# Efficacy and Safety of Rosuvastatin in Taiwanese Patients

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**Background:** Statins are effective in decreasing low-density lipoprotein cholesterol (LDL-C). The efficacy and safety of rosuvastatin, a newly launched statin, have not been determined in Taiwanese patients.

**Methods:** Patients with hypercholesterolemia receiving rosuvastatin 10 mg/d in this hospital were prospectively followed and retrospectively analyzed. Men and women with primary hypercholesterolemia were eligible for inclusion in the study if they were either lipid-lowering therapy (LTT)-naïve or had been receiving starting doses of other LLT that had proved ineffective in reaching goals. The primary measurement was the percentage of change in LDL-C from baseline at 12 weeks. Other measurements included: percentages of change from baseline in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), TC/HDL ratio, percentage of patients reaching therapeutic goals, and any adverse effects at 12 weeks. Both intention-to-treat analysis and on-treatment analysis were used.

**Results:** A total of 447 patients, including 375 LTT-naïve and 72 switched patients were enrolled. In LLT-naïve patients, rosuvastatin 10 mg/d reduced LDL-C by a mean of 48.9% from baseline ($p < 0.0001$) by the on-treatment analysis and by a mean of 44.2% from baseline ($p < 0.0001$) by the intention-to-treat analysis. In switched patients, LDL-C was reduced by a mean of 26.2% from baseline ($p < 0.0001$) by both analyses. TC, TG, and TC/HDL ratio, but not HDL-C, were also significantly reduced. Overall, more than 75% patients reached their therapeutic goals. The safety profiles were excellent. Only 2.2% of patients complained of myalgia, 0.2% had elevation of creatine kinase $> 3 \times$ upper limit of normal (ULN), and 0.6% had an elevation of ALT $> 3 \times$ ULN. All the abnormal laboratory tests returned to pretreatment values after drug discontinuation. Only 2.7% of patients discontinued medication due to adverse effects.

**Conclusion:** Rosuvastatin 10 mg/d is safe and effective in Taiwanese patients. [*J Chin Med Assoc* 2008;71(3):113–118]

**Key Words:** hypercholesterolemia, low-density lipoprotein cholesterol, rosuvastatin, statin

## Introduction

Coronary heart disease (CHD) was the number 1 killer in the world in the year 2000 and will continue to be in the year 2025.[1,2] More than 80% of patients with CHD have at least 1 modifiable risk factor, suggesting that CHD is preventable or the event can be delayed.[3] Hypercholesterolemia has been identified as a very important risk factor for vascular disease, especially for CHD. Indeed, in the INTERHEART study, hyperlipidemia has been identified as the most important risk factor with the highest attributable risk among all the 9 factors that accounted for 90% risk in patients with myocardial infarction.[4] Ample epidemiologic data and many randomized controlled trials (RCTs) including primary prevention ones[5–7] and secondary prevention ones[8–12] have shown that serum low-density lipoprotein cholesterol (LDL-C) level correlates with the risk of CHD. For every 1% increase in LDL-C, the risk of CHD increases by 1%.[13] Since the introduction of lovastatin, the first 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin), in 1987, statins have become the mainstay therapy in cardiovascular medicine.

Rosuvastatin is the latest launched statin with the highest potency in decreasing LDL-C comparing with other statins.[14] In Caucasians, 10 mg/d rosuvastatin decreased the serum level of LDL-C by about 45%,

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and more than 80% of patients receiving rosuvastatin 10 mg/d could reach the therapeutic goal suggested by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III).[15] Regarding the use of rosuvastatin in Asian patients, one important concern is that with a single dose of rosuvastatin 40 mg, the plasma concentration in Asians determined by the area under the curve is roughly double that in Caucasians.[16] Although the registration trials in many Asian countries have shown similar efficacy and safety as those in Western countries, they were mostly small-scaled. For instance, there were only 25 patients in the registration trial in Taiwan and 35 in that in Korea. It may be prudent to decide the efficacy and safety in Taiwanese patients by an analysis incorporating more patients. Thus, the purpose of this study was to explore the efficacy and safety of the standard dose of rosuvastatin, 10 mg/d, for 12 weeks in patients with hypercholesterolemia in Taiwan.

## Methods

Patients with hypercholesterolemia receiving rosuvastatin 10 mg/d in this hospital were prospectively followed and their medical records retrospectively analyzed. We enrolled patients in our outpatient clinic from October 2005 to December 2006. All patients were given a coding number, and all the data were kept confidential and used exclusively for scientific publication. The laboratory data were collected from medical charts, and any adverse event (AE) was recorded. The study protocol was approved by the Institution Review Board of Taipei Veterans General Hospital. Since the study involved only the review of records obtained as a part of routine medical care, patient consent was waived.[17,18]

Men and women aged ≥18 years with primary hypercholesterolemia were eligible for inclusion in the study if they were either lipid-lowering therapy (LTT)-naïve or had been receiving starting doses of other LLT that had proved ineffective in reaching goals (switched). The definition of hypercholesterolemia was in line with the original NCEP ATP III criteria[15] and the 2004 updated version.[13] Patients were further classified according to their risk level, as follows:[13]

- Low risk group: 0 to 1 risk factor, 10-year CHD risk ≤10%;
- Moderate risk group: ≥2 risk factors, 10-year CHD risk between 10% and 20%;
- High risk group: CHD or CHD risk equivalents (peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease, diabetes), and ≥2 risk factors with 10-year CHD risk >20%;
- Very high risk group: presence of established cardiovascular disease and
  - Multiple major risk factors (especially diabetes);
  - Severe and poorly controlled risk factors (especially continued cigarette smoking);
  - Multiple risk factors of the metabolic syndrome (especially high triglyceride [TG] ≥200 mg/dL plus non-high-density lipoprotein [non-HDL] cholesterol ≥130 mg/dL with low HDL-C [<40 mg/dL]);
  - Patients with acute coronary syndrome.

The 10-year CHD risk was presumably >30% for the very high risk group.

Patients with the following were not included: a history of homozygous familial hypercholesterolemia; secondary hypercholesterolemia of any cause; active liver disease or dysfunction indicated by levels of alanine aminotransferase (ALT) >3× upper limit of normal (ULN); unexplained serum creatine kinase (CK) level >3×ULN; serum creatinine >2.0 mg/dL; and a history of hypersensitivity to statins.

The primary measurement was the percentage of change in LDL-C from baseline at 12 weeks. Other measurements included: percentage of change from baseline in total cholesterol (TC), HDL-C, TG, and TC/HDL ratio at 12 weeks. Both the intention-to-treat analysis (i.e. patients who received ≥1 dose of study medication, and who had a baseline reading and ≥1 post-baseline reading for ≥ lipid variables) and the on-treatment analysis (patients who had a compliance rate ≥80%) were used. In order to see whether there were racial differences in the effects of rosuvastatin, we also compared our results with those obtained from other studies: the STELLA trial, in which most patients (86%) were Caucasians,[14] the IRIS trial, in which all patients were South Asians,[19] the DISCOVERY-Asia study, in which patients in China, Hong Kong, Korea, Malaysia, Taiwan, and Thailand were enrolled,[20] and the Chinese registration trial, in which all patients were from mainland China.[21]

The LDL-C goals for patients in each risk level were set according to the updated version of NCEP ATP III:[13] <160 mg/dL for low risk group; <130 mg/dL for moderate risk group; <100 mg/dL for high risk group; and <70 mg/dL for very high risk group. The proportions of patients reaching goals according to different risk levels were calculated. AE and serious AE (SAE); relevant laboratory data, such as CK, ALT, and creatinine were also recorded. The compliance rate was carefully examined by an experienced study

nurse. A compliance rate less than 80% was defined as poor compliance.

ANOVA was used for statistical analyses for the changes in lipid parameters. Unpaired *t* test was used for age difference in different groups. Fisher's exact test and $\chi^2$ test for trend were used for categorical data when appropriate. A $p$ value $< 0.05$ was considered statistically significant.

## Results

A total of 447 patients with hypercholesterolemia were enrolled in the study. Among them, 375 patients were LTT-naïve and 72 were switched patients. Other baseline characteristics of patients are shown in Table 1. LTT-naïve patients had more hypertension, but less diabetes. More switched patients (30.6%) than LLT-naïve patients were categorized as very high risk group. This is self-explanatory since LDL-C goal is < 70 mg/dL for patients with very high risk and is more difficult to achieve, so that previous LLT might fail in these patients. In general, patients had significant comorbid conditions in both groups. Altogether, 78% of patients had hypertension, 38% CHD, 39% diabetes, 7% heart failure, and 7% atrial fibrillation. The high prevalence of comorbid conditions suggested this cohort had relatively high CV risk. In this study, statin was used for primary prevention in only 23.7% (low risk patients plus moderate risk patients), while in 76.3% (high risk patients and very high risk patients) it was used for secondary prevention.

Thirty-eight patients (8.5%) had a compliance rate < 80%, and they were all LLT-naïve patients. All patients who were switched from other LLT had a compliance rate ≥ 80%. Thus, on-treatment analysis was performed in 409 patients and intention-to-treat analysis was performed in 447 patients. For patients who were switched from other LLT, the results were exactly the same by both analyses because all of them had a compliance rate ≥ 80%. In LLT-naïve patients, rosuvastatin 10 mg/d reduced LDL-C by a mean of 48.9% from baseline ($p < 0.0001$) by the on-treatment analysis and by a mean of 44.2% from baseline ($p < 0.0001$) by the intention-to-treat analysis (Table 2). In patients who were switched from other LLT, rosuvastatin 10 mg/d reduced LDL-C by a mean of 26.2% from baseline ($p < 0.0001$) by both analyses. Table 2 also shows the changes in other lipid parameters. In LLT-naïve patients, TC, TG, and TC/HDL-C ratios were all significantly reduced from baseline by both analyses ($p < 0.0001$, $< 0.0001$, and $< 0.001$, respectively), but HDL-C was not significantly changed. In patients switched from other LLT, TC and TC/HDL-C were significantly reduced from baseline by both analyses ($p < 0.0001$ and $< 0.01$, respectively), but HDL-C and TG were not significantly changed.

The results of lipid lowering in this study were compared with those of other studies (Figure 1). The efficacy of rosuvastatin 10 mg/d in Taiwanese patients in decreasing LDL-C, TC, and TG was similar to those in Caucasians, South Asians, and other Asian patients using the same dose of rosuvastatin. The effects on HDL-C seemed different. There were

**Table 1.** Baseline characteristics

| | LLT-naïve | Switched | Total |
|---|---|---|---|
| Patient number | 375 | 72 | 447 |
| Mean (SD) age, yr | 68.1 (11.2)* | 64.9 (11.4) | 67.6 (11.3) |
| Range | 29–92 | 34–85 | 29–92 |
| Men | 215 (57.3%) | 37 (51.4%) | 252 (56.4%) |
| History of hypertension | 303 (80.8%)† | 47 (65.3%) | 350 (78.3%) |
| History of coronary heart disease | 139 (37.1%) | 31 (43.1%) | 170 (38.0%) |
| History of diabetes | 131 (34.9%) | 41 (56.9%)† | 175 (39.1%) |
| History of heart failure | 27 (7.2%) | 6 (8.3%) | 33 (7.4%) |
| History of atrial fibrillation | 24 (6.4%) | 7 (9.7%) | 31 (6.9%) |
| NCEP ATP III risk category | | | |
| Low | 21 (5.6%) | 3 (4.2%) | 24 (5.4%) |
| Moderate | 72 (19.2%) | 10 (13.9%) | 82 (18.3%) |
| High | 211 (56.3%) | 37 (51.4%) | 248 (55.5%) |
| Very high | 71 (18.9%) | 22 (30.6%)* | 93 (20.8%) |

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$. LLT = lipid-lowering therapy.

**Table 2.** Changes from baseline in serum lipid levels at 12 weeks

| | On-treatment analysis ($n = 409$) | | | | Intention-to-treat analysis ($n = 447$) | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline mg/dL (SD) | 12 wk mg/dL (SD) | % change LMS (SE) | *p* | Baseline mg/dL (SD) | 12 wk mg/dL (SD) | % change LMS (SE) | *p* |
| LDL-C | | | | | | | | |
| LLT-naïve | 152.5 (26.7) | 77.6 (21.6) | −48.9 (0.6) | <0.0001 | 150.3 (27.7) | 82.8 (26.7) | −44.2 (1.0) | <0.0001 |
| Switched | 130.9 (33.1) | 94.2 (30.0) | −26.2 (2.7) | <0.0001 | 130.9 (33.1) | 94.2 (30.0) | −26.2 (2.7) | <0.0001 |
| TC | | | | | | | | |
| LLT-naïve | 226.9 (32.5) | 148.4 (28.0) | −34.0 (1.1) | <0.0001 | 223.1 (34.2) | 150.3 (28.5) | −31.6 (1.2) | <0.0001 |
| Switched | 206.9 (35.7) | 165.0 (34.5) | −19.8 (2.2) | <0.0001 | 206.9 (35.7) | 165.0 (34.5) | −19.8 (2.2) | <0.0001 |
| HDL-C | | | | | | | | |
| LLT-naïve | 54.1 (13.3) | 54.3 (14.3) | +1.7 (1.2) | 0.84 | 54.1 (13.3) | 54.2 (14.1) | +1.5 (1.1) | 0.92 |
| Switched | 54.1 (13.5) | 54.7 (15.2) | +2.4 (2.8) | 0.79 | 54.1 (13.5) | 54.7 (15.2) | +2.4 (2.8) | 0.79 |
| TG | | | | | | | | |
| LLT-naïve | 169.4 (91.8) | 129.1 (73.2) | −18.5 (2.0) | <0.0001 | 168.6 (90.2) | 131.6 (72.4) | −16.5 (1.9) | <0.0001 |
| Switched | 172.3 (89.6) | 151.9 (75.1) | −4.2 (4.7) | 0.18 | 172.3 (89.0) | 151.9 (75.1) | −4.2 (4.7) | 0.18 |
| TC/HDL-C ratio | | | | | | | | |
| LLT-naïve | 4.44 (1.30) | 2.85 (0.73) | −34.1 (1.3) | <0.001 | 4.38 (1.31) | 2.93 (0.80) | −31.0 (1.5) | <0.001 |
| Switched | 3.86 (0.78) | 3.18 (0.90) | −17.0 (3.2) | <0.01 | 3.86 (0.78) | 3.18 (0.90) | −17.0 (3.2) | <0.01 |

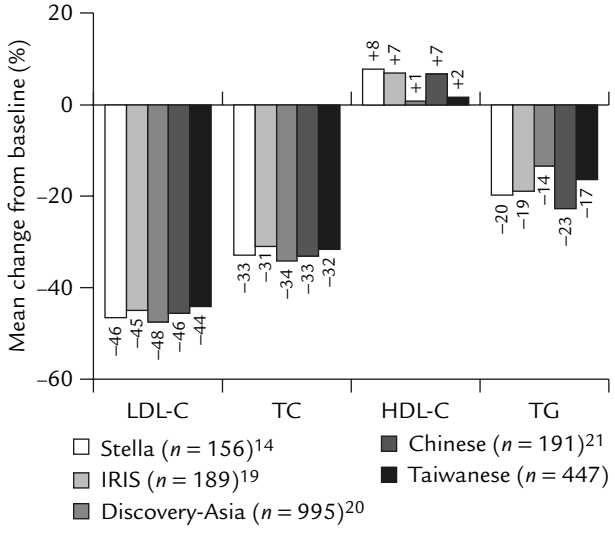


**Figure 1.** Comparisons of our data with those from other studies.

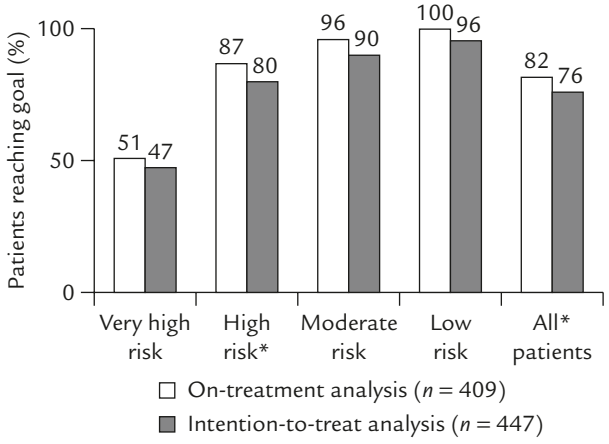


**Figure 2.** Percentage of patients who achieved NCEP ATP III LDL-C goals.[13] Both the on-treatment analysis and the intention-to-treat analysis showed that with increasing level of risk, it was more difficult for patients to reach goals ($\chi^2$ for trend, both $p < 0.0001$). *$p < 0.05$. LDL-C goals were <160 mg/dL for the low risk group; <130 mg/dL for the moderate risk group; <100 mg/dL for the high risk group; and <70 mg/dL for the very high risk group.[13]

only a 2% increase in HDL-C in our patients, similar to that in the DISCOVERY-Asia study (+1%), but less than those in the STELLA trial (+8%), Iris trial (+7%), and the Chinese Registration trial (+7%). Because these data were from different studies, no statistical analyses could be made.

The percentages of patients reaching goals are shown in Figure 2. After 12 weeks of treatment with rosuvastatin 10 mg/d, goal achievement ranged from 51% in the very high risk group to 100% in the low risk group by the on-treatment analysis. Figure 2 also showed that with increasing level of risk, it was more difficult to reach goals. The percentages of goal achievement were significantly higher in high risk patients and in all patients by on-treatment analysis compared with those by intention-to-treat analysis, suggesting compliance had impact on goal achievement. Overall, 76% (intention-to-treat) to 82% (on-treatment)

**Table 3.** Safety and laboratory data

| | Intention-to-treat analysis Rosuvastatin 10 mg ($n = 447$) |
|---|---|
| Myalgia | 8 (1.8%) |
| Any AE leading to treatment discontinuation | 12 (2.7%) |
| SAE | 0 |
| SAE leading to treatment discontinuation | 0 |
| Creatine kinase > 3 ULN | 1 (0.2%) |
| Creatine kinase > 10 ULN | 0 |
| ALT > 3 ULN | 3 (0.6%) |
| Creatinine > 100% increase from baseline | 0 |

*AE = adverse event; SAE = serious adverse event; ULN = upper limit of normal; ALT = alanine aminotransferase.*

patients reached therapeutic goals. Thus, a standard dose of rosuvastatin could ensure goal achievement in more than 3 quarters of patients.

The overall safety profile in this study was excellent (Table 3). Only 10 patients (2.2%) complained of myalgia, and 8 of them discontinued the medication. None developed SAE. Only 1 patient (0.2%) had elevation of creatine kinase > 3 × ULN and stopped the medication. No patient had creatine kinase > 10 × ULN. Three patients (0.6%) had an elevation of ALT > 3 × ULN and discontinued medication. No patient had 2-fold increase in serum creatinine. All the abnormal laboratory tests returned to pretreatment values after drug discontinuation. Only 2.7% of patients discontinued medication due to AE.

## Discussion

This study showed that rosuvastatin, in a dose of 10 mg/d, is effective and safe in Taiwanese patients with hypercholesterolemia. With on-treatment analysis, it could reduce almost 50% of LDL-L from baseline. Even with intention-to-treat analysis, there was still a 44% reduction of LDL-C. The potency was similar to that of Caucasians,[14] South Asians,[19] other Asians,[20] and patients from mainland China.[21] It is also remarkable that more than 75% of patients could reach the currently most stringent therapeutic goals with excellent tolerability. Only 2.7% of patients discontinued medication due to AE.

Despite rosuvastatin's documented beneficial effect on HDL-C,[14,22] we did not see any significant elevation of HDL-C in this study. This finding was in line with some Asian studies. There was only a 0.7% increase in HDL-C by rosuvastatin 10 mg/d in the DISCOVERY-Asia study,[20] and only 1.6% elevation of HDL-C was observed in 1 Taiwanese study by the same dose of rosuvastatin.[23] This may be explained by the dose-dependent effect of rosuvastatin in raising HDL-C seen in Caucasian studies such as STELLAR. We might observe a significant elevation of HDL-C by higher doses. Nevertheless, LDL-C is the primary target for statin therapy, and standard dose (10 mg/d) of rosuvastatin is potent enough in lowering LDL-C.

Most of the previous statin trials checked the effect on goal achievement according to the previous 2001 NCEP ATP III goals[15] or the 2003 European LDL-C goals, in which LDL < 100 mg/dL or < 97 mg/dL, respectively, were set for patients with high risk. There was no mention of the goal achievement for the very high risk patients who have a 10-year CHD risk > 30%. This study was the first to look at the goal achievement in these patients (< 70 mg/dL). It is shown that even in patients with very high risk with a stringent therapeutic goal (LDL-C < 70 mg/dL), patients taking monotherapy with rosuvastatin in a standard dose could have a 50% chance to reach goal. Overall, more than 75% of patients could reach therapeutic goal with a single starting dose without dose escalation, suggesting that rosuvastatin is currently the most effective statin for Taiwanese patients.

Rosuvastatin was well tolerated by patients in this study. Only 2.2% complained of myalgia, 0.2% had significant elevation of creatine kinase (> 3 × ULN), and 0.6% had asymptomatic elevation of ALT > 3 × ULN. Altogether, only 2.7% of patients discontinued the medication due to AE. This is consistent with previous findings from Caucasians for rosuvastatin.[14,24,25] One pharmacokinetic study showed that with a single oral dose of 40 mg rosuvastatin, the plasma concentration in the Asians was roughly double that in the Caucasians.[16] The authors did not show whether 10 mg rosuvastatin also had different pharmacokinetic property in Asians. In fact, the safety profile of rosuvastatin 10 mg/d in this study is similar to those from other Asian studies[20] and other Caucasian studies,[14] suggesting that the different pharmacokinetic property of rosuvastatin 40 mg did not translate into increased AE in Asians and Taiwanese when taking 10 mg/d rosuvastatin.

Some of the limitations of the study were that this was not a double-blind, randomized trial and did not compare rosuvastatin with other statins. Thus, its potency and safety relative to other statins cannot be concluded. The long-term benefits of rosuvastatin in reducing CV events could not be determined by the present study, although it is generally believed that

decreasing LDL-C is beneficial in reducing CV events in the long term.

In conclusion, rosuvastatin 10 mg/d is effective and safe in Taiwanese patients. More than 75% of patients could reach therapeutic goal without dose escalation.

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