

# Comparative efficacy of daily versus alternate-day dosing of atorvastatin in Type 2 diabetic patients

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**Background:** The aim of this study was to compare the efficacy of alternate-day dosing and once-daily dose regimens of atorvastatin reduction of low-density lipoprotein (LDL) in Type 2 diabetic patients. **Methods:** A prospective, randomized non-blinded controlled clinical trial was performed. A total of 40 patients with Type 2 diabetes mellitus who met the inclusion criteria were randomly assigned to receive atorvastatin 10 mg in an every- or alternate-day dosing regimen. **Results:** A total of 34 patients correctly completed the study. After 8 weeks, LDL decreased by 28 and 36% in the alternate-day and every-day groups, respectively ( $p = 0.013$ ). The target LDL goal was maintained in 33 and 68% of the patients in the alternate-day and every-day groups, respectively. None of the 34 patients had significant elevation of liver enzymes or creatine kinase and no patients had signs or symptoms of myopathy. **Conclusion:** Alternate-day administration of atorvastatin has lower efficacy than the everyday regimen.

Type 2 diabetes mellitus is a common disease that is increasing to near epidemic level in industrial nations [1]. It has been demonstrated that Type 2 diabetes mellitus is associated with dyslipidemia and an independent and significant risk of coronary heart disease (CHD) [2–4]. Patients with Type 2 diabetes often exhibit a specific pattern of abnormal lipid levels that is characterized by increased levels of triglycerides (TGs), decreased levels of high-density lipoprotein (HDL), and, often, elevated levels of low-density lipoprotein (LDL). Recent large-scale clinical studies have shown that the treatment of dyslipidemia in both diabetic and nondiabetic individuals significantly improves lipid levels and reduces the risk of CHD [5,6]. In individuals with Type 2 diabetes, the normalization of lipid values has a positive effect on morbidity and mortality that is independent of the degree of glycemic control [7]. Type 2 diabetics have a two- to four-fold excess risk of coronary artery disease compared with nondiabetic patients [8]. Furthermore, after an acute coronary event, diabetic subjects develop congestive heart failure more frequently and have a higher mortality rate than nondiabetic individuals [9].

Both the National Cholesterol Education Panel (NCEP) and the American Diabetes Association (ADA) give achievement of the LDL target first priority [9]. Statins are the first-choice pharmacological therapy to address diabetic dyslipidemia owing to their effectiveness at lowering LDL levels in patients with diabetes [10], but their cost is a major disadvantage.

Previous investigations have demonstrated that alternate-day dosing of simvastatin, lovastatin and atorvastatin in lowering LDL levels in patients with dyslipidemia may be an effective alternative to daily dosing [11–17].

Atorvastatin is one of the most potent statins and is metabolized to at least two active, long-lasting metabolites with potencies similar to the parent compound. It is a competitive inhibitor of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the rate-limiting step in cholesterol biosynthesis. Moreover, because of the long-lasting metabolites of atorvastatin, the half-life of HMG-CoA reductase inhibition reaches 20–30 h, although the mean terminal elimination half-life ( $t_{1/2\beta}$ ) of atorvastatin is 14 h [14,18]. Diabetes mellitus is often associated with symptoms and complicated diseases, therefore, diabetics almost use several drug categories that affect individuals and incur additional cost and inconvenience related to drug contraindications.

This investigation aimed to compare the efficacy of alternate-day dosing of atorvastatin with once-daily dose treatment in diabetic Type 2 patients with hypercholesterolemia.

## Methods

### Patient selection

In this randomized, prospective, nonblinded controlled clinical trial, we recruited 40 patients with Type 2 diabetes mellitus, aged  $54.45 \pm 1.36$  years from the Endocrinology and Metabolism outpatient clinic of a university

hospital. Diabetic patients were chosen according to ADA criteria [19]. Diabetics with hypercholesterolemia who met the criteria for pharmacologic treatment according to NCEP Adult Treatment Panel III (ATP III) guideline for diabetic patients were recruited [20].

Exclusion criteria were as follows: hypertriglyceridemia (TG > 400 mg/dl), hypothyroidism, myocardial infarction, coronary artery bypass graft or percutaneous transluminal coronary angioplasty within the last 3 months, Type 1 diabetes, elevated liver enzymes or active liver disease (alanine aminotransferase, aspartate aminotransferase  $\geq$  three-times the upper limit), creatine kinase (CK)  $\geq$  three-times the upper limit, if they consumed alcoholic drinks, and those taking concomitant lipid-lowering drugs, receiving immunosuppressant drugs,azole antifungal agents, or warfarin, or who were pregnant or breastfeeding.

The subjects were completely informed of the purpose, procedure and hazards of the trial and were free to leave the trial at any time. All patients signed informed written consent before being included in the study. The research protocol was approved by Tehran University of Medical Sciences (TUMS) Institutional Review Board.

Patients who met the eligibility criteria were randomly assigned to one of two treatment groups by a computer-generated table. Group I (n = 20) received atorvastatin 10 mg everyday and group II (n = 20) received atorvastatin 10 mg every other day. Patients were not receiving other lipid-lowering agents. The subjects were counseled about the importance of compliance to diet according to the NCEP step III diet, which was assessed regularly during the study period [20].

The primary end points of this study were changes in total cholesterol (TC) and LDL values. On the basis of a literature research of cholesterol-lowering clinical trials, a change in TC and LDL values over 10% was determined to be clinically significant [21–24]. Secondary end points included changes in HDL and TG values.

#### **Efficacy criteria**

The efficacy criterion was the change of LDL from baseline after an 8 week period. All patients were assessed at week 8 as to whether they met their LDL goal as defined by the NCEP ATP III guidelines [20].

#### **Laboratory measurements**

TC, HDL and TG were measured by enzymatic methods and LDL was calculated using Friedewald's formula [25].

#### **Safety, follow-up & monitoring**

Safety and tolerability were evaluated throughout the study on the basis of adverse events reporting, laboratory studies and physical findings. Complete blood count, serum chemistry, liver function tests, CK, fasting lipid profile, fasting blood glucose and HbA1c were performed at the baseline. The liver function tests, CK, fasting lipid profile, fasting blood glucose and HbA1c were repeated at the end of the study.

#### **Statistical analysis**

The statistical analysis was performed with the use of Stats Direct version 2.6.2. Continuous data are expressed as mean  $\pm$  standard error (SE). Statistical analysis was initially performed by Kolmogorov-Smirnov normality test. Baseline characteristics were compared between groups with the use of unpaired two-sample student's t-test for continuous data and with the use of Chi squared test for categorical data if applicable. A p-value of less than 0.05 was considered to be statistically significant.

#### **Results**

Of the 40 patients enrolled, 34 completed the 8-week study period (19 patients in the every day group and 15 patients in the alternate-day group). Six patients who did not complete the study were noncompliant during the treatment period, which was not due to adverse drug reactions.

As shown in Table 1, at the beginning of the study, the groups were similar with respect to age, sex, BMI, TC, LDL, HDL, TG and HbA1c.

At 8 weeks, the percentage change in mean LDL was reduced by 28 and 36% in the alternate-day and every day groups, respectively (p = 0.013; Table 2). Although there was an increase in HDL level at 8 weeks in every day group but an unexpected decrease in HDL in group 2 at 8 weeks was seen (Table 2).

No statistically significant difference was seen among groups in regard to total or percentage decrease in TC, LDL and TG at 8 weeks compared with baseline, while a significant difference in total and percentage change from baseline HDL between two groups were observed

**Table 1. Baseline patient characteristics.**

	Group I (n = 20)	Group II (n = 20)	p-value
Age (years)	53.45 ± 2.11	55.45 ± 1.74	NS
Sex	40% F, 60% M	45% F, 55% M	NS
BMI (kg/m <sup>2</sup> )	25.98 ± 0.71	25.87 ± 0.78	NS
TC (mg/dl)	252.2 ± 8.79	239.1 ± 5.95	NS
LDL (mg/dl)	153.7 ± 6.95	149.45 ± 4.62	NS
HDL (mg/dl)	45.6 ± 2.62	48.45 ± 2.03	NS
TG (mg/dl)	239.2 ± 19.4	185.2 ± 14.4	NS
HbA1c (%)	8.34 ± 0.23	7.98 ± 0.23	NS

F: Female; HbA1c: Hemoglobin A1c; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; M: Male; NS: Not significant; TC: Total cholesterol; TG: Triglycerides.

(Tables 2 & 3). Target LDL goal was met in 68% and 33% of the patients in the every-day and alternate-day groups, respectively.

Of 34 patients who finished the study, no patients had signs or symptoms of myopathy, none had significant elevation of liver enzymes or CK and both treatments were well tolerated.

### Discussion

This study showed that atorvastatin 10 mg administered every other day for 8 weeks was slightly less effective than 10 mg administered daily. The results also indicated that more patients achieved their LDL goal in the every day group than in the alternate-day group (68 vs 33%).

Several studies evaluated the efficacy of alternate-day atorvastatin in hypercholesterolemia [14–17]. In one study, 46 patients were divided into three groups; group 1 received atorvastatin 10 mg every day, group 2 received atorvastatin 10 mg every other day and group 3 received atorvastatin 20 mg every other day for 6 weeks. No statistically significant difference was observed between the three groups with regard to total or percentage decrease in TC and LDL

for 6 weeks compared with baseline. It indicated that alternate-day dosing of atorvastatin is an efficacious and safe alternative to daily dosing. The researchers concluded that this change in the prescribing pattern of atorvastatin may result in a significant cost reduction for consumers [14].

In another study, 60 patients with hypercholesterolemia, despite diet therapy, were enrolled into the study. They received atorvastatin 10 mg every other day for 8 weeks. The investigators concluded that in hypercholesterolemic patients, atorvastatin 10 mg administered every other day is safe and effective in lowering TC, TG, LDL with a slight increase in HDL [15]. Another comparative study of alternate-day dosing of atorvastatin and standard once-daily dosing in 44 Type 2 diabetics for 12 weeks showed that 57.6% of patients in the alternate-day group meet the target LDL concentration of less than 100 mg/dl. It has been revealed that alternate-day dosing of atorvastatin could be an effective and safe alternative to daily dosing in some Type 2 diabetic patients [16]. In another trial, comparative efficacy of alternate-day dosing of atorvastatin (atorvastatin 10 mg as an initial dose everyday or every other day and the dose was doubled if the goal was not reached) compared with the standard once-daily dose based on mean LDL reduction at 6 and 12 weeks. Although higher doses of atorvastatin were used on alternate days, the results suggested that the alternate-day administration of atorvastatin can produce a reduction in LDL comparable to that of daily administration in patients with hypercholesterolemia, and yet provide some cost savings [17].

**Table 2. Percent change from baseline in TC, TG, LDL and HDL after 8 weeks.**

	Group I	Group II	p-value
TC (%)	-27 ± 4	-22 ± 3	0.414
TG (%)	-10 ± 12	-3 ± 9	0.147
LDL (%)	-36 ± 3	-28 ± 4	0.013
HDL (%)	+16 ± 7	-6 ± 4	0.637

Group I received atorvastatin 10 mg everyday  
Group II received atorvastatin 10 mg every other day  
HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TC: Total cholesterol; TG: Triglycerides.

**Table 3. Change from baseline in TC, TG, LDL and HDL after 8 weeks.**

	Group I	Group II	p-value
TC (mg/dl)	-70 ± 10.37	-53.92 ± 7.04	0.228
TG (mg/dl)	-53.21 ± 24.73	-13.53 ± 17.42	0.199
LDL (mg/dl)	-56.05 ± 6.74	-42.27 ± 5.38	0.134
HDL (mg/dl)	+5.40 ± 2.9	-3.27 ± 2.02	0.021

Group I received atorvastatin 10 mg every day.

Group II received atorvastatin 10 mg every other day.

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TC: Total cholesterol; TG: Triglycerides.

Despite the aforementioned reports, the present study results do not support efficacy of alternate-day administration of atorvastatin. To explain this discrepancy, we think that the study period should be longer than 8 weeks until LDL target level is observed. Also, the initial dose of atorvastatin or its maintenance dose can be increased to reach the treatment target. In addition, using larger sample size may provide further information. The small sample size itself could be a reason for unexpected decrease in HDL level in patients in group II [17]. The issue of compliance with an every other day regimen should be also taken into account in patients requiring statin therapy.

Taking collectively, it is concluded that alternate-day administration of atorvastatin had not only lower efficacy on reduction of LDL, TC and TG but also decreases the beneficial HDL in diabetic Type 2 patients. A convincing conclusion remains to be reached by larger, randomized clinical trials.

### Future perspective

In contrast to many previously reported studies, the results of this study indicate that alternate-day administration of atorvastatin had not only lower efficacy on reduction of LDL, TC and TG but it also decreases the beneficial HDL in Type 2 diabetic patients. To explain this discrepancy, we believe that the study period should be longer than 8 weeks until LDL target level is observed. Also, the initial dose of atorvastatin or its maintenance dose can be increased to reach the treatment target. In addition, using larger sample size may provide further information. The issue of compliance with an every-other-day regimen should be also taken into account in patients requiring statin therapy. A convincing conclusion remains to be reached by larger randomized clinical trials.

### Financial disclosure

This study was supported by a grant from TUMS.

### Executive summary

- The aim of this study was to compare the efficacy of alternate-day dosing and once-daily dose regimens of atorvastatin for the reduction of low-density lipoprotein (LDL) in Type 2 diabetic patients using a prospective, randomized nonblinded controlled clinical trial.
- A total of 40 patients with Type 2 diabetes mellitus who met the inclusion criteria were randomly assigned to receive atorvastatin 10 mg in an every- or alternate-day dosing regimen and 34 patients correctly completed the study.
- After 8 weeks, LDL decreased by 28 and 36% in the alternate-day and every-day groups, respectively. The target LDL goal was maintained in 68 and 33% of the patients in the every-day and alternate-day groups, respectively.
- None of the 34 patients had significant elevation of liver enzymes or creatine kinase and no patients had signs or symptoms of myopathy.
- Alternate-day administration of atorvastatin resulted not only in lower efficacy on reduction of LDL, total cholesterol and triglyceride, but also decreased the beneficial high-density lipoprotein in Type 2 diabetic patients.
- A convincing conclusion remains to be reached by larger randomized clinical trials.

## Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

- Vijan S, Hayward RA: Pharmacologic lipid-lowering therapy in Type 2 diabetes mellitus: background paper for the American College of Physicians. *Ann. Intern. Med.* 140(8), 650–658 (2004).
- Rahimi R, Nikfar S, Larijani B, Abdollahi M: A review on the role of antioxidants in the management of diabetes and its complications. *Biomed. Pharmacother.* 59, 365–373 (2005).
- Reusch JE: Current concepts in insulin resistance, Type 2 diabetes mellitus, and the metabolic syndrome. *Am. J. Cardiol.* 90(5A), 19G–26G (2002).
- Powers AC: Diabetes mellitus: In: *Harrison's Principles of Internal Medicine*. Braunwald E, Fauci AS, Kasper DL *et al.* (Eds), 15<sup>th</sup> Edition. McGraw-Hill Professional, New York, NY, USA, 2109–2138 (2001).
- Pederson TR, Kjekshus J, Berg K *et al.*: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 344(8934), 1383–1389 (1994).
- Downs JR, Clearfield M, Weis S *et al.*: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 279, 1615–1622 (1998).
- Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo controlled trial. *Lancet* 360, 7–22 (2002).
- Marcus AO: Lipid disorders in patients with Type 2 diabetes: meeting the challenges of early, aggressive treatment. *Postgrad. Med.* 110(1), 111–123 (2001).
- Solano MP, Goldberg RB: Management of dyslipidemia in diabetes. *Cardiol. Rev.* 14(3), 125–135 (2006).
- Moon YS, Kashyap ML: Pharmacologic treatment of Type 2 diabetic dyslipidemia. *Pharmacotherapy* 24(12), 1692–1713 (2004).
- Heather RC, Robert DS: Daily dosing versus alternate-day dosing of Simvastatin in patients with hypercholesterolemia. *Pharmacotherapy* 22(9), 1110–1116 (2002).
- Rindone JP, Achacoso R, Bledsoe R: Effect of lovastatin administered every other day on serum low-density lipoprotein cholesterol >160 mg/dl. *Am. J. Cardiol.* 76, 312–313 (1995).
- Dennis VC, Britton ML, Sirmans SM, Letassy NA, Freeman DA: The use of alternate-day lovastatin in hypercholesterolemic men. *Ann. Pharmacother.* 31(6), 708–712 (1997).
- Jafari M, Ebrahimi R, Ahmadi-Kashani M, Balian H, Bashir M: Efficacy of alternate-day dosing versus daily dosing of atorvastatin. *J. Cardiovasc. Pharmacol. Ther.* 8(2), 123–126 (2003).
- **Showed that alternate-day dosing of atorvastatin is an efficacious and safe alternative to daily dosing.**
- Piamsomboon C, Laothavorn P, Saganwong S *et al.*: Efficacy and safety of atorvastatin 10 mg every other day in hypercholesterolemia. *J. Med. Assoc. Thai.* 85(3), 297–300 (2002).
- **Indicates that in hypercholesterolemic patients, atorvastatin 10 mg administered every other day is safe and effective in lowering total cholesterol, triglyceride, low-density lipoprotein and a slight increase in high-density lipoprotein.**
- Ferrer-García JC, Perez-Silvestre J, Martínez-Mir I, Herrera-Ballester A: Alternate-day dosing of atorvastatin: effects in treating Type 2 diabetic patients with dyslipidaemia. *Acta Diabetol.* 43(3), 75–78 (2006).
- **They concluded that alternate-day dosing of atorvastatin could be an effective and safe alternative to daily dosing in some Type 2 diabetic patients.**
- Matalaka MS, Ravnan MC, Deedwania PC: Is alternate daily dose of atorvastatin effective in treating patients with hyperlipidemia? The Alternate Day Versus Daily Dosing of Atorvastatin Study (ADDAS). *Am. Heart J.* 144(4), 674–677 (2002).
- **Revealed that the alternate-day administration of atorvastatin can produce a reduction in LDL comparable to that of daily administration in patients with hypercholesterolemia.**
- Iliff RD: Weekly versus daily dosing of atorvastatin. *J. Fam. Pract.* 51(4), 365–366 (2002).
- American Diabetes Association. Standards of medical care in diabetes – 2006. *Diabetes care* 29, S4–S42 (2006).
- Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 106(25), 3143–3421 (2002).
- Schectman G, Haitt J: Dose-response characteristics of cholesterol-lowering drug therapies: implications for treatment. *Ann. Intern. Med.* 125, 990–1000 (1996).
- Downs JR, Clearfield M, Weis S *et al.*: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. *JAMA* 279, 1615–1622 (1998).
- Frick MH, Elo O, Haapa K *et al.*: Helsinki Heart Study. *N. Engl. J. Med.* 317, 1237–1245 (1987).
- Hilleman DE, Heineman SM, Foral PA: Pharmacoeconomic assessment of HMG-CoA reductase inhibitor therapy: an analysis based on the CURVES study. *Pharmacotherapy* 20, 819–822 (2000).
- Friedewald WT, Levy RJ, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of preparative ultracentrifuge. *Clin. Chem.* 18, 499–502 (1972).