), on an individual basis, to receive either atorvastatin calcium (Lipitor®, Pfizer, USA) in the standard-dose regimen of 10 mg daily orally for 6 weeks (group A=30 patients), or the same medication in an alternate-day regimen of 10 mg orally every other day for the same duration (Group B=30 patients). Two groups of drug containers were supplied to the outpatient clinic: one group which contained all tablets with the medication, and another which contained time-calendared tablets of alternating medication and placebo (all of the same size and appearance). Patients were instructed to receive the tablets according to the specified time calendar of each container. Patients were requested to take their medication after dinner. The drug was dispensed in 6-week-supply calendar packs. All patients were individually given written and verbal instructions to follow step II diet according to the US National Cholesterol Education Program Adult Treatment Panel III (10), and they remained in the same allocation throughout the study period. Standard anti-ischemic medications were allowed and remained unchanged during the study period. None of the patients received any other lipid-modifying agent during the study period. All patients were regularly questioned about compliance with

their study medication, and whether they experienced any adverse effects, such as muscle pain, weakness, or dark urine. Safety and tolerability were evaluated throughout the study period on the basis of adverse effect reporting, physical examination, and laboratory analysis.

Laboratory measurements

Blood samples were collected in the morning after a 12-hour fasting period, during the second and third visits, and lipid measurements were performed. In the alternate-day regimen group (group B), samples were obtained in the morning when the patient did not receive the pill. Serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured calorimetrically on Synchron Cx5 (Beckman Coulter Instruments Inc., CA, USA) using Beckman Coulter reagents. Total cholesterol was measured by the cholesterol oxidase method, HDL cholesterol with a homogeneous assay, and triglycerides by enzymatic hydrolysis followed by the measurement of free glycerol. For the assay of HDL, precipitation of LDL-C and very low-density lipoprotein cholesterol (VLDL-C) was performed by phosphotungistic acid in the presence of magnesium ions; they were then removed by centrifugation. The cholesterol in HDL-C fraction, which remains in the supernatant, was assayed in the same way as total cholesterol on Beckman Coulter Synchron Cx5 autoanalyzer. The precipitating reagents used for the determination of HDL were purchased from Quimica Clinica Aplicada (QCA 43870-Amposta, Tarragona, Spain). LDL-C concentrations were calculated according to the Friedewald equation (11). If any patient had a triglyceride level above 300 mg/dl, LDL-C was measured directly by ultracentrifugation (β-quantification; direct LDL-C). High-sensitivity CRP was quantified by means of high-sensitivity immunophelometry (hs-CRP; Dade Behring, Inc). Standardization was conducted according to the recommendations of the International Federation of Clinical Chemistry with reagents and standards from Beckman Coulter. In addition, alanine aminotransferase, aspartate aminotransferase, and creatine phosphokinase were measured initially and at the follow-up visit.

Primary efficacy criterion

The primary efficacy criterion included changes in serum LDL-C and hs-CRP from the initial values measured at randomization during the second visit, to the follow-up values measured during the third visit 6 weeks following treatment assignment, in response to the standard-dose regimen as compared with the alternate-day regimen.

Secondary efficacy criterion

The secondary efficacy criterion included changes in serum total cholesterol, HDL-C, and serum triglycerides from the initial values, to the follow-up values, in response to the standard-dose regimen as compared with the alternate-day regimen.

Statistical analysis

Analyses were performed with SPSS version 12.0 statistical package (SPSS Inc., Chicago, IL, USA). All continuous variables were presented as mean±SD, if they were normally distributed. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Categorical variables were described with absolute and relative (percentage) frequencies. Since the study was a pilot one, no formal sample size calculation was performed. Comparisons between the 2 individual groups were performed using the unpaired t-test, and the Pearson Chi-square test for continuous and categorical variables, respectively. All tests were two-sided and a probability value of $p<0.05$ was considered statistically significant.

Results

Baseline clinical characteristics

A total of 60 patients with documented coronary artery disease who have their LDL-C level already brought to the target level of less than 100 mg/dl on the conventional regimen of atorvastatin 10 mg daily orally, were enrolled in the current study. Recruitment was performed during the period from the 1st of May 2009 to the 30th of November 2009. These patients include 30 patients randomly assigned to receive atorvastatin in the standard-dose regimen of 10 mg daily orally for 6 weeks (group A=30 patients), and 30 others randomly assigned to receive atorvastatin in an alternate-day regimen of 10 mg orally every other day for the same duration (Group B=30 patients). Among patients evaluated, we excluded 9 patients who did not meet the criteria for enrollment (2 patients with a recent myocardial infarction 3 and 4 months before, 3 who underwent coronary angioplasty within the preceding 6 months, 2 with unstable angina, 1 with recently diagnosed diabetes mellitus, and 1 with chronic inflammatory disease). Figure 1 shows the flow diagram of the study design. Table 1 shows the baseline clinical characteristics of the whole series, as well as the 2 individual study groups. The mean age of the whole study series was 54.5±7.7 years, 42 (70%) being males. The 2 individual groups were well

Table 1. Baseline clinical characteristics of the whole series as well as the 2 individual study groups

Variables	Whole series (n=60)	Group A (n=30)	Group B (n=30)	*p
Age, years	54.4±7.7	55±8.9	53.9±6.4	0.559
Male gender, n (%)	42 (70)	22 (73.3)	20 (66.7)	0.573
Smoking, n (%)	41 (68.3)	22 (73.3)	19 (63.3)	0.604
Hypertension, n (%)	43 (71.7)	21 (70)	22 (73.3)	0.774
DM, n (%)	26 (43.3)	15 (30)	11 (36.7)	0.297
FH of CAD, n (%)	20 (33.3)	9 (30)	11 (36.7)	0.584

Data are presented as mean±SD and as numbers (percentage)
*unpaired t-test, and Pearson Chi-square test
CAD - coronary artery disease, DM - diabetes mellitus, FH - family history

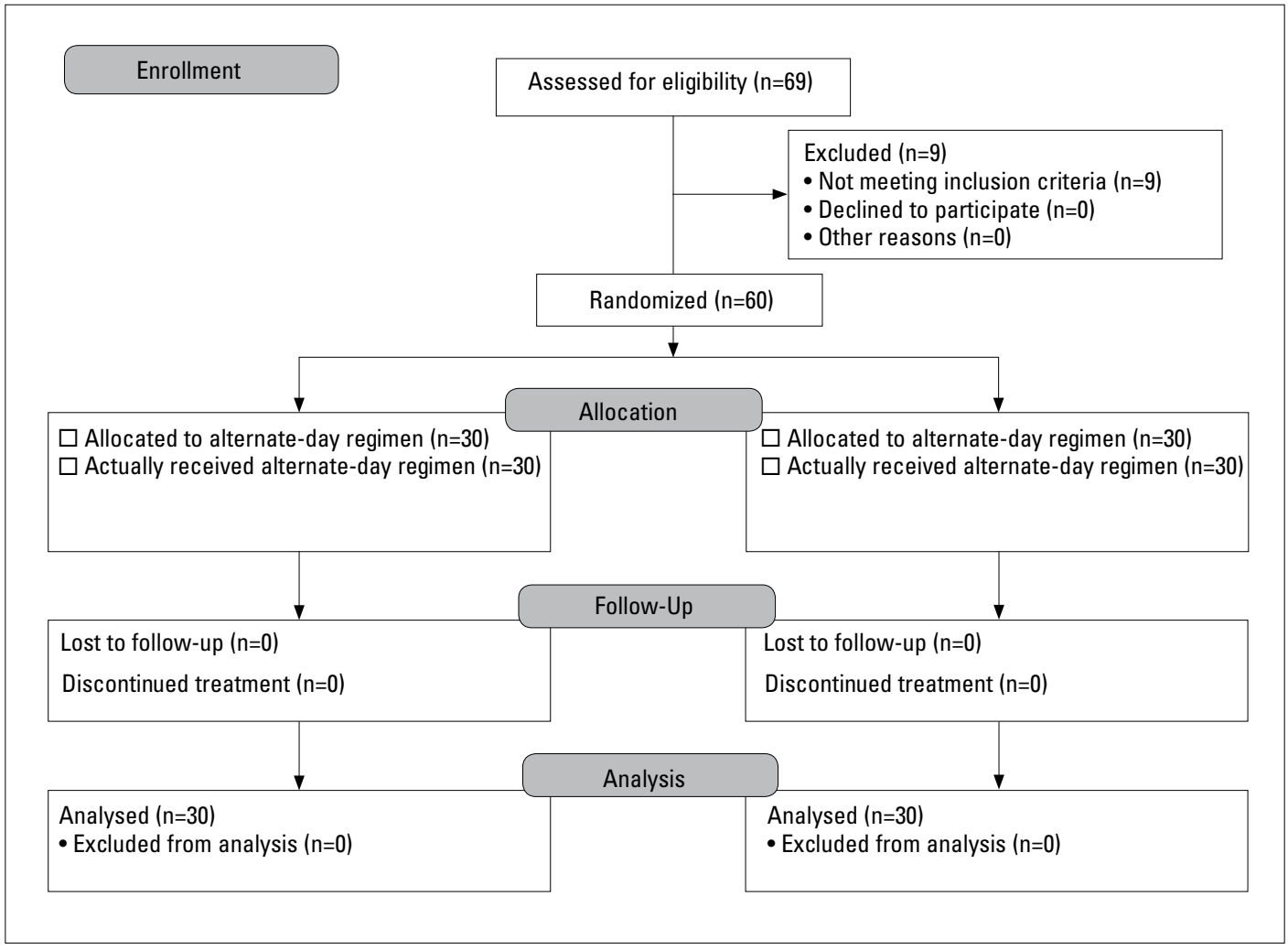

Figure 1. The flow diagram of the study design

balanced regarding age, gender, and risk factors for coronary artery disease (Table 1).

All patients completed 6 weeks follow-up at the 15th of January 2010, with no cross-over between the groups. Data analysis included all patients enrolled in the study (30 patients in Group A and 30 in Group B), and was performed by original group assigned. The drug was well-tolerated by all patients with no reported symptoms or signs of myopathy during the 6-week treatment period, and no patient in either group had a significant rise of serum transaminases, or creatine phosphokinase. Moreover, no patient reported any clinical events during the study period.

Lipid profile measurements and hs-CRP values

Although all lipid measurements and hs-CRP values were statistically similar between the two groups at baseline, LDL-C was significantly lower in Group A as compared with Group B at 6-week follow-up (88±21 versus 105±26 md/dl, respectively, p=0.008). Moreover, there was a trend toward a lower total cholesterol in group A as compared with Group B at 6-week follow-up (158±29 versus 171±30 mg/dl, respectively, p=0.091). Otherwise, all other lipid measurements as well as the hs-CRP values were statistically similar between the two groups at 6-week follow-up (p>0.05 for all) (Table 2). Among group A, LDL-C remained below the recommended value of 100 mg/dl in 19 (63.3%) patients, as compared with 11 (36.7%) patients in group B.

The mean percent increase of total cholesterol from baseline to final assessment was significantly lower in Group A as compared with Group B (3.2±0.7 versus 18.2±3.6%, respectively, p<0.001). Similarly, the mean percent increase of LDL-C from baseline to final assessment was significantly lower in group A as compared with Group B (1.5±0.2 versus 32.8±6.2%, respectively, p<0.001). Otherwise, the mean percent change of all other lipid measurements as well as the hs-CRP value from baseline to final assessment were statistically similar between the two groups (p>0.05 for all) (Table 3).

Cost analysis

Based on the price of the utilized brand of atorvastatin, group A had an annual cost per patient of $376 as compared with $188 in Group B. This provides an annual cost saving per patient of $188. The mean annual cost per patient necessary for each further 10 mg/dl reduction of LDL-C, from the value of group B to that of group

Table 2. Initial and final lipid measurements and hs-CRP values in the 2 individual study groups

Measurement time	Variables	Group A (n=30)	Group B (n=30)	*p
Initial measurement	Total cholesterol, mg/dl	153±21	144±26	0.18
	Triglycerides, mg/dl	157±28	142±25	0.404
	HDL-C, mg/dl	35±11	37±10	0.402
	LDL-C, mg/dl	87±16	79±19	0.109
	VLDL-C, mg/dl	32±8	28±6	0.287
	hs-CRP, mg/L	3.7±1.2	4±1.5	0.378
Final measurement	Total cholesterol, mg/dl	158±29	171±30	0.091
	Triglycerides, mg/dl	175±32	141±27	0.111
	HDL-C, mg/dl	35±9	38±8	0.173
	LDL-C, mg/dl	88±21	105±26	0.008
	VLDL-C, mg/dl	35±11	28±5	0.101
	hs-CRP, mg/L	4.9±1.2	3.8±1.8	0.231

All variables are presented as mean±SD
* unpaired t-test
hs-CRP - high-sensitivity C - reactive protein, HDL-C - high-density lipoprotein cholesterol, LDL-C - low-density lipoprotein cholesterol, VLDL-C - very low-density lipoprotein cholesterol

Table 3. Mean percent change of lipid measurements and hs-CRP values from initial to final measurement in the 2 individual treatment regimens for the whole series

Variables	Group A (n=30)	Group B (n=30)	*p
Total cholesterol, %	3.2±0.7	18.2±3.6	<0.0001
Triglycerides, %	11.4±3.6	-0.6±0.2	0.391
HDL-C, %	-0.1±0.05	1.7±0.8	0.679
LDL-C, %	1.5±0.2	32.8±6.2	0.000
VLDL-C, %	8.3±1.9	-1.3±0.3	0.918
hs-CRP, %	33.2±3.7	-6.1±1.8	0.108

All variables are presented as mean±SD
*unpaired t-test
hs-CRP - high-sensitivity C - reactive protein, HDL-C - high-density lipoprotein cholesterol, LDL-C - low-density lipoprotein cholesterol, VLDL-C - very low-density lipoprotein cholesterol

A, was calculated at $110.59. Moreover, the mean annual cost per patient necessary for each further 1% reduction of LDL-C, from the value of group B to that of group A, was calculated at $11.6.

Discussion

The results of the current pilot study demonstrated that an alternate-day regimen of atorvastatin 10 mg given every other day to patients with coronary artery disease who have already had controlled LDL-C levels, was less effective in maintaining serum LDL-C below the recommended target level (<100 mg/dl) as compared with the standard-dose regimen of atorvastatin 10 mg given daily. However, the alternate-day regimen achieved a better albeit statistically insignificant - effect on hs-CRP.

Many previous studies have attempted to use the alternate-day dosing regimen of statin administration in patients with hypercholesterolemia (12-24). Results, however, have been controversial; being discouraging for short-half-life statins: lovastatin, fluvastatin, pravastatin, and simvastatin (12-14, 19, 20). Extremely important when adopting a long-interval dosing regimen is knowledge of the half-life of the medication employed. Besides its long half-life of 14 hours, the long-lasting active metabolites of atorvastatin confer an HMG-CoA reductase inhibition up to 20-30 hours (25). Moreover, following discontinuation of atorvastatin, an increase in total cholesterol makes appearance, on average, 48 hours later; LDL-C and apo-B increase within 72 hours (26). Added to its great potency in reducing LDL-C, these properties would, reasonably, make atorvastatin an 'ideal' statin for an alternate-day regimen. No wonder, therefore, that alternate-day atorvastatin administration was demonstrated as an effective and safe alternative to the 'conventional' daily dosing regimen in reducing serum LDL-C levels (15, 17, 18, 22).

All these prior studies, nevertheless, enrolled patients with hypercholesterolemia, either not yet receiving cholesterol-lowering therapy, or following a relevant wash-out period off their current cholesterol-lowering medication. Instead, we opted to employ the alternate-day atorvastatin regimen in a series of patients with documented coronary artery disease. It is well known that the response of serum cholesterol to statin therapy is characterized by a high individual variability. Since it is hard to foretell which individuals will be good responders to statin therapy, and which will be poor responders, we decided to include only those whose serum LDL-C was already 'brought to target' with 'standard-dose' atorvastatin. Assuming that those were the 'good responders', we tested the hypothesis that keeping LDL-C level well below the target can be achieved by a maintenance alternate-day atorvastatin regimen.

Although our results failed to demonstrate 'non-inferiority' of the alternate-day regimen in keeping LDL-C below the recommended level, as compared with the 'standard-dose' regimen, the resulting mean LDL-C (105 mg/dl) in the alternate-day group was well close to the 'target'. The fact that 63.3% of patients in the alternate-day group were 'off-target' (36.7% in the standard-dose group), again, reemphasizes the impact of high and unpredictable - individual variability of response, not only to the initiation of therapy, but also to the maintenance therapy in those initially considered as 'good responders', whether this maintenance was achieved by the standard-dose or the alternate-day regimen. Similarly, Graham et al. (19), reported that step-down of pravastatin therapy to the alternate-day regimen in those who already achieved LDL-C target level on the conventional daily regimen did not succeed to maintain LDL-C below target at the end of the day. Yet, surprisingly, the alternate-day regimen demonstrated a better - although not meeting statistical significance - effect on hs-CRP, as compared with the standard regimen. This is of paramount significance since hs-CRP was shown to be an important risk predictor of myocardial infarction and stroke (27).

Clinical implications

Based on the cost analysis, the alternate-day regimen provided a 50% reduction of the annual cost of atorvastatin per patient with coronary artery disease. The fact that this patient category obviously needs statin therapy indefinitely highlights the importance of cost saving, especially in drug classes considered on the top of the list of expensive medications. When a cost-effectiveness analysis is considered, the higher the individual cardiac risk of a patient, the greater the investment per life saved. Employing the alternate-day regimen in patients with coronary artery disease would, undoubtedly, provide cost saving, as well as a justification for medication use (28). In the modern era of mounting healthcare costs, physicians will do both patients and "the Healthcare System" a great favor by resorting to less costly means of maintaining serum LDL-C levels, at least in those considered as 'good responders' to initial therapy.

Study limitations

Our findings are based on a single center study with a relatively small sample size of the cohort, a fact that makes it difficult to generalize our results to all patients with coronary artery disease and controlled serum cholesterol levels. Multi-center studies using the same protocol and examining a larger number of patients are clearly needed before solid conclusions can be made. Moreover, our results cannot be extrapolated to patients whose LDL-C levels were not yet brought to target. Furthermore, the high individual variability of response to statin therapy might further confound the results. Additionally, outcome was based on the 'surrogate', rather than the 'hard' endpoints. Another question concerns the levels of IL-6 which determines CRP production in the liver, yet, this may constitute a potential venue for future research. Finally, a longer period of follow-up was necessary to elucidate the long-term effects of statins in this patient category with life-long statin prescription.

Conclusion

The current pilot study demonstrated that in patients with documented coronary artery disease who have already achieved the target level of LDL-C, maintenance on alternate-day atorvastatin 10 mg did not prove to be non-inferior to daily atorvastatin in keeping LDL-C below the target level (p =0.008), however, it produced a similar effect on hs-CRP (p =0.231).

Conflict of interest: None declared.

Authorship contributions: Concept - O.R.; Design - O.R.; Supervision - W.N., A.Z.; Resources - A.Z.; Material - A.Z.; Data collection&/or Processing: A.Z.; Analysis &/or Interpretation - W.N., A.Z.; Literature Search - A.Z. W.N.; Writing -W.N., A.Z.; Critical review - W.N., O.R.

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