Efficacy of Generic Atorvastatin in a Real-World Setting

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Panisa Manasirisuk¹
Nanthaphan Chainirun^{1,2}
Somsak Tiamkao^{2,3}
Sunee Lertsinudom⁴
Kutcharin Phunikhom⁵
Bundit Sawunyavisuth⁶
Kittisak Sawanyawisuth³

¹Department of Pharmacy Service, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; ²Integrated Epilepsy Research Group, Khon Kaen University, Khon Kaen, Thailand; ³Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; ⁴Division of Pharmaceutical Care, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen, Thailand; ⁵Department of Pharmacology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; ⁶Department of Marketing, Faculty of Business Administration and Accountancy, Khon Kaen University, Khon Kaen, Thailand

Background: The ability of statins to reduce LDL-c plays an important role in both primary and secondary prevention of atherosclerotic cardiovascular diseases. Such treatment can often be costly, but using generic atorvastatin may reduce cost by up to US\$2635. In addition, a previous 8-week study found that it exhibited comparable efficacy to the brand-name medication. This study aimed to evaluate the efficacy of generic atorvastatin over a longer period of six months in a real-world setting.

Methods: This was a retrospective cohort study in adult patients who had received brand-name atorvastatin for at least three months and then had switched to generic atorvastatin for at least six months. Lipid and safety profiles were evaluated at six months after switching. Adjusted analyses for age, sex, co-morbid disease, dosage, and indications for statin therapy were also performed.

Results: During the study period, there were 488 patients who met the study criteria. The mean (SD) age of the patients was 60.97 (12.26) years, and 48.36% were male (236 patients). At six months, average total cholesterol, HDL-c, and LDL-c were all lower, from 174.43 to 166.15 mg/dL, from 51.64 to 49.51 mg/dL, and from 110.08 to 100.78 mg/dL ($p < 0.001$), respectively. There were no significant differences in terms of any other laboratory test results. LDL-c exhibited the highest significant reduction at 9.30 mg/dL. Stratified analyses by age, sex, co-morbid disease, dose, and indications for statin therapy revealed similar decreases in HDL-c and LDL-c as in the study population as a whole.

Conclusion: Generic atorvastatin resulted in significantly lower LDL-c than name-brand atorvastatin but less of an increase in HDL-c.

Keywords: low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, HMG CoA reductase inhibitors

Introduction

Dyslipidemia is a contributing factor to major cardiovascular diseases. In 2013, there were approximately 17 million deaths globally from cardiovascular diseases.¹ Approximately half of patients with established cardiovascular diseases have accompanied dyslipidemia,² the prevalence of which is up to 85% higher in patients with premature coronary heart disease.^{3,4} As low-density lipoprotein cholesterol (LDL-c) is the main cause of atherosclerosis, the ability of HMG CoA reductase inhibitors (statins) to reduce LDL-c plays an important role in both primary and secondary prevention of atherosclerotic cardiovascular diseases.

Despite the benefits of statin therapy for patients with atherosclerotic cardiovascular diseases, this type of treatment can be expensive. The use of generic statins may help to mitigate these costs. A previous study found the medical costs incurred by patients

Correspondence: Nanthaphan Chainirun
Department of Pharmacy Service,
Srinagarind Hospital, Faculty of Medicine,
Khon Kaen University, Khon Kaen, 40002,
Thailand
Email kanokwanchainirun@yahoo.com

Kittisak Sawanyawisuth
Department of Medicine, Faculty of
Medicine, Khon Kaen University, Khon
Kaen, 40002, Thailand
Tel +66-43-363664
Fax +66-43-348399
Email kittisak@kku.ac.th

using brand-name medications to be three times higher than in those using generic drugs.⁵ In addition, the average income in the former group was 10 times higher than that in the latter.⁵ Although treatment with generic atorvastatin could save patients an estimated US\$2635,⁶ data are limited with regard to its clinical efficacy. However, a 2013 study from Korea found the efficacy of generic atorvastatin to be on par with that of the name-brand version over an 8-week period.⁷ Several other studies found generic atorvastatin to be effective over periods ranging from 8–12 weeks,^{8,9} the largest of which had a sample size of 266 patients.^{10,11} This study aimed to evaluate the efficacy of generic atorvastatin over a longer period (six months) and with a larger sample size in a real-world setting.

Methods

This was a retrospective cohort study conducted at Srinagarind Hospital, a 1000-bed University Hospital in Khon Kaen, Thailand. Adult patients who had received brand-name atorvastatin for at least three months and were then put on a generic version for at least six months at the same dosage. Those who had taken other lipid-lowering medications or medications that affect lipid levels, who had no follow-up lipid profile data, or who had been given differing doses of atorvastatin during the treatment period were excluded. Those taking gemfibrozil, fenofibrate, ezetimibe, cholestyramine, prednisolone, dexamethasone, hydrocortisone, or fludrocortisone as concomitant medications were also excluded. The brand-name atorvastatin used was Xarator (Pfizer Pharmaceuticals, Puerto Rico), while the generic was Atorvastatin Sandoz (Lek Pharmaceuticals, Slovenia). The generic atorvastatin had a bioequivalence of over 90% to the brand-name atorvastatin to be approved by the Thai Food Drug Administration. The prescriptions in this study were filled by the patients. The study period was between October 2016 and March 2018.

Data of eligible patients were retrieved from the hospital's electronic database. Clinical data were reviewed and recorded including age, sex, education level, insurance, co-morbid diseases, atorvastatin dosage, body mass index, lipid profiles (total cholesterol, triglyceride, high-density lipoprotein cholesterol [HDL-c], and LDL-c), serum blood urea nitrogen, serum creatinine, estimated glomerular filtration rate, serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), and serum creatinine kinase (CK). Laboratory results at baseline or prior to treatment with generic atorvastatin and six months after initiation of treatment were recorded and compared. The study protocol was approved by the ethic committee

in human research, Khon Kaen University, Khon Kaen, Thailand and complied with the Declaration of Helsinki. An informed consent was not required by the ethic committee to retrospective data collection and patients data are confidential.

Statistical Analyses

A paired *t*-test was used to compute differences between the two time points. Data were presented as means (SD), and mean differences between baseline and at six months with their 95% confidence intervals (CIs). Lipid profiles were adjusted for age, sex, common co-morbid disease, dosage, and indications for statin therapy. Atorvastatin treatment was considered to be secondary prevention in patients who had suffered from coronary artery disease or stroke. Differences with *p* values less than 0.05 were considered statistically significant. Statistical analyses were performed using STATA (College Station, Texas, USA).

Results

During the study period, there were 1044 patients who had switched treatment from brand-name atorvastatin to the generic version. Of those, 556 were excluded due to concurrent treatment with lipid-lowering agents (240 patients), lack of follow-up lipid profile data (187 patients), and differing atorvastatin dosages (129 patients), as shown in [Figure 1](#). In total, there were 488 patients who met the study criteria. The mean (SD) patient age was 60.97 (12.26) years and 48.36% were male (236 patients). Most commonly, patients had basic health insurance (206 patients; 42.21%), and 17.21% were unemployed ([Table 1](#)). Hypertension was the most common co-morbid disease (272 patients; 55.74%). Atorvastatin treatment was administered as secondary prevention in 93 patients (19.06%). The two most common dosages were 20 and 40 mg/day (42.42% and 46.13%).

Three factors differed significantly after six months of treatment with the generic atorvastatin including total cholesterol level, HDL-c level, and LDL-c level (*p* value < 0.001), as shown in [Table 1](#). At six months, total cholesterol, HDL-c and LDL-c had decreased from 174.43 to 166.15 mg/dL, from 51.64 to 49.51 mg/dL, and from 110.08 to 100.78 mg/dL, respectively. No other laboratory test results differed significantly. The highest significant reduction was in LDL-c, at 9.30 mg/dL ([Table 2](#)). Stratified analyses by age, sex, co-morbid disease, dosage, and indications for statin therapy showed decreases in HDL-c and LDL-c similar to those of the study population as a whole ([Tables 3–7](#)). The largest LDL-c reduction was found in those under 60 years of age at −11.90 mg/dL.

Figure 1 Study flow.

Discussion

This real-world, long-term evaluation of generic atorvastatin revealed significant reductions in LDL-c compared with brand-name atorvastatin. Several studies have demonstrated atorvastatin's ability to significantly reduce LDL-c levels.^{7–12} One study, for example, showed that brand-name atorvastatin was able to lower LDL-c by 42% after 8 weeks of treatment.¹² In this study, there was no such reduction from pre-treatment, but treatment with the generic formulation resulted in significant reductions compared with the brand-name medication. This differed from another previous study, which found no significant differences between these two regimens (LDL difference of -2.32 to 5.24).⁷ While there have also been other studies showing no significant differences between brand-name and generic atorvastatin,^{8–11} we found in this study that switching to generic atorvastatin resulted in an average LDL reduction of 9.30 mg/dL, with a 95% CI of -12.99 mg/dL. These contrasting findings may be explained by the larger sample size in this study, the longer study period of 6 months, and/or differences in the type of generic atorvastatin used.^{7,8,11} Generic atorvastatin may also result in LDL-c reductions similar to those from rosuvastatin (p 0.91).¹ Though atorvastatin is reported to increase HDL-c by 6–7%,¹⁴ our generic atorvastatin had

Table 1 Clinical Parameters of Dyslipidemia Patients Who Switched Treatment from Brand-Name Atorvastatin to Generic Atorvastatin

Factors	Mean (SD) or Number (%)
Age	60.97 (12.26)
Male sex	236 (48.36)
Education	
Primary school	7 (1.43)
Secondary school	4 (0.82)
College	3 (0.61)
Unknown	475 (97.34)
Insurance	
Basic	206 (42.21)
Social security	95 (19.47)
Government	161 (32.99)
Self-pay	25 (5.12)
Occupation	
Government officer	11 (2.25)
Private company	45 (9.22)
Farmer	31 (6.35)
Unemployed	84 (17.21)
Unknown	313 (64.14)
Co-morbid disease	
Hypertension	272 (55.74)
Atrial fibrillation	17 (3.48)
Diabetes	222 (45.49)
Chronic kidney disease	56 (11.48)
Heart failure	16 (3.28)
Coronary artery disease	62 (12.70)
Stroke	31 (6.35)
Dose of atorvastatin, mg	
10	3 (0.61)
20	207 (42.42)
40	270 (46.13)
60	7 (1.43)
80	1 (0.20)

less of an effect on HDL-c than the brand-name medication, with lower average HDL-c levels than at baseline (-2.13 mg/dL). As a result of LDL-c and HDL-c reduction, total cholesterol was also significantly lower than at baseline (-8.28). Results adjusted for age, sex, co-morbid disease, dosage, and indications for statin therapy were similar to those of the overall population.

Regarding safety profiles, only ALT levels were slightly higher (by 4.37 U/L) in the generic versus the name-brand group. However, these increases were not clinically significant, as the mean value was lower than

Table 2 Clinical Parameters of Dyslipidemia Patients Before Switching Treatment from Brand-Name to Generic Atorvastatin and 6 Months After

Factors	Baseline	6th Month	Mean Differences	95% CI	p value
BMI	26.57 (5.36)	26.48 (5.33)	-0.09	-0.25, 0.07	0.285
Chol	174.43 (49.58)	166.15 (44.25)	-8.28	-12.38, -4.19	<0.001
Tg	144.20 (69.71)	145.55 (77.50)	1.35	-5.48, 8.19	0.696
HDL	51.64 (13.43)	49.51 (13.04)	-2.13	-3.08, -1.17	<0.001
LDL	110.08 (44.72)	100.78 (43.03)	-9.30	-12.99, -5.59	<0.001
BUN	17.32 (10.57)	17.82 (12.32)	0.50	-0.49, 1.50	0.323
Cr	1.22 (1.14)	1.23 (1.12)	0.01	-0.02, 0.05	0.496
eGFR	72.93 (26.44)	72.84 (26.97)	-0.09	-0.93, 0.74	0.828
AST	30.85 (28.27)	30.07 (21.08)	-0.78	-7.29, 5.74	0.841
ALT	30.30 (17.00)	34.67 (37.73)	4.37	-2.34, 11.10	0.199
CK	235.30 (107.31)	205.84 (90.82)	-29.46	-79.70, 20.78	0.225

Abbreviations: CI, confidence interval; BMI, body mass index (kg/m²); Chol, cholesterol (mg/dL); Tg, triglyceride (mg/dL); HDL, high-density lipoprotein-cholesterol (mg/dL); LDL, low-density lipoprotein-cholesterol (mg/dL); BUN, blood urea nitrogen (mg/dL); Cr, creatinine (mg/dL); eGFR, estimated glomerular filtration rate (mL/min/1.73m²); ALT, alanine aminotransferase (U/L); AST, aspartate aminotransferase (U/L); CK, creatinine kinase (U/L).

Table 3 Lipid Parameters of Dyslipidemia Patients Before Switching Treatment from Brand-Name to Generic Atorvastatin and 6 Months After Stratified by Age

Factors	Baseline	6th Month	Mean Differences	95% CI	p value
Age					
< 60 (n = 216)					
Chol	180.85 (54.92)	170.04 (46.24)	-9.58	-15.38, -3.78	0.001
Tg	149.82 (75.60)	157.17 (91.39)	4.10	-7.11, 15.31	0.471
HDL	52.08 (13.71)	49.21 (12.75)	-2.39	-3.74, -1.04	< 0.001
LDL	115.66 (49.73)	103.76 (40.51)	-11.90	-16.76, -7.04	< 0.001
≥ 60 (n = 272)					
Chol	169.43 (43.30)	162.00 (40.07)	-7.18	-12.96, -1.39	0.015
Tg	137.95 (63.12)	137.44 (63.86)	-1.01	-9.37, 7.33	0.810
HDL	51.38 (13.47)	49.24 (13.21)	-1.89	-3.24, -0.54	0.006
LDL	105.65 (39.85)	98.42 (44.87)	-7.23	-12.64, -1.81	0.009

Abbreviations: CI, confidence interval; Chol, cholesterol (mg/dL); Tg, triglyceride (mg/dL); HDL, high-density lipoprotein-cholesterol (mg/dL); LDL, low-density lipoprotein-cholesterol (mg/dL).

40 U/L. Both brand-name and generic atorvastatin had good safety profiles.^{7,12} Atorvastatin may cause liver toxicity 1.4 times compared with simvastatin (0.32%) of cases, but it can be severe, particularly with high doses.¹⁵ A previous report found that atorvastatin at a dosage of

40–80 mg was 7.3 times more likely to cause severe hepatotoxicity (AST or ALT > 400 U/L) than low-dose simvastatin.¹⁵ Another study from Japan reported that one out of 26 patients (3.84%) receiving atorvastatin at 10 mg had ALT 2–3 times the upper normal limit.

Table 4 Lipid Parameters of Dyslipidemia Patients Before Switching Treatment from Brand-Name to Generic Atorvastatin and 6 Months After Stratified by Sex

Factors	Baseline	6th Month	Mean Differences	95% CI	p value
Sex					
Female (n = 252)					
Chol	178.30 (47.79)	171.17 (45.08)	-7.12	-12.88, -1.37	0.015
Tg	140.98 (65.84)	141.07 (71.80)	0.08	-9.36, 9.53	0.985
HDL	53.74 (13.92)	52.05 (13.05)	-1.68	-3.07, -0.30	0.017
LDL	111.78 (42.38)	102.30 (36.98)	-9.48	-13.89, -5.07	< 0.001
Male (n = 236)					
Chol	170.76 (51.08)	161.37 (43.03)	-9.38	-15.24, -3.53	0.001
Tg	147.53 (73.51)	150.21 (82.91)	2.67	-7.31, 12.65	0.598
HDL	49.52 (12.59)	46.94 (12.56)	-2.58	-3.90, -1.25	< 0.001
LDL	108.27 (47.11)	99.16 (48.69)	-9.10	-15.16, -3.03	0.003

Abbreviations: CI, confidence interval; Chol, cholesterol (mg/dL); Tg, triglyceride (mg/dL); HDL, high-density lipoprotein-cholesterol (mg/dL); LDL, low-density lipoprotein-cholesterol (mg/dL).

Table 5 Lipid Parameters of Dyslipidemia Patients Before Switching Treatment from Brand-Name to Generic Atorvastatin and 6 Months After Stratified by Co-Morbid Disease

Factors	Baseline	6th Month	Mean Differences	95% CI	p value
Hypertension					
No (n = 216)					
Chol	174.82 (49.83)	165.58 (46.57)	-9.23	-14.97, -3.49	0.001
Tg	142.48 (69.98)	141.24 (76.05)	-1.24	-10.98, 8.50	0.801
HDL	51.84 (13.74)	49.57 (13.29)	-2.27	-3.58, -0.95	< 0.001
LDL	111.14 (46.48)	103.88 (52.05)	-7.25	-13.44, -1.06	0.021
Yes (n = 272)					
Chol	174.12 (49.50)	166.62 (42.32)	-7.49	-13.31, -1.67	0.011
Tg	145.62 (69.61)	149.12 (78.66)	3.50	-6.10, 13.10	0.473
HDL	51.48 (13.20)	49.47 (12.87)	-2.01	-3.38, -0.63	0.004
LDL	109.24 (43.34)	98.32 (34.12)	-10.91	-15.40, -6.43	< 0.001

Abbreviations: CI, confidence interval; Chol, cholesterol (mg/dL); Tg, triglyceride (mg/dL); HDL, high-density lipoprotein-cholesterol (mg/dL); LDL, low-density lipoprotein-cholesterol (mg/dL).

There were some limitations to this study. First, some factors associated with atherosclerotic cardiovascular diseases were not studied.^{16–18} In addition, lifestyle modification was not evaluated, as this was a retrospective study and because it may be difficult to monitor patients' lifestyles in a real-world setting. We assumed that the patients as a whole had not made significant lifestyle

modifications, as any changes would vary from patient to patient. We also assumed that the patients exhibited good compliance as they had refilled their prescriptions regularly and had not missed any follow-up visits for at least nine months. Some data were limited or missing including education level, socioeconomic status, and baseline lipid values. Finally, as this was a retrospective, observational

Table 6 Lipid Parameters of Dyslipidemia Patients Before Switching Treatment from Brand-Name to Generic Atorvastatin and 6 Months After Stratified by Dose

Factors	Baseline	6th Month	Mean Differences	95% CI	p value
Dose					
10–20 mg (n = 210)					
Chol	169.71 (45.68)	163.64 (35.88)	−6.07	−12.34, 0.19	0.057
Tg	134.33 (62.48)	136.70 (61.71)	2.37	−66.55, 11.29	0.600
HDL	53.33 (12.49)	50.85 (12.64)	−2.48	−3.64, −1.31	< 0.001
LDL	105.69 (41.71)	97.50 (31.88)	−8.18	−13.20, −3.15	0.001
40–80 mg (n = 278)					
Chol	178.14 (52.25)	168.11 (49.84)	−10.02	−15.45, −4.59	< 0.001
Tg	152.58 (74.42)	153.08 (88.17)	0.49	−9.69, 10.68	0.923
HDL	50.24 (14.04)	48.40 (13.30)	−1.83	−3.30, −0.37	0.014
LDL	113.40 (46.67)	103.26 (49.74)	−10.14	−15.43, −4.84	< 0.001

Abbreviations: CI, confidence interval; Chol, cholesterol (mg/dL); Tg, triglyceride (mg/dL); HDL, high-density lipoprotein-cholesterol (mg/dL); LDL, low-density lipoprotein-cholesterol (mg/dL).

Table 7 Lipid Parameters of Dyslipidemia Patients Before Switching Treatment from Brand-Name to Generic Atorvastatin and 6 Months After Stratified by Indications for Dyslipidemia Treatment

Factors	Baseline	6th Month	Mean Differences	95% CI	p value
Indications					
Primary (n = 398)					
Chol	176.08 (48.27)	167.08 (44.26)	−9.00	−13.53, −4.46	< 0.001
Tg	142.37 (68.81)	143.76 (78.56)	1.38	−6.32, 9.10	0.723
HDL	52.04 (13.36)	50.04 (13.14)	−2.00	−3.04, −0.96	< 0.001
LDL	111.61 (44.32)	101.75 (44.48)	−9.85	−14.05, −5.64	< 0.001
Secondary (n = 90)					
Chol	166.15 (55.43)	161.46 (44.25)	−4.69	−14.30, 4.91	0.332
Tg	153.93 (74.10)	155.14 (71.40)	1.20	−12.78, 15.18	0.864
HDL	49.48 (13.72)	46.67 (12.25)	−2.80	−5.28, −0.32	0.027
LDL	103.33 (46.11)	96.48 (35.81)	−6.84	−14.51, 0.83	0.079

Abbreviations: CI, confidence interval; Chol, cholesterol (mg/dL); Tg, triglyceride (mg/dL); HDL, high-density lipoprotein-cholesterol (mg/dL); LDL, low-density lipoprotein-cholesterol (mg/dL).

study, it is possible that there were confounding factors, and we were unable to evaluate any impact on long-term morbidity and morbidity.

We found that generic atorvastatin resulted in significantly lower LDL-c than brand-name atorvastatin but less of an increase in HDL-c. Further randomized controlled trials over longer study periods may be necessary.

Disclosure

The authors report no conflicts of interest in this work.

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