Efficacy and Safety of High-Dose Atorvastatin in Moderate-to-High Cardiovascular Risk Postmenopausal Korean Women with Dyslipidemia

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ABSTRACT

Objective: Postmenopausal women show a more atherogenic lipid profile and elevated cardiovascular risk compared to premenopausal women. The aim of this study was to investigate the efficacy and safety of high-dose atorvastatin on the improvement of the blood lipid profile of postmenopausal women in Korea.

Methods: This study is a prospective, open-label, single-arm clinical trial that was conducted in 3 teaching hospitals. Postmenopausal women with a moderate-to-high cardiovascular risk, according to guidelines from the Korean Society of Lipid & Atherosclerosis, were enrolled. Participants were administered 20 mg of atorvastatin daily for the first 8 weeks, and if the targeted low-density lipoprotein cholesterol (LDL-C) level was not achieved, the dose was increased to 40 mg for the second 8 weeks. The primary endpoint was percentage change of LDL-C from baseline after 16 weeks of drug administration.

Results: Forty-four women were enrolled, 28 of whom (75.6%) had diabetes mellitus. By the end of treatment period (16 weeks) all patients had achieved LDL-C target levels, with 33 (94.2%) of the participants achieving it after only 8 weeks of administration. After 16 weeks, LDL-C decreased by 45.8±16.7% (p<0.001) from the baseline, and total cholesterol (33.2±10.9%; p<0.001), triglyceride (24.2±37.5%; p=0.001), and apolipoprotein B (34.9±15.6%; p<0.001) also significantly decreased. Blood glucose and liver enzyme levels slightly increased, but none of the participants developed serious adverse events that would cause them to prematurely withdraw from the clinical trial.

Conclusion: 20 and 40 mg atorvastatin was effective and safe for treating dyslipidemia in postmenopausal Korean women with moderate-to-high cardiovascular risk.

Keywords: Postmenopause; Koreans; Dyslipidemia; Atorvastatin

INTRODUCTION

Statins, which are 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, have revolutionized today's cardiovascular management, as they markedly decrease blood cholesterol levels and effectively prevent atherosclerotic cardiovascular disease (CVD).
Author Contributions

Conceptualization: Shin HH; Formal analysis: Moon J, Yoo S, Koh G; Funding acquisition: Koh G, Shin HH; Investigation: Yoo S, Koh G, Min KW, Shin HH; Project administration: Shin HH; Writing - original draft: Moon J, Koh G; Writing - review & editing: Moon J, Koh G.

Multiple large-scale clinical trials have confirmed that statin-induced reduction of low-density lipoprotein cholesterol (LDL-C) has a log-linear relationship with CVD prevention effects, where a 1 mM (38.7 mg/dL) reduction of LDL-C lowers the incidence of cardiovascular events by 22%. Atorvastatin has a longer plasma half-life than other statins and is an effective inhibitor of HMG-CoA reductase, thereby substantially lowering blood cholesterol levels. Furthermore, owing to its tolerability, efficacy, and safety, and CVD preventative effects, it is currently one of the most widely used statins.

Reduction of LDL-C as a result of statin administration is proportional to the pre-administration concentration, so percentage reduction, as opposed to absolute reductions (mmol/L), is utilized as an indicator of statin efficacy. Intensity of statin therapy is divided into 3 efficacy categories: high-intensity that reduces LDL-C by more than 50%, moderate-intensity that reduces LDL-C by 49%–30%, and low-intensity that reduces LDL-C by less than 30%. The American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend high-intensity or moderate-intensity statin for patients with diabetes mellitus or intermediate-to-high risk. However, even low-dose statin therapy is known to significantly lower LDL-C in Asians, including Koreans, and some guidelines suggest administration of low-dose statin to Asians.

In general, women have low CVD risk, but as they reach menopause, when their blood estrogen levels decrease, their blood total cholesterol (TC) and LDL-C levels gradually increase, and postmenopausal women even have higher LDL-C levels than their male counterparts. Moreover, high-density lipoprotein cholesterol (HDL-C) concentration also slightly declines after menopause. Additionally, the incidence of coronary artery disease (CAD) is about 2–3 times higher after menopause. Therefore, treating dyslipidemia is critical for postmenopausal women with CVD or high cardiovascular risk. However, the main participants of past large-scale clinical trials on statins were men. Hence, more clinical trial data on the use of statin among postmenopausal women is needed.

Therefore, we have designed a prospective multicenter clinical trial to investigate the changes of blood lipid profile and adverse reactions of moderate-to-high intensity atorvastatin in postmenopausal Korean women at risk of CVD.

MATERIALS AND METHODS

1. Study subjects

Postmenopausal women aged 45 years or older, who had moderate-to-high CVD risk and whose blood LDL-C levels were higher than the target levels set by the second edition of the Korean Society of Lipid & Atherosclerosis (KSoLA) guidelines, were enrolled. Menopause was defined as bilateral oophorectomy, or at least 2 months of amenorrhea in an interval of 60 or more days in the past 12 months, or hysterectomy with follicle-stimulating hormone ≥40 IU/L and estradiol <50 pg/mL. CVD risk was classified based on the second edition of the KSoLA guideline, where individuals with 2 or more major risk factors excluding LDL-C was classified as the moderate-risk group and individuals with CAD, carotid artery disease, peripheral vascular disease, abdominal aneurysm, or diabetes mellitus as the high-risk group. LDL-C target was below 130 mg/dL and 100 mg/dL for the moderate-risk and high-risk groups, respectively.
Exclusion criteria included the following: history of acute myocardial infarction or congestive heart failure within 3 months prior to clinical trial participation, body mass index (BMI) <18.5 or >30 kg/m², liver enzyme level 2-fold higher than the normal upper limit, creatine kinase level 2-fold higher than the normal upper limit (excluding cases due to trauma, intramuscular injection, and exercise), creatinine levels >2.5 mg/dL, fasting triglyceride (TG) levels ≥400 mg/dL, hemoglobin A1c (HbA1c) ≥11%, or fasting glucose ≥200 mg/dL, risk factors of rhabdomyolysis, and if undergoing hormone replacement therapy, use of another hyperlipidemia medication within 4 weeks of the study drug administration; or inability to participate in clinical trial as determined by the investigator.

2. Study design
This study is a 16-week prospective, open-label, single-arm clinical trial conducted at 3 teaching hospitals in Korea. This clinical trial was approved by the Institutional Review Board (IRB No. JEJUNUH 2010-32) at each hospital. Written informed consent was obtained from all participants, and we adhered to the Declaration of Helsinki. This clinical trial was conducted at Cheil General Hospital and Eulji Hospital in Seoul and Jeju National University Hospital from November 2010 to December 2011.

Eligible participants, postmenopausal women with a moderate-to-high cardiovascular risk, were administered atorvastatin for a total of 16 weeks. First, atorvastatin (20 mg) was administered daily for the first 8 weeks. If the LDL-C levels measured after 8 weeks reached the target, the same dose was continued for another 8 weeks. If the target was not achieved, the dose was increased to 40 mg for another 8 weeks. LDL-C target was set to <130 mg/dL for the moderate-risk group and <100 mg/dL for the high-risk group, per KSoLA guidelines. Use of any drugs that may impact the results was prohibited during the study period.

3. Study assessments
Participants’ demographics and disease history were taken at the baseline visit, and drug history, anthropometric parameters, study drug adherence, vital signs, abnormal symptoms, and adverse reactions were assessed at the baseline visit and weeks 8 and 16 of drug administration. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, creatine kinase, total bilirubin, fasting glucose, HbA1c, high sensitivity C-reactive protein (hsCRP), TC, TG, HDL-C, LDL-C, apolipoprotein B (apoB), and apolipoprotein A1 (apoAI) were measured at the baseline visit and at weeks 8 and 16 of drug administration. These lab tests were conducted on blood samples taken after at least 12 hours of fasting, at each institution. LDL-C was measured directly without using an equation for calculation.

The primary endpoint was percentage change of LDL-C from baseline after 16 weeks of atorvastatin administration. The secondary endpoints were percentage changes of TC, TG, HDL-C, apoB, apoA-I, and hsCRP.

4. Statistical analyses
This clinical trial was a pilot study, with a target sample size of 45 (15 from each institution) without statistical computation.

Efficacy analysis was performed on full analysis (FA) and per protocol (PP) sets, and analysis of baseline characteristics and safety were performed on a safety set. The FA set consisted of participants who met the inclusion/exclusion criteria, and had taken at least one dose of the study drug after prescription and underwent at least one efficacy assessment. In the PP set,
the following cases were excluded from the FA set: violation of inclusion/exclusion criteria, use of prohibited drug during the study period, omission of tests for efficacy parameters, medication adherence <80%. The safety set consisted of participants who have taken at least one dose of the study drug and underwent at least one safety-related interview.

Statistical significance on the changes of efficacy parameters after study drug administration was analyzed with paired $t$-test (parametric test) or Wilcoxon’s signed-rank test (non-parametric test).

**RESULTS**

1. **Patient disposition**

A total of 58 participants were selected, 44 of whom provided written consent to participate. However, 7 were excluded per the inclusion/exclusion criteria, so 37 participants were administered the study drug (safety set). Of them, 35 participants, after excluding 2 participants with omitted efficacy parameters since study drug administration, were included in the FA set; and 31 of these participants, after excluding 4 participants with a medication adherence of below 80% or omitted baseline efficacy parameters, were included in the PP set (Fig. 1).

2. **Baseline characteristics**

All participants were postmenopausal women, and the cause of menopause was natural for the majority of participants. The mean BMI was 25.3 and the mean waist circumference was 84.7 cm. A total of 75.6% of the participants had diabetes mellitus, a condition for the high

![Patient disposition diagram](https://e-jla.org)

**Fig. 1.** Patient disposition.

FA, full analysis; PP, per protocol.
CVD risk group. The highest percentage of participants had 2 of 5 major CVD risk factors (51.3%), followed by participants with one major risk factor (21.6%), participants with no risk factor (24.3%), and participants with 3 risk factors (2.7%; Table 1).

3. Efficacy analysis

After 8 weeks of atorvastatin (20 mg), 33 (94.2%) participants reached the LDL-C target, and these participants maintained the same daily dose for the following 8 weeks. Two participants who did not reach the LDL-C target after the first 8 weeks took an increased dose (40 mg) in the second 8 weeks, after which they reached the LDL-C target. In the end, all participants achieved the LDL-C target after 16 weeks of atorvastatin administration (Table 2).

In the FA set, the percent change of LDL-C from baseline after 16 weeks of atorvastatin administration, the primary endpoint of this study, was −45.8%, showing a statistically significant reduction of LDL-C (p<0.001). TC, TG, and apoB were also significantly reduced by 33.2%, 24.2%, and 34.9%, respectively. However, HDL-C, apoAI, and hsCRP were not significantly changed (Table 3). The results of analyses on the PP set were similar to that of the FA set (Supplementary Table 1).

### Table 1. Clinical and laboratory characteristics of the study subjects (safety set)

| Variable                                | Value          |
|-----------------------------------------|----------------|
| No.                                     | 37             |
| Age (yr)                                | 61.9±7.0       |
| Female, No. (%)                         | 37 (100)       |
| Height (cm)                             | 154±3.5        |
| Body weight (kg)                        | 60.4±6.9       |
| Body mass index (kg/cm²)                | 25.3±2.2       |
| Waist circumference (cm)                | 84.7±6.7       |
| Systolic BP (mmHg)                      | 125±12.7       |
| Diastolic BP (mmHg)                     | 75.8±12.3      |
| Diabetes mellitus, No. (%)              | 28 (75.6)      |
| Hypertension, No. (%)                   | 24 (64.8)      |
| Smoking, No. (%)                        | 1 (2.7)        |
| Family history of premature CAD, No. (%)| 0 (0.0)        |
| No. of major risk factors*              | 4 (10.8)       |
| 1                                       | 5 (13.5)       |
| 2                                       | 8 (21.6)       |
| 3                                       | 19 (51.3)      |
| 4                                       | 1 (2.7)        |

| Type of menopause                               | Value          |
|------------------------------------------------|----------------|
| Natural menopause                              | 31 (83.7)      |
| Bilateral oophorectomy                         | 4 (10.8)       |
| Unilateral oophorectomy                        | 2 (5.4)        |

Data are expressed as mean±standard deviation or frequencies (%).

BP, blood pressure; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol.

*1) Smoking, 2) Hypertension (BP ≥140/90 mmHg or antihypertensive medication), 3) Low HDL-C (<40 mg/dL), 4) Family history of premature CAD, and 5) Age (male ≥45, female ≥55 years); High HDL-C (≥60 mg/dL) is considered as a protective factor, and one factor is excluded from the total number of risk factors.

### Table 2. Percentage of subjects who reached the low-density lipoprotein cholesterol goals* at 8 and 16 weeks of treatment (full analysis set)

| Duration (wk) | Treatment (n=35) |
|---------------|------------------|
| 8             | 33 (94.2)        |
| 16            | 35 (100.0)       |

Value are given as a number (%).

*Subjects with diabetes <100 mg/dL, subjects with 2 or more major risk factors <130 mg/dL.
After 16 weeks of atorvastatin administration, the mean fasting blood glucose was elevated by 9.5 mg/dL, with no significant changes in HbA1c. Creatinine, total bilirubin, and creatine kinase were not significantly changed. AST and ALT increased by 2.2 and 4.2 U/L, respectively, but no participants had more than 3-fold increase from the normal upper limit (Table 4). Among the 37 participants who received atorvastatin administration, a total of 9 participants had abnormal symptoms: respiratory (n=3), digestive (n=2), musculoskeletal (n=2), urological (n=2), or eye (n=1). Both musculoskeletal symptoms were fractures, and none of the participants complained of myalgia. Most of these abnormal symptoms were not related to atorvastatin, and only one case of mild indigestion was determined to be possibly related (Table 5). None of the participants were prematurely withdrawn from the clinical trial for adverse reactions or abnormal symptoms.

### Table 3. Changes in efficacy measures from baseline to week 16 (full analysis set)

| Variable             | Baseline (wk 0) (n=35) | Wk 16 (n=35) | Change from baseline (%) | p value |
|----------------------|------------------------|--------------|--------------------------|---------|
| Total cholesterol (mg/dL) | 229.6±27.9            | 153.3±31.0   | −33.2±10.9               | <0.001* |
| Triglyceride (mg/dL)  | 147.7±75.0             | 116.1±60.7   | −34.2±37.5               | 0.001*  |
| HDL-C (mg/dL)        | 57.1±14.2              | 56.4±13.8    | −1.2±15.3                | 0.642*  |
| LDL-C (mg/dL)        | 146.7±25.5             | 79.4±24.7    | −45.8±16.7               | <0.001* |
| apoB (mg/dL)         | 113.0±19.6             | 73.5±19.5    | −34.9±15.6               | <0.001* |
| apoAI (mg/dL)        | 150.8±22.9             | 150.8±23.3   | 0.0±11.8                 | 0.999*  |
| hsCRP (mg/L)         | 0.1±0.1                | 0.1±0.2      | 28.1±206.7               | 0.426†  |

Data are shown as mean±standard deviation.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; apoB, apolipoprotein B; apoAI, apolipoprotein AI; hsCRP, high sensitivity C-reactive protein.
*Paired t-test; †Wilcoxon's signed-rank test.

### Table 4. Summary of adverse events reported during the treatment period (safety set)

| Number (%) of patients | Treatment (n=37) | Attribution       |
|------------------------|------------------|-------------------|
| Respiratory system disorders | 3 (8.1)          | Unlikely, unrelated |
| Upper respiratory infection | 2 (5.4)          | Unrelated         |
| Common cold            | 1 (2.7)          | Unlikely          |
| Gastro-intestinal system disorders | 2 (5.4)         | Possible          |
| Dyspepsia               | 1 (2.7)          | Likely            |
| Gastritis               | 1 (2.7)          | Unlikely          |
| Musculo-skeletal system disorders | 2 (5.4) | Unrelated          |
| Fracture lower limb     | 2 (5.4)          | Unrelated         |
| Urinary system disorders | 1 (2.7)          | Unrelated         |
| Haematuria              | 1 (2.7)          | Unrelated         |
| Vision disorders        | 1 (2.7)          | Unrelated         |
| Dry eyes                | 1 (2.7)          | Unrelated         |
| Total                   | 9 (24.3)         |                   |

Value are given as a number (%).

### Table 5. Changes in clinical laboratory parameters from baseline to week 16 (full analysis set)

| Variable             | Baseline (wk 0) (n=35) | Wk 16 (n=35) | Δ, Mean (95% CI) | p value |
|----------------------|------------------------|--------------|------------------|---------|
| Glucose (mg/dL)      | 117.1±24.7             | 126.6±34.3   | 9.5 (1.5, 17.4)  | 0.020*  |
| HbA1c (%)            | 6.6±0.7                | 6.8±1.1      | 0.2 (−0.1, 0.3)  | 0.303*  |
| Creatinine (mg/dL)   | 0.8±0.1                | 0.8±0.2      | 0.0 (−0.0, 0.0)  | 0.162*  |
| Total bilirubin (mg/dL) | 0.6±0.2            | 0.7±0.3      | 0.1 (0.0, 0.1)   | 0.050*  |
| AST (IU/L)           | 23.8±8.5               | 26.0±8.9     | 2.2 (0.4, 4.1)   | 0.016*  |
| ALT (IU/L)           | 22.5±11.6              | 26.8±14.8    | 4.3 (1.3, 7.3)   | 0.005*  |
| Creatine kinase (IU/L) | 90.2±47.8            | 97.2±52.6    | 7.0 (2.3, 21.4)  | 0.367†  |

Data are expressed as mean±standard deviation.
*Paired t-test; †Wilcoxon's signed-rank test.
HbA1c, hemoglobin A1c; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
DISCUSSION

According to the AHA/ACC guideline, the dosages of atorvastatin (20 or 40 mg) used in our study are those recommended for moderate- and high-intensity statin therapies, respectively, which were presumed to reduce LDL-C by 30–49 and >50%, respectively. Most of our participants were administered a moderate-intensity dosage (20 mg) for 16 weeks, and only 2 participants (5.8%) received an elevated dose (40 mg) during the second 8 weeks. Most previous clinical trials of atorvastatin in Koreans used a 10 mg dose, which reduced LDL-C levels by 33.3%–41.8%. In the present study, where most participants were administered 20 mg, LDL-C was reduced by 45.8%, suggesting that atorvastatin reduces LDL-C dose-dependently in Koreans, and a daily dose of 20 mg is more effective than 10 mg.

TC, TG, and apoB, the secondary endpoints of this clinical trial, decreased by 33.2%, 24.2%, and 34.9%, respectively, which are not markedly different from those of other atorvastatin studies. However, in the present study, HDL-C and apoAI did not significantly change (~1.2% and 0.0%, respectively) which differs from the significant elevation of HDL-C commonly observed in general statin studies. Although the exact reason is unknown, we speculate that changes of HDL-C caused by statin may vary according to the drug ingredients and patient’s race. The majority of atorvastatin studies in Koreans support this hypothesis, as they found that HDL-C tended to decrease after drug administration. High sensitivity CRP, another secondary endpoint, did not significantly change in our study, presumably because participants’ baseline hsCRP levels were low. Exclusion of participants with recent diagnosis of CVD is likely the cause of low baseline hsCRP. In fact, the mean baseline hsCRP in participants of the JUPITER trial, a study that objectively proved the effects of statins for reducing hsCRP and CVD risk, was 4.3 mg/L, which is over 3-fold higher than that of our study.

Statins are known to increase blood glucose and diabetes mellitus risk. In the present study, fasting blood glucose was significantly elevated after 16 weeks of atorvastatin. However, the mean elevation of blood glucose was not large, at 9.5 mg/dL, and there were no significant changes in HbA1c. According to the UK Prospective Diabetes Study, a 1% reduction of HbA1c leads to 14% reduction of CAD, and according to the meta-analysis by Baigent et al., a 38.7 mg/dL reduction of LDL-C can lower CAD by 22%. Therefore, the cardiovascular benefit of 45.8% reduction of LDL-C (77.1 mg/dL) in this study far outweighs the harm from a 9.5 mg/dL elevation of fasting blood glucose. However, the impact of high-dose statins on glycemic control or new-onset diabetes cannot be neglected, and large-scale, long-term clinical trials are required to substantiate this further. In the present study, liver enzyme levels were mildly elevated after atorvastatin administration. However, meaningful elevation of liver enzymes by statins is defined as greater than 3-fold increase from the upper normal limit, which did not occur in the present study. Statin-induced myalgia is a highly common side effect, with an incidence of about 5%–20%, but no participants complained of myalgia. However, this may be a result of the small sample size or neglect of the mild symptoms. The only abnormal symptom related to the atorvastatin in this study was indigestion, which was observed in one participant, and such gastrointestinal disturbance has been identified as the most common adverse reaction of atorvastatin by multiple clinical trials.

This study has quite a few limitations. First, there was no control group. Therefore, we cannot eliminate the possibility that a change of lifestyle during the study period may have led to the improvements of blood lipid levels. Secondly, only 2 participants (5.8%) were given 40 mg of
atorvastatin. As the vast majority of participants (94.2%) were given a daily dose of 20 mg, we cannot assess the efficacy and safety of high-intensity therapy (40 mg atorvastatin). Thirdly, the sample size was small, niche, and not properly calculated. To efficiently proceed with the clinical trial, we planned to recruit 45 participants. One of the reasons behind the absence of significant changes in HDL-C and hsCRP in the present study may the small sample size. This study was only conducted on postmenopausal women, so it may be inappropriate to generalize the findings of this clinical trial to all patients with dyslipidemia in Korea. As this was a pilot study and there was no preliminary study data, sample size could not be calculated using an appropriate statistical technique. In addition, we did not use a low-dose atorvastatin group. This study only involved a single atorvastatin group (20/40 mg), therefore, we cannot definitively conclude that high-dose atorvastatin administration is more effective than or equally safe as 10 mg of atorvastatin. Lastly, the incidence of CVD was not measured. A clinical trial that overcomes the above shortcomings is needed to objectively assess the effects, safety, and CVD preventative effects of high-dose atorvastatin in Koreans.

In the present study, 16 weeks of atorvastatin (20 or 40 mg) lowered LDL-C, the primary endpoint, by an average of 45.8% from baseline, and all participants (Korean postmenopausal women with moderate-to-high cardiovascular risk) reached the LDL-C target. TC, TG, and apoB were significantly reduced from baseline by 33.2%, 24.2%, and 34.9%, respectively, and abnormal symptoms or adverse reactions were not observed. To the best of our knowledge, this study is the first prospective clinical trial assessing the efficacy and safety of atorvastatin in postmenopausal Korean women. Based on the findings of this study, we can conclude that moderate- or high-intensity atorvastatin therapy safely and markedly improves blood lipid profiles of postmenopausal Korean women, and we can predict that it will suppress the onset of CVD related to dyslipidemia.

**SUPPLEMENTARY MATERIAL**

**Supplementary Table 1**
Changes in efficacy measures from baseline to week 16 (per protocol set)

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**REFERENCES**

1. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-1278.

2. Poli A. Atorvastatin: pharmacological characteristics and lipid-lowering effects. Drugs 2007;67 Suppl 1:3-15.

3. Black DM, Bakker-Arkema RG, Nawrocki JW. An overview of the clinical safety profile of atorvastatin (lipitor), a new HMG-CoA reductase inhibitor. Arch Intern Med 1998;158:577-584.

4. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). Am J Cardiol 1998;81:582-587.
5. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549-559.

6. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau IL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495-1504.

7. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SI, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685-696.

8. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149-1158.

9. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003;326:1423.

10. Grundy SM, Stone NJ, Bailey AL, Beam C, Bircher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol 2019;73:e285-e350.

11. Stone NJ, Robinson JG, Lichtenstein AH, Baier Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol 2014;63:2889-2934.

12. Kobayashi T, Homma Y. Effects of low-dose pravastatin on plasma levels of lipids and apolipoproteins in Japanese type II hyperlipoproteinaemic subjects with apolipoprotein E phenotype E3/2, E3/3, and E4/3. J Clin Pharmacol 2001;41:1055-1058.

13. Kong SH, Koo BK, Moon MK. Efficacy of moderate intensity statins in the treatment of dyslipidemia in Korean patients with type 2 diabetes mellitus. Diabetes Metab J 2017;41:23-30.

14. Kwun JE, Kim J, Hyeon S, Won H, Shin SY, Lee KJ, et al. Cholesterol lowering effects of low-dose statins in Korean patients. J Lipid Atheroscler 2014;3:21-28.

15. Matsuzawa Y, Kita T, Mabuchi H, Matsuzaki M, Nakaya N, Oikawa S, et al. Sustained reduction of serum cholesterol in low-dose 6-year simvastatin treatment with minimum side effects in 51,321 Japanese hypercholesterolemie patients. Circ J 2003;67:267-294.

16. Wu CC, Sy R, Tanphaichitr V, Hin AT, Suyono S, Lee YT. Comparing the efficacy and safety of atorvastatin and simvastatin in Asians with elevated low-density lipoprotein-cholesterol—a multinational, multicenter, double-blind study. J Formos Med Assoc 2002;101:478-487.

17. Arai H, Sasaki J, Teramoto T. Comment on the new guidelines in USA by the JAS guidelines committee. J Atheroscler Thromb 2014;21:79-81.

18. McPherson R, Frohlich J, Fodor G, Genest J; Canadian Cardiovascular Society. Canadian Cardiovascular Society position statement—recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. Can J Cardiol 2006;22:913-927.

19. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. N Engl J Med 1989;321:641-646.

20. Wu ZY, Wu XK, Zhang YW. Relationship of menopausal status and sex hormones to serum lipids and blood pressure. Int J Epidemiol 1990;19:297-302.
21. Bush TL. The epidemiology of cardiovascular disease in postmenopausal women. Ann N Y Acad Sci 1990;592:263-271.

22. Kannel WB. Metabolic risk factors for coronary heart disease in women: perspective from the Framingham Study. Am Heart J 1987;114:413-419.

23. Davidson MH, Maki KC, Karp SK, Ingram KA. Management of hypercholesterolaemia in postmenopausal women. Drugs Aging 2002;19:169-178.

24. Son JJ, Chin SO, Woo JT. Treatment guidelines for dyslipidemia: summary of the expanded second version. J Lipid Atheroscler 2012;1:45-59.

25. Koh JH, Shin JH, Kim HS, Takh SJ, Choi BI, Kim D, et al. Efficacy and safety of atorvastatin in patients with hypercholesterolemia. Korean Circ J 1999;29:928-936.

26. Park JS, Kim YJ, Choi YJ, Kim YN, Hong TJ, Kim DS, et al. Comparative study of low doses of rosuvastatin and atorvastatin on lipid and glycemic control in patients with metabolic syndrome and hypercholesterolemia. Korean J Intern Med 2010;25:27-35.

27. Park SY, Lee MK, Lim SC. Comparative drug evaluation of atorvastatin versus rosuvastatin in pharmacotherapy of Korean patients with dyslipidemia. Biomol Ther (Seoul) 2008;16:54-60.

28. Semenkovich CF, Goldberg AC, Goldberg II. Disorders of lipid metabolism. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. Williams textbook of endocrinology. 13th ed. Philadelphia (PA): Saunders; 2016. p.1660-1700.

29. John SS, Park JH, Chung HI, Son JC, Kim KM, Kim BT. The effect of atorvastatin on serum lipid levels among patients with hypercholesterolemia. J Korean Acad Fam Med 2004;25:46-51.

30. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195-2207.

31. Stratton IM, Adler AI, Neil HA, Matthews DR, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-412.

32. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2016;37:2999-3058.