Original Article

A Comparison of Effectiveness of Crystalline and Amorphous Atorvastatin

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Background: Atorvastatin is a widely used statin, of which there are two available polymorphs: crystalline (original) and amorphous (generic). Pharmacological studies showed the similarity between both forms. However, the lipid-lowering effectiveness of the amorphous form was still uncertain.

Objective: To compare the effectiveness of crystalline and amorphous form of atorvastatin.

Materials and Methods: The authors conducted an observational cross-sectional analytic study by retrospectively collecting data from January 1, 2016 to December 31, 2017 of the patients at Queen Sirikit Heart Center of the Northeast where the original regimen of crystalline atorvastatin had been replaced by the amorphous atorvastatin at the same dose. Patients must have been prescribed each form of atorvastatin for at least six weeks. The lipid profiles taken at the closest to the switching point (before and after) were used. The primary outcome was changes in low-density lipoprotein (LDL) levels. The secondary outcomes were changes in total cholesterol (TC), triglyceride (TG), and high-density lipoprotein (HDL) levels, as well as a comparison of LDL levels in patients whose tablets were split.

Results: Eight hundred twenty-five patients were included in the present study. The mean age was 63.7±9.9 years. Five hundred sixty-eight patients (68.8%) were male, and 736 (89.2%) were treated as secondary prevention. The mean LDL levels during crystalline and amorphous atorvastatin use were 92.4±39.0 and 91.8±41.0 mg/dL, respectively (mean difference –0.6; 95% confidence interval [CI], –2.2 to 1.0; p=0.460). The mean TC, TG, and HDL levels during crystalline and amorphous form use were 153.1±43.3 and 152.0±48.6 mg/dL (p=0.400), 153.4±129.0 and 155.0±148.3 (p=0.740), 43.6±11.9, and 44.4±12.0 (p=0.004), respectively. Among the patients who had tablet splitting, the mean LDL levels during crystalline and amorphous atorvastatin use were 89.2±28.3 and 91.0±30.8 mg/dL, respectively (p=0.279). Side effects were recorded in nine patients, one of which was rhabdomyolysis.

Conclusion: The effectiveness of amorphous atorvastatin at lowering lipids was comparable to that of atorvastatin in its crystalline form, and patients were generally able to tolerate amorphous atorvastatin.

Keywords: Atorvastatin, Crystalline, Amorphous, Lipid-lowering, Low-density lipoprotein

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Hypercholesterolemia is a common health problem that results in atherosclerosis, which is a precursor of major cardiovascular diseases such as coronary heart disease, cerebrovascular disease, and peripheral arterial disease. As numerous studies have found that lowering cholesterol reduces the risk of coronary heart disease[1], the 2016 European guideline in cardiovascular prevention[2] and the 2018 ACC and AHA guideline on the management of blood cholesterol[3], recommended treating high cholesterol level in both primary and secondary preventions.

Atorvastatin is a commonly used statin that inhibits the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme that reduces low-density lipoprotein (LDL) cholesterol production in the liver. Currently, there are two forms of atorvastatin available, classified by their polymorphs: crystalline (original brand) and amorphous (generic brand).

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The crystalline form of atorvastatin has a more exact shape and is more stable, as it has a highly organized molecular structure. In contrast, the amorphous form has uncertain shape and is less stable due to its molecular structure being less organized[4]. This difference raises concerns about the effectiveness of the amorphous atorvastatin in terms of LDL lowering effect as well as its potential side effects. These concerns were supported by a study from Japan that found that amorphous atorvastatin was 50% less effective in reducing LDL cholesterol levels than crystalline atorvastatin[5]. However, bioavailability studies showed no significant difference in pharmacokinetic and pharmacodynamics parameters between the two forms[6-8].

Due to the limitation of the health insurance, many patients at Queen Sirikit Heart Center of the Northeast in Khon Kaen, Thailand have switched their medications from crystalline atorvastatin (Xarator®) to amorphous atorvastatin (Atorvastatin Sandoz®). Thus, the authors aimed to compare the effectiveness of amorphous atorvastatin to that of crystalline atorvastatin in reducing blood lipid levels in these patients.

Materials and Methods

Study design

The present study was an observational cross-sectional analysis to assess the effectiveness in lipid-lowering effect between amorphous and crystalline atorvastatin in the same patients at Khon Kaen University's Queen Sirikit Heart Center of the Northeast in Thailand from January 1, 2016 to December 31, 2017.

Study population

Eligible patients were those 18 years or older who received crystalline atorvastatin and were later switched to amorphous atorvastatin. The patients must have been prescribed each form for at least six weeks. The main exclusion criteria were receiving only one form of atorvastatin or being titrated other lipid-lowering agents such as niacin, fibrate, ezetimibe, and bile acid sequestrants concomitantly during the study period. In addition, patients who received medications known to interact with atorvastatin that might affect atorvastatin dosage or serum lipid levels, such as diltiazem, verapamil, and amiodarone, or received diabetic medications that alter serum lipid levels, such as the glucagon-like peptide-1 (GLP-1) receptor agonists and thiazolidinedione were excluded.

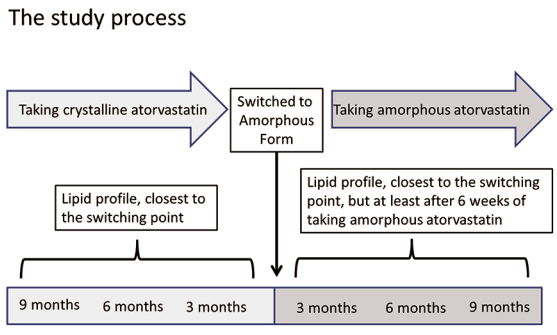

Figure 1. The study protocol.

Study procedures and outcomes

The authors retrospectively collected data in patients whose original regimen of crystalline atorvastatin had been replaced by amorphous atorvastatin at the same dose. The lipid profiles examined closest to the switching point (before and after) were used. The primary outcome was changes in LDL levels. The secondary outcomes were changes in total cholesterol (TC), triglyceride (TG), and high-density lipoprotein (HDL) levels, as well as comparison of LDL levels in patients who had tablet splitting. The study protocol is shown in Figure 1.

Statistical analysis

The required sample size for the present study was calculated to be 568 patients based on the results of the authors' local pilot data. The power of the present study was 0.8, the alpha error was 0.05, and the delta was 2. All continuous variables were described as mean and standard deviation (SD), while categorical variables were shown as frequency and percentage. The primary outcome (changes in LDL levels) and the secondary outcomes (changes in TC, TG, and HDL levels and changes in LDL levels in patients who had tablet splitting) were analyzed using a paired t-test in which a p-value of less than 0.05 was considered statistically significant. In addition, post-hoc analyses among interesting subgroups in terms of difference of the mean LDL were performed. IBM SPSS Statistics, version 22 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

The Ethics Committee of Khon Kaen University approved this study protocol on 13 March 2019 (reference number: HE611070).

Results

Study patients

A search of the hospital database revealed 2,123

Table 1. Baseline characteristics

Characteristics	Patients (n=825) n (%)
Age (years); mean±SD	63.73±9.92
Sex: male	568 (68.8)
Body mass index (kg/m^2); mean±SD	24.40±4.28
Smoking	115 (13.9)
Comorbidities	
Hypertension	395 (47.8)
Diabetes mellitus	305 (36.9)
HbA1C (%); mean±SD	7.77±1.65
Stroke	21 (2.5)
Peripheral arterial disease	29 (3.5)
Coronary artery disease	707 (85.7)
Post myocardial infarction	569 (80.4)
Chronic stable angina	138 (19.5)
Percutaneous coronary intervention	434 (61.3)
Coronary artery bypass graft	247 (34.9)
Chronic kidney disease ≥ stage 3	254 (30.7)
• Creatinine clearance ≥ 30 mL/minute	218 (85.8)
• Creatinine clearance <30 mL/minute	36 (14.1)
Indication	
Primary prevention	89 (10.7)
Secondary prevention	736 (89.2)
Medications	
Atorvastatin 20 mg	114 (13.8)
Atorvastatin 40 mg	607 (73.5)
Atorvastatin 60 mg	25 (3)
Atorvastatin 80 mg	78 (9.4)
Non-statin therapy (niacin, fibrate, ezetimibe, bile acid sequestrants)	60 (7.2)
Antihypertensive drug (verapamil, diltiazem)	14 (1.6)
Antiarrhythmic drug (amiodarone)	5 (0.6)
Hypoglycemic drug (GLP-1 receptor agonist, thiazolidinedione)	36 (4.3)
Lipid profiles (mg/dL); mean±SD	
Total cholesterol	153.06±43.30
Triglyceride	153.36±128.93
HDL	43.55±11.95
LDL	92.42±38.86

SD=standard deviation; GLP-1=glucagon-like peptide-1; HDL=high-density lipoprotein; LDL=low-density lipoprotein

patients receiving amorphous atorvastatin during the study period. Furthermore, 1,021 had been switched from crystalline atorvastatin. Of these patients, 825 met the inclusion criteria. Baseline characteristics

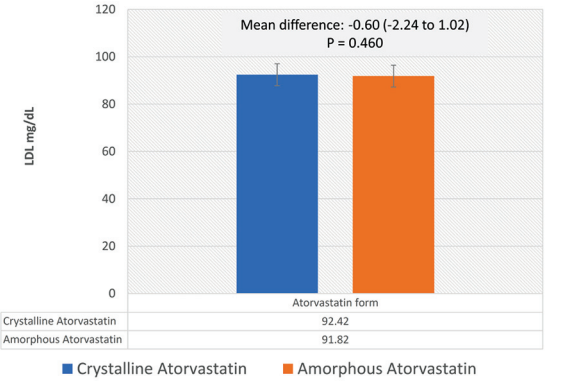

Figure 2. The primary outcome: mean LDL levels before and after switching to amorphous atorvastatin.

of the study population are shown in Table 1. The mean age was 63.7±9.9 years. Five hundred sixty-eight patients (68.8%) were male, 395 (47.8%) had hypertension, 305 (36.9%) had diabetes mellitus, and 254 (30.7%) had chronic kidney disease (CKD) stage 3 or higher. Seven hundred thirty-six patients (89.2%) took statin as secondary prevention, while only 89 (10.7%) were treated as primary prevention. In patients being treated as secondary prevention, coronary artery disease was the most common indication (96.0%). Some of the patients had received other medications that altered atorvastatin efficacy such as fibrate (7.2%), diltiazem or verapamil (1.6%), amiodarone (0.6%), and thiazolidinedione (4.3%). The average time of lipid profile examination was 77 days before and 153 days after the switching point. Baseline mean TC, TG, HDL, and LDL before switching were 153.06±43.30, 153.36±128.93, 43.55±11.95, and 92.42±38.86, respectively.

Primary outcome

The mean LDL levels during crystalline and amorphous atorvastatin administration were 92.4±39.0 and 91.8±41.0 mg/dL, respectively. The mean difference was –0.60 mg/dL; 95% confidence interval (CI) –2.24 to 1.02; p=0.460, as shown in Figure 2.

Secondary outcomes

The secondary outcomes are shown in Figure 3. The mean TC, TG, and HDL levels during crystalline and amorphous atorvastatin administration were 153.1±43.3 and 152.0±48.6 mg/dL (mean difference was –1.07 mg/dL; 95% CI –3.59 to 1.45; p=0.400), 153.4±129.0 and 155.0±148.3 mg/dL (mean difference was 1.59 mg/dL; 95% CI –7.91 to 11.10; p=0.740),

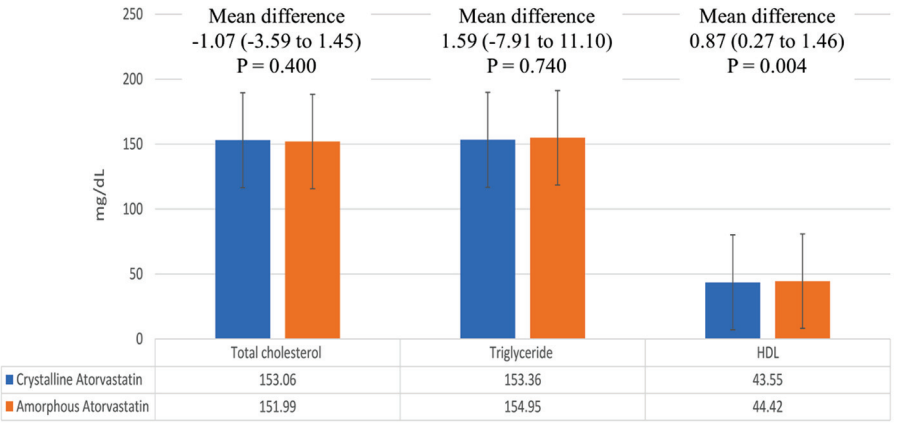

Figure 3. The secondary outcomes: mean total cholesterol, triglyceride, and HDL levels before and after switching to amorphous atorvastatin.

Table 2. The effect of tablet splitting during crystalline form and amorphous form of atorvastatin on LDL levels

	LDL during crystalline atorvastatin administration Mean±SD	LDL during amorphous atorvastatin administration Mean±SD	p-value
Tablet splitting (n=140)	89.17±28.32	90.95±30.80	0.279
Intact tablet (n=685)	93.09±40.66	91.99±42.77	0.247

SD=standard deviation; LDL=low-density lipoprotein

43.6±11.9 and 44.4±12.0 mg/dL (mean difference was 0.87 mg/dL; 95% CI 0.27 to 1.46; p=0.004), respectively. Among the patients whose tablets were split, the mean LDL levels during the amorphous atorvastatin administration did not significantly differ from those during the crystalline atorvastatin administration (p=0.279), as shown in Table 2.

Subgroup analysis

Major subgroup analyses were performed based on several characteristics of treatment groups (primary and secondary prevention), age, gender, body mass index (BMI), smoking status, diabetes mellitus, previous stroke, CKD, and HbA1C. There was no significant difference in mean LDL cholesterol during the crystalline atorvastatin administration and after switching to the amorphous atorvastatin in any of the subgroups, as shown in Figure 4.

Safety and adverse events

During the study period, nine patients experienced adverse events (six patients had muscle pain, one patient experienced dizziness, one patient had abdominal discomfort, and one patient suffered from rhabdomyolysis). Because of this, two patients had to stop using the drug and five patients had to reduce their dosage. The remaining two patients were able to continue taking atorvastatin at the same dosage. There were also nine patients without record of side effects whose atorvastatin dosage was reduced. There were 63 patients whose dosages were increased, and two patients were added non-statin lipid-lowering agents to improve their LDL target attainment. Data regarding safety and adverse events are shown in Table 3.

Discussion

The present study is a large trial comparing the effectiveness of crystalline (original brand) and amorphous (generic brand) atorvastatin in terms of LDL-lowering effect in the same patients. Although the two forms of the drug differ in terms of molecular stability and solubility, the present study found no significant difference in LDL lowering effect (primary outcome) between the two forms of atorvastatin. Moreover, there was no significant differences in TC or TG levels (secondary outcomes). The only statistically significant change was in HDL levels, with a mean difference of 0.87 mg/dL. In addition, the present study also evaluated the effect of tablet splitting, a practice that can reduce the stability and efficacy of the drug. However, the LDL levels in

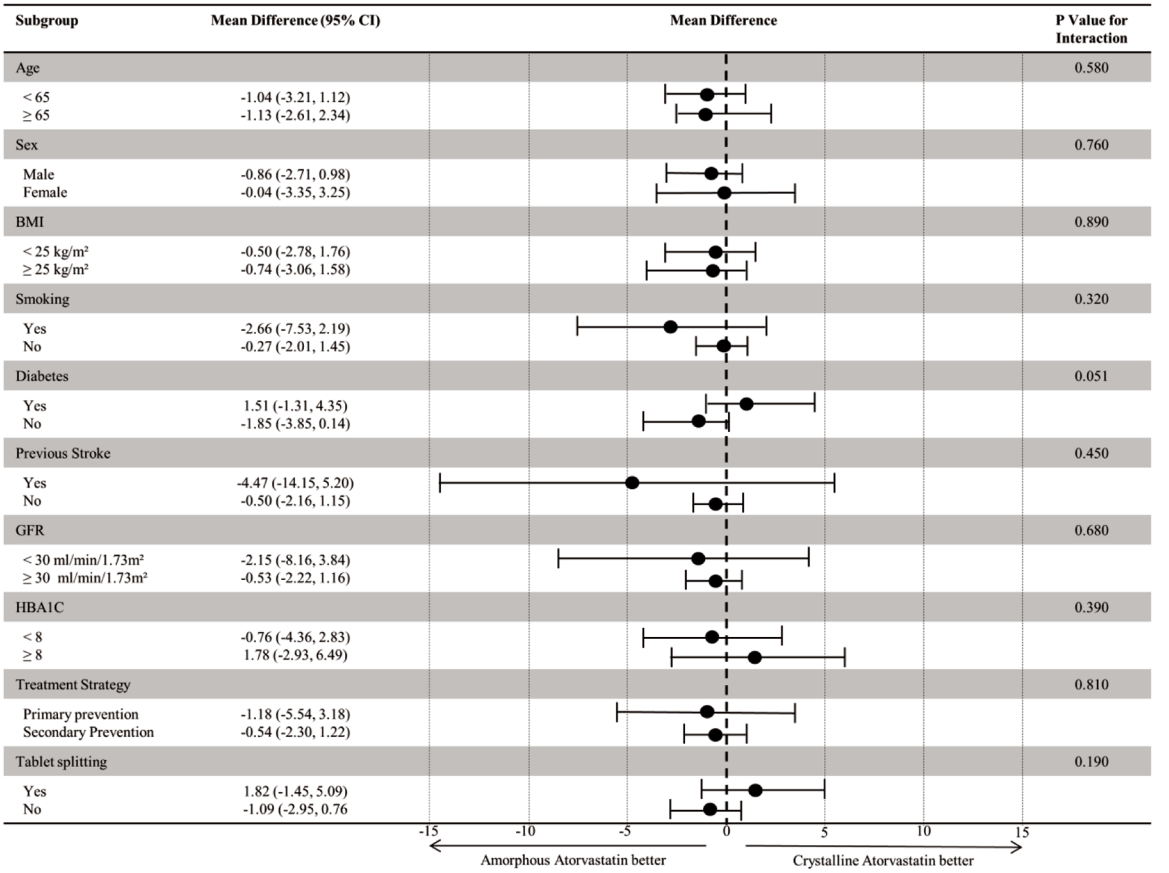

Figure 4. Subgroup analyses.

Table 3. Safety and adverse events

Events	Number of patients	Clinical characteristics
Adverse effects	9	• Myalgia in six patients • Dizziness in one patient • Abdominal discomfort in one patient • Rhabdomyolysis in one patient
Discontinuation of medication	2	One due to rhabdomyolysis and one due to dizziness
Decrease in medication dosage	14	Myalgia in five patients, no data recorded in nine patients

patients splitting their tablets did not significantly differ between the two forms of atorvastatin.

The results of studies by Kim et al[9,10] were similar to that of the present study in terms of efficacy, but differed with regard to the side effects of the drug. These studies were randomized, double-blind, double-dummy trials examined LDL-lowering effect of the two polymorphs of atorvastatin in hypercholesterolemic patients in Korea. They found no significant difference in LDL cholesterol changes between generic and brand-name atorvastatin. Likewise, the percentages of change in TC, TG, and HDL did not significantly differ between the two groups. However, one of these studies[10] found that crystalline and amorphous atorvastatin caused side effects in 27% and 31% of patients, respectively, while the present study found only 1% of patients experienced side effects after switching medication. This might be explained by the fact that the present study compared the two forms of atorvastatin at the same dosage and in the same patients, meaning they had already tolerated to atorvastatin before changing.

In addition, it could also be due to under-report of adverse events.

The present study had some limitations. Firstly, it was a retrospective observational study, therefore, the authors could not control or track compliance data regarding the study medications, lifestyle, diet, or other drugs that might interact with atorvastatin and affect lipid profile levels. Some data, especially side effects and reasons for increasing or decreasing drug dosage, were not recorded in patients' charts. Secondly, the timing of blood sampling for LDL, TC, TG, and HDL in each patient before and after the switching point differed, causing variations in lipid levels. The authors tried to mitigate this limitation and make the blood sample measurements more consistent by using the lipid profile taken closest to the switching point (with a maximum distance of nine months). Furthermore, the dosages of both forms of atorvastatin had to be the same, and there had to be no changes in the administration of other medications that might affect atorvastatin levels after switching.

In terms of clinical application, the amorphous atorvastatin exhibited similar efficacy to that of the crystalline form in hypercholesterolemic patients. The adverse effects were also comparable and acceptable. These results provided physicians with an option of cholesterol-lowering treatment when the cost is a major concern. A future study comparing these two forms of atorvastatin in terms of hard clinical outcomes may be necessary.

Conclusion

The lipid-lowering effectiveness of amorphous atorvastatin was comparable to that of crystalline atorvastatin, and patients were generally able to tolerate the amorphous form.

What is already known on this topic?

Atorvastatin is a high potency statin for the treatment of hypercholesterolemia, of which there are two available forms, crystalline (original brand) and amorphous (generic brand). Pharmacological studies showed the similarity between both forms. However, lipid-lowering effectiveness and safety of amorphous form were still uncertain.

What this study adds?

The amorphous atorvastatin had similar efficacy in LDL-lowering when compared to the crystalline form, and tablet splitting did not alter the effectiveness of amorphous atorvastatin. In addition, patients who used to take crystalline atorvastatin were generally able to tolerate the amorphous form.

Conflicts of interest

The authors declare no conflict of interest.

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