The renoprotective effects of simvastatin and atorvastatin in patients with acute coronary syndrome undergoing percutaneous coronary intervention

An observational study

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Abstract

Some statins, such as atorvastatin, have proven renoprotective effects. The comparative renoprotective potential of simvastatin is less clear. This study aimed to compare the renoprotective effects of simvastatin with atorvastatin in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). This observational study examined the medical records of 271 patients who were treated at the Guangdong Cardiovascular Institute from April 2004 to February 2008. Patients had received either 40mg simvastatin (n = 129) or 20mg atorvastatin (n = 142), daily, for a period of at least 6 months following PCI. Declined renal function (DRF) was defined at the occurrence of chronic kidney disease (CKD) or elevated CKD stages at 6-months post-PCI. Results showed that the incidence of DRF was similar among patients taking simvastatin or atorvastatin (25.00% vs 26.57%, respectively). Kaplan–Meier survival analysis showed that patients who developed DRF had a higher incidence of mortality and major adverse cardiovascular events (MACEs) than those without DRF (17.41% vs 28.57%, P = .0308). Multivariate logistic regression analysis identified diabetes and baseline estimated glomerular filtration rate as independent risk factors for DRF. Collectively, our results indicate that simvastatin has comparable renoprotective effects to atorvastatin in ACS patients undergoing PCI. Further studies are warranted to confirm the comparative renoprotective effects of statins.

Abbreviations: ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, ACS = acute coronary syndrome, BUN = blood urea nitrogen, CAD = carotid artery disease, CIN = contrast-induced nephropathy, CKD = chronic kidney disease, DRF = declined renal function, eGFR = estimated glomerular filtration rate, LDL-C = high-density lipoprotein cholesterol, HMG-CoA = the 3-hydroxy-3-methylglutaryl coenzyme A, LM = left main artery, MACEs = major adverse clinical events, NO = nitric oxide, PCI = percutaneous coronary intervention, SCR = serum creatinine, TG = triglyceride.

Keywords: acute coronary syndrome, atorvastatin, percutaneous coronary intervention, renal function, simvastatin

1. Introduction

Statins are a family of cholesterol-lowering drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme with a central role in the production of cholesterol. Statins inhibit several pathological pathways involved in acute coronary syndrome (ACS), such as endothelial dysfunction, thrombus formation, and the activation of inflammatory and coagulation cascades. Patients with ACS often require percutaneous coronary intervention (PCI) that can lead to complications such as contrast-induced nephropathy (CIN), which is associated with long-term morbidity, mortality, and increased health care costs. These inflict substantial burdens on the individual and society.

Recently, meta-analyses and large randomized controlled trials have shown statins to have clinically relevant renoprotective effects that could justify their use during the early stages of chronic kidney disease (CKD). Renoprotective effects have been established for atorvastatin, simvastatin, and rosuvastatin. Moreover, several studies have compared these renoprotective effects in different clinical settings.

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rosuvastatin vs atorvastatin[26]). Collectively, these studies suggest that atorvastatin might have the strongest renoprotective effects.[6,10,22]

The renoprotective effects of simvastatin have been demonstrated in several pre-clinical studies.[19,27] Simvastatin ameliorated low-dose streptozotocin-induced nephropathy in an experimental rat model of type 2 diabetes. This was thought to be via its ability to lower cholesterol, reduce oxidative stress, and inflammation.[20] When applied to angiotensin II stimulated human mast cells, simvastatin also suppressed inflammation and alleviated oxidative stress. Furthermore, it had a protective effect in a pre-clinical model of CKD.[28] In another study, simvastatin alleviated oxidative stress. Furthermore, it had a protective effect to its ability to lower cholesterol, reduce oxidative stress, and inflammation.[30] In another study, simvastatin was shown to exhibit beneficial effects on vascular endothelium,[30] and to prevent the progression of renal fibrosis.[31] In a clinical setting, studies have shown beneficial effects of simvastatin on renal microvascular dysfunction, ischemia-reperfusion injury,[32] and the incidence of CIN.[21] Despite these promising findings, the renoprotective effects of simvastatin are yet to be compared with other statins.

This study aimed to determine the renoprotective effect of simvastatin versus atorvastatin in patients with ACS undergoing PCI.

2. Methods

This study was approved by the Guangdong General Hospital ethics committee and was conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients involved.

2.1. Patients

We enrolled consecutive CHD patients undergoing PCI who agreed to attend “CHD club” at Guangdong Cardiovascular Institute, Guangdong General Hospital between April 2004 and February 2008. Patients in the “CHD club” receive CHD secondary prevention education, which include guiding lifestyle changes, taking medication, and biochemical investigation also conducted if necessary during hospitalization and follow-up period. The follow-up period includes 1, 3, 6, 12, 24, and 36 months after cardiac catheterization. Adults with ACS and undergoing PCI were included in the study if they had received either simvastatin (40 mg daily) or atorvastatin (20 mg daily) from admission for PCI to the sixth month after PCI. Patients who had taken other statins, who changed statins during the 6 month period, who did not have recorded serum creatinine (SCR) concentrations at baseline or at 6-months follow-up, or who discontinued their use of simvastatin or atorvastatin due to adverse events, were excluded from the study (Fig. 1). Baseline demographics and clinical characteristics were identified from the time of PCI.

2.2. PCI and medications

PCI was performed by experienced interventional cardiologists according to standard national practice. Nonionic, low-osmolar contrast medium was employed for all patients (iopamiron or ultravist, both at 370mg I/mL). Statins, antiplatelet agents (aspirin/clopidogrel), β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, diuretics, and inotropic drugs were used at the attending cardiologist’s discretion, according to clinical protocol derived from national interventional guidelines.

2.3. Biochemical parameters measurement

Biochemical test results were isolated from medical records of the first, third, sixth, 24th, and 36th months following PCI. The concentrations of SCR, serum triglyceride concentration (TG), and low-density lipoprotein cholesterol (LDL-C) were identified at admission and at 6 months post-PCI. The levels of blood urea nitrogen (BUN), electrolytes, fasting glucose, fasting lipid, and other standard clinical parameters were obtained from the morning of the PCI. The estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease equation based on Chinese patients.

2.4. Clinical outcomes

The primary outcome was the occurrence of declined renal function (DRF), defined as the incidence of CKD or the elevated eGFR decline from 90mL/min/1.73m² at baseline to <90mL/min/1.73m² at 6 months follow-up. Additional outcomes included...
major in-hospital or long-term adverse clinical events (major adverse clinical events; MACEs), such as mortality, nonfatal myocardial infarction, target vessel revascularization, or stroke.

### 2.5. Statistical analysis

Data were analyzed using IBM SPSS version 19 software. Comparisons between the groups of patients (simvastatin vs atorvastatin) were performed using Student t tests or the Wilcoxon rank sum test (if not normally distributed) for continuous variables. Alternatively, Chi-square or Fisher exact tests were used for categorical variables. All statistical significance was inferred if \( P < .05 \).

SCr and eGFR were compared between patients taking simvastatin and atorvastatin at baseline and at 6 months post-PCI.

A multivariate analysis was conducted to identify the clinical factors affecting the incidence of DRF (dependent variable). Age (≥75 years), serum TG, LDL-C, having diabetes, gender, and eGFR at baseline were included as potential variables. Those that were statistically significant according to a univariate analysis were included in the multivariate model.

### Table 1

**Baseline clinical characteristics of study participants.**

|                | Simvastatin (n = 128) | Atorvastatin (n = 143) | \( P \) |
|----------------|-----------------------|------------------------|------|
| **Demographics** |                       |                        |      |
| Age, mean (SEM) | 62.2 ±10.2            | 61.2 ±9.7              | .397 |
| Age ≥75 y, n (%)| 12 (9.4)              | 11 (7.7)               | .620 |
| Body mass index (SEM) | 23.4 ±2.4              | 23.8 ±2.9              | .215 |
| Systolic blood pressure (mm Hg ±SEM) | 126.2 ±19.5           | 124.1 ±21.9           | .401 |
| Diastolic blood pressure (mm Hg ±SEM) | 73.8 ±9.8              | 71.6 ±11.7             | .395 |
| Female, n (%)   | 29 (22.7)             | 34 (23.8)              | .828 |
| Medical history, n (%) |                   |                        |      |
| Smokers         | 54 (42.2)             | 65 (45.5)              | .96  |
| Hypertension    | 76 (60.4)             | 88 (61.5)              | .716 |
| Heart failure   | 17 (13.3)             | 12 (8.4)               | .194 |
| Diabetes        | 32 (25.0)             | 29 (20.3)              | .353 |
| Family History: Congestive heart disease | 3 (2.3)               | 6 (4.2)                | .396 |
| Family History: Diabetes | 12 (9.4)              | 6 (4.2)                | .087 |
| Family History: Hypertension | 24 (18.7)            | 24 (16.8)              | .672 |
| **Laboratory findings (mmol/L ±SEM)** |                   |                        |      |
| Fasting glucose | 6.80 ±2.13            | 6.37 ±2.31             | .116 |
| Total cholesterol | 4.90 ±1.38            | 4.50 ±1.28             | .016* |
| HDL-C           | 1.12 ±0.43            | 1.01 ±0.32             | .016* |
| LDL-C           | 2.76 ±1.05            | 2.60 ±1.04             | .225 |
| TG              | 1.83 ±1.47            | 1.69 ±2.06             | .548 |
| Apoprotein A    | 1.72 ±6.41            | 1.76 ±7.21             | .962 |
| Apoprotein B    | 0.84 ±0.34            | 0.83 ±0.31             | .729 |
| Medication, n (%) |                   |                        |      |
| ACE/ARB         | 115 (89.5%)           | 130 (90.8%)            | .766 |
| \( β \)-blocker | 113 (88.2%)           | 129 (90.0%)            | .608 |
| Calcium channel blocker | 31 (23.5%)          | 31 (21.3%)             | .619 |
| Diuretics       | 3 (6.5%)              | 13 (8.8%)              | .383 |
| Vessel treated, n (%) |                   |                        |      |
| LM or multivessel | 89 (69.5)             | 107 (74.8)             | .672 |

\( P \) value calculated using a Student t test or the Wilcoxon rank sum test (if not normally distributed) for continuous variables; alternatively, a Chi-square or Fisher exact test was used for categorical variables. \( \text{ACE} / \text{ARB} = \text{angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, LDL-C= high-density lipoprotein cholesterol, HDL-C= low density lipoprotein cholesterol, LM = left main artery, TG = serum triglyceride.} \)

### 3. Results

#### 3.1. Baseline characteristics of patients receiving simvastatin or atorvastatin

Of the 271 patients with ACS undergoing primary PCI whose medical records were included in the study, 128 had received daily simvastatin (40 mg) and 143 had received daily atorvastatin (20 mg) for at least 6 months post-PCI. As summarized in Table 1, there were no demographical or procedural differences between the groups.

The concentrations of total serum cholesterol and high-density lipoprotein cholesterol (HDL-C) were higher in patients who had received simvastatin than in those who had received atorvastatin. These differences were not significant at 6 months post-PCI.

#### 3.2. Effect of atorvastatin and simvastatin on renal function after PCI

In the 6 months following PCI, there was a significant deterioration in renal function in patients of both groups (Figs. 2 and 3), as shown by significant increases in SCr (Fig. 2 and Table 2) and significant decreases in eGFR (Fig. 3 and Table 2).

There were no differences in the percentage increases in SCr, or the percentage decrease in eGFR, between the 2 groups (Fig. 4). DRF was defined in 70 of 271 patients (25.83%; Fig. 5). Among the 70 patients with DRF, there was a significantly higher incidence of mortality and MACEs than that in patients without DRF (17.41% vs 28.57%, \( P = .046 \); Fig. 5). The incidence of DRF was similar among patients treated with simvastatin or atorvastatin (25.00% vs 26.57%, \( P = .768 \)).

#### 3.3. Analysis of clinical factors affecting the incidence of DRF in the 6 months post-PCI

Multivariate logistic regression analysis revealed that diabetes and the level of eGFR at baseline were independently associated with the incidence of DRF (Table 3).
Other baseline characteristics [age (≥75 years), serum TG, LDL-C, and gender] did not affect the incidence of DRF.

3.4. Clinical outcomes during the entire follow-up

The median follow-up period for all patients was 25.23 ± 2.94 months. Kaplan–Meier survival analysis showed that patients who developed DRF had a higher rate of mortality and MACEs than those without DRF (17.41% vs 28.57%, \( P = 0.031 \); Fig. 6).

4. Discussion

Cardiovascular events and impaired renal function are associated with increased morbidity, decreased quality of life, and higher mortality rates.\(^4,5\) Several risk factors have been identified for renal impairment following cardiovascular events, including dyslipidemia, hypertension, and diabetes.\(^4,5,8\) Fortunately, there

Table 2
Serum creatinine and estimated glomerular filtration rate levels at baseline and 6 months after percutaneous coronary intervention.

| Variables | Simvastatin (n=128) | Atorvastatin (n=143) | \( P \) |
|-----------|----------------------|-----------------------|-------|
| SCr       |                      |                       |       |
| Baseline  | 1.04 ± 0.29          | 1.03 ± 0.32           | .502  |
| 6 mo      | 1.09 ± 0.43          | 1.12 ± 0.41           | .484  |
| \( \Delta \) | 0.05 ± 0.28          | 0.09 ± 0.32           | .126  |
| eGFR      |                      |                       |       |
| Baseline  | 73.21 ± 17.55        | 75.09 ± 20.38         | .554  |
| 6 mo      | 71.7 ± 19.31         | 70.11 ± 21.40         | .349  |
| \( \Delta \) | −1.51 ± 13.66       | −4.98 ± 16.10         | .107  |

Comparisons of between-groups differences were performed using the Mann–Whitney U test. \( \Delta \) = change from baseline to 6 mo, eGFR = estimated glomerular filtration rate, SCr = serum creatinine.

Figure 3. Time-course of estimated glomerular filtration rate (eGFR) from baseline to 6 months post-percutaneous coronary intervention (PCI).

Other baseline characteristics [age (≥75 years), serum TG, LDL-C, and gender] did not affect the incidence of DRF.

Table 3
Multivariate analysis of clinical factors affecting the incidence of declining renal function.

| \( \beta \) | SE(B) | \( P \) | Odds ratio (95% CI) |
|---------|-------|-------|---------------------|
| TG      | 0.086 | 0.105 | .412                | 1.09 (0.887–1.34) |
| Apoprotein B | −1.996 | 1.009 | .048                | 0.136 (0.019–0.981) |
| SCr at baseline | 0.517 | 0.928 | .577                | 1.678 (0.272–10.334) |
| eGFR at baseline | 0.028 | 0.014 | .049                | 1.029 (1–1.058) |
| Heart failure | 0.662 | 0.503 | .189                | 1.938 (0.725–5.198) |
| Diabetes | 0.991 | 0.438 | .024                | 2.603 (1.141–6.358) |
| Smoker  | −0.386 | 0.347 | .267                | 0.68 (0.344–1.344) |
| Age ≥75 y | 0.941 | 0.688 | .159                | 2.562 (0.692–9.489) |
| LDL-C   | 0.206 | 0.287 | .473                | 1.229 (0.72–2.158) |
| HDL-C   | −0.123 | 0.552 | .824                | 0.884 (0.3–2.61) |
| LDL-C/HDL-C > 2 | 0.326 | 0.556 | .557                | 1.386 (0.466–4.121) |
| Body mass index | 0.037 | 0.066 | .572                | 1.038 (0.912–1.235) |
| Constant | −5.311 | 2.944 | .071                |

\( \beta \) = confidence interval, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SCr = serum creatinine, TG = serum triglyceride.
HMG-CoA to mevalonic acid.\[36,37\] CoA reductase is also the rate-limiting step in the conversion of cholesterol to mevalonic acid with the production of cholesterol.\[38,39\] Statins have pleotropic effects, and some of their effects are some well characterized therapeutics available to manage these risk factors.\[9\]

Statins are a family of drugs widely used to lower serum cholesterol. Several statins have been shown to have renoprotective effects in patients with cardiovascular events (e.g., ACS).\[1,8,9,33\] Atorvastatin,\[10–18\] simvastatin,\[19–21\] rosuvastatin,\[22,23,26\] and pravastatin\[25\] have all been shown to have beneficial effects in different clinical settings; however, this is the first comparative study of simvastatin versus another statin in a clinical setting. In the present study, we reviewed the clinical records of patients with ACS who received simvastatin or atorvastatin for at least 6 months following PCI. Previous studies\[34,35\] have suggested that simvastatin exerts a renoprotective effect. We found that the effects of simvastatin and atorvastatin were comparable in our study population at 6 months post-PCI; this was in terms of the concentration of Scr, eGFR, and the incidence of DRF.

As expected, patients experiencing DRF had poorer clinical outcomes. There is currently a lack of effective strategies to prevent DRF; therefore, the renoprotective effects of statins hold much promise. Statins are well characterized in the clinic and are widely available for use in at-risk patients.

The underlying mechanisms for the renoprotective effect of statins need to be further delineated. Statins are well known HMG-CoA reductase inhibitors, which is the mechanism by which they reduce cholesterol biosynthesis, modulate hepatic lipid metabolism, and lower plasma lipid concentration.\[36,37\] Our analysis of the clinical factors affecting the incidence of DRF showed that plasma lipid concentration was not of key importance. Statins have pleotropic effects, and some of their actions may be mediated by other pathways. For example, HMG-CoA reductase is also the rate-limiting step in the conversion of HMG-CoA to mevalonic acid.\[36,37\]

It has been suggested that the renoprotective effects of statins could result from an effect on endothelial cell function. Nitric oxide (NO) mediates endothelial-derived vasodilatation and also promotes both natriuresis and diuresis by increasing renal blood flow and GFR.\[38,39\] NO also increases renin secretion.\[39\] Statins have been shown to improve basal NO activity and NO-dependent endothelium-derived vasodilatation in healthy volunteers and in patients with heart disease.\[40\] They have also been shown to significantly ameliorate endothelial dysfunction in patients with carotid artery disease (CAD) via the regulation of endothelial NO synthase function and phosphatidylinositol 3-kinase/Akt signaling.\[41–43\] Atorvastatin increases NO availability, prevents the production of oxygen free radicals, and downregulates the expression of cyclooxygenase 2.\[44\] In keeping with these findings, short-term atorvastatin treatment in patients with CAD is associated with a reduction in endothelial apoptosis.\[45\] Other studies have also reported that simvastatin can improve endothelial function.\[46,47\]

Inflammation is highly prevalent in patients with CKD and CAD; it is associated with endothelial dysfunction, low endothelial NO production, microcirculation failure, and atherosclerosis.\[48\] The anti-inflammatory effects of statins are well known and may be of relevance to their renoprotective effects.\[6,49\]

The renoprotective effect of statins in patients with ACS undergoing PCI is likely to derive from the action of several synergistic pathways. This might include increased NO synthase activity, reduction in oxidative stress,\[50–55\] reduction in renal vascular permeability and tubular hypoxic injury,\[51,56\] or reduced incidence of CIN. Further interventional studies would be needed to delineate the actions of statins on these processes.

Our results suggest that the renoprotective effect of atorvastatin is similar to that of simvastatin for patients with ACS undergoing PCI. Interestingly, statins have been shown to have unique lipid-lowering, anti-inflammatory, and renoprotective profiles.\[53,36,57\] Atorvastatin is more expensive than other statins but has been reported to have stronger LDL-C lowering and renoprotective properties. Compared with 40 mg simvastatin, 10 mg atorvastatin further reduced hsCRP and anti-inflammatory effects in a crossover study of patients with type 2 diabetes.\[58\] As elevated C-reactive protein is a common feature of CKD, this finding would suggest that atorvastatin might have a stronger anti-inflammatory profile than simvastatin. However, the effects of simvastatin and atorvastatin were comparable in our study. The beneficial renal and cardiovascular effects of atorvastatin and simvastatin might be situation dependent. In a rat model of cigarette smoke-induced acute lung inflammation, simvastatin attenuated inflammation and oxidative stress more than atorvastatin.\[59\] The ability of simvastatin to reduce oxidative stress and reverse the decline of NO was also observed in a study of CIN in rats.\[21\] Further studies are warranted to confirm the activity of statins in different cardiovascular and inflammatory disease scenarios.

5. Conclusion

We studied the medical records of patients with ACS undergoing PCI to compare the renoprotective effects of atorvastatin and simvastatin. Our study revealed that the decline of eGFR and increase in Scr was similar in patients who received atorvastatin or simvastatin for 6 months after PCI. Further studies are warranted to compare the clinical effectiveness of statins in situations where there is a risk of renal injury.

5.1. Limitations

There are several limitations of the current study. First, considering ethical requirement, we did not include a placebo...
control in the present study, and no definitive conclusions can be drawn in this regard. Second, MDRD study equation to estimate renal function was used in this study. However, certain study reported that this equation was less accurate in populations without CKD. In their opinion, eGFR of less than 90 mL/min/1.73 m² is lower than direct measurements. As such, more specific tests need to be used to test the potential effect of statins on renal function in future studies.

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