The Incidence of Kidney Injury for Patients Treated With a High-Potency Versus Moderate-Potency Statin Regimen After an Acute Coronary Syndrome

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Background—Observational studies have raised concerns that high-potency statins increase the risk of acute kidney injury. We therefore examined the incidence of kidney injury across 2 randomized trials of statin therapy.

Methods and Results—PROVE IT-TIMI 22 enrolled 4162 subjects after an acute coronary syndrome (ACS) and randomized them to atorvastatin 80 mg/day versus pravastatin 40 mg/day. A-to-Z enrolled 4497 subjects after ACS and randomized them to a high-potency (simvastatin 40 mg/day × 1 months, then simvastatin 80 mg/day) versus a delayed moderate-potency statin strategy (placebo × 4 months, then simvastatin 20 mg/day). Serum creatinine was assessed centrally at serial time points. Adverse events (AEs) relating to kidney injury were identified through database review. Across both trials, mean serum creatinine was similar between treatment arms at baseline and throughout follow-up. In A-to-Z, the incidence of a 1.5-fold or ≥0.3 mg/dL rise in serum creatinine was 11.4% for subjects randomized to a high-potency statin regimen versus 12.4% for those on a delayed moderate-potency regimen (odds ratio [OR], 0.91; 95% confidence interval [CI], 0.76 to 1.10; P=0.33). In PROVE IT-TIMI 22, the incidence was 9.4% for subjects randomized to atorvastatin 80 mg/day and 10.6% for subjects randomized to pravastatin 40 mg/day (OR, 0.88; 95% CI, 0.71 to 1.09; P=0.25). Consistent results were observed for different kidney injury thresholds and in individuals with diabetes mellitus or with moderate renal dysfunction. The incidence of kidney injury-related adverse events (AEs) was not statistically different for patients on a high-potency versus moderate-potency statin regimen (OR, 1.06; 95% CI, 0.68 to 1.67; P=0.78).

Conclusions—for patients enrolled in 2 large randomized trials of statin therapy after ACS, the use of a high-potency statin regimen did not increase the risk of kidney injury. (J Am Heart Assoc. 2014;3:e000784 10.1161/JAHA.114.000784)

Key Words: acute coronary syndrome • acute kidney injury • kidney • statins
editorial concluded that clinicians should use a low-potency statin regimen whenever possible to provide CV benefit without the increased risk of AKI.12

Because high-potency statins are routinely used in patients after ACS and may be prescribed to a growing number of individuals for primary prevention of MACE, we examined trends in serum creatinine and incidence of kidney injury across 2 large randomized trials of an intensive versus moderate-potency statin regimen in patients after ACS.

Methods

Study Populations

The study designs of the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22) and Phase Z of the A-to-Z trial have been previously described.13,14 In brief, PROVE IT-TIMI 22 was a double-blind, randomized trial that enrolled 4162 patients within 10 days of non-ST-elevation ACS and randomized them to receive either a moderate (pravastatin 40 mg daily) or intensive (atorvastatin 80 mg daily) statin regimen. Subjects were followed for a mean duration of 2 years.

The Z phase of the A-to-Z trial was a double-blind, randomized trial that enrolled 4497 subjects within 5 days of ACS to a strategy of early, high-potency statin therapy (simvastatin 40 mg daily for 1 month, then simvastatin 80 mg daily) versus a strategy of a delayed, lower-potency statin regimen (placebo for 4 months, then simvastatin 20 mg daily). Mean time from symptom onset to randomization was 3.7 days. Subjects were followed for a median of 721 days and up to 24 months.

For both trials, patients were excluded from participation if their serum creatinine was known to be ≥2.0 mg/dL during screening. Both studies were approved by institutional review committees, and all subjects gave informed consent before study participation.

Study Outcomes

Across both trials, serum creatinine was to be assessed in a central lab at baseline and at serial predefined time points during follow-up. For the current analysis, we first examined temporal trends in serum creatinine, as assessed through the central laboratory, stratified by treatment arm. Subsequently, we examined the incidence of kidney injury events for patients randomized to a high-potency versus moderate-potency statin regimen. The definition of kidney injury was adapted according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification of AKI,15 with the baseline creatinine used as the referent. In particular, we identified those subjects who had more than 1.5-fold or ≥0.3-mg/dL rise, or 2- or 3-fold (or absolute rise in serum creatinine to >4.0 mg/dL) rise, in serum creatinine at any time during study follow-up. Because serum creatinine was captured at predefined intervals according to study protocol, we omitted the term “acute” in reference to kidney injury because the timing of the injury could not be confirmed. Estimated glomerular filtration rate (eGFR) was calculated based on the Modification of Diet in Renal Disease equation. Chronic kidney disease (CKD) stage was determined based on the eGFR at randomization according to the KDIGO classification.16

As a secondary analysis, the incidence of all investigator-reported adverse events (AEs) relating to kidney injury was determined through a review of the serious and nonserious AE database and included any event terms pertaining to a new or worsening renal failure or AKI event.

Statistical Analysis

Continuous variables were compared using a Student t test or Wilcoxon rank-sum test (as appropriate); categorical variables were compared by chi-square testing. Event frequencies are reported as incidence rates by treatment arm with corresponding odds ratios (ORs; 95% confidence intervals [CI]). When temporal changes in serum creatinine were analyzed, the analysis was restricted to those subjects with a serum creatinine available at all time points. A linear mixed model with repeated measures was used to evaluate changes in serum creatinine by treatment arm over time. Model covariates included time, treatment arm, time × treatment arm, and baseline serum creatinine. The end-of-treatment visit was excluded from this portion of the analysis, because relatively fewer samples were available. Analyses that examined the incidence of kidney injury used all available serum creatinine values. Sensitivity analyses were conducted for those subjects with a history of diabetes mellitus (DM) or impaired renal function (eGFR <60 mL/min per 1.73 m²) at randomization. Because an earlier analysis suggested that the risk for kidney injury was highest during the first 120 days of therapy,11 we conducted an additional sensitivity analysis that was restricted to the first 4 months of therapy. In A-to-Z, the control arm was administered placebo for the first 4 months of the trial, thereby allowing for a placebo-controlled period of observation. All analyses were conducted in the on-treatment study population in order to avoid the potential dilution of a safety signal by individuals who were no longer on study drug. The PROVE IT-TIMI 22 data set had 80% power to detect a ≈24% increase and 90% power to detect a ≈27% rise in the incidence of a 1.5-fold or ≥0.3-mg/dL rise in serum creatinine in the atorvastatin arm. The A-to-Z data set had 80% power to detect a 20% increase and 90% power to detect the same safety signal in the higher-potency statin arm. The combined data set had 80% power to detect a 15% increase and 90%
power to detect an 18% increase in the incidence of a ≥1.5-fold or 0.3-mg/dL rise in serum creatinine in the higher-potency versus moderate-potency statin arms. Because all analyses were considered exploratory, P<0.05 was considered significant. All analyses were conducted with SAS 9.3 (SAS Institute Inc., Cary, NC).

Results
Of the 4162 subjects enrolled in the PROVE IT-TIMI 22 study, 9.2% reported a known history of renal failure and 14.4% had chronic kidney disease. Baseline mean serum creatinine was 1.03 (±0.24) mg/dL, and mean eGFR was 80.0 (±19.6) mL/min per 1.73 m² (Table 1).

In the A-to-Z trial, 61.1% of subjects had an eGFR <60 mL/min per 1.73 m² at randomization. Baseline mean serum creatinine was 1.14 (±0.26) mg/dL, and mean eGFR was 60.2 (±19.7) mL/min per 1.73 m² (Table 1).

Table 1. Baseline Characteristics by Treatment Arm in the PROVE IT-TIMI 22 Trial

| Characteristic                          | Placebo/Simvastatin 80 mg QD (n=2063) | Placebo/Simvastatin 40 mg QD (n=2099) |
|----------------------------------------|----------------------------------------|----------------------------------------|
| Age, y (mean±SD)                       | 58.1±11.2                              | 58.3±11.3                              |
| Male                                   | 77.9%                                  | 78.4%                                  |
| White race                             | 91.0%                                  | 90.5%                                  |
| Diabetes mellitus                      | 17.8%                                  | 17.5%                                  |
| Hypertension                           | 51.3%                                  | 49.2%                                  |
| History of renal failure               | 8.82%                                  | 9.14%                                  |
| Serum creatinine (mean±SD, mg/dL)      | 1.03±0.25                              | 1.04±0.24                              |
| eGFR (mean±SD, mL/min per 1.73 m²)     | 80.0±20.1                              | 79.0±19.1                              |
| PCI for qualifying event               | 69.1%                                  | 68.7%                                  |
| ACE-I or ARB at hospital discharge     | 60.4%                                  | 62.4%                                  |

Table 2. Baseline Characteristics by Treatment Arm in the A-to-Z Trial

| Characteristic                          | Placebo/Simvastatin 20 mg QD (n=2232) | Simvastatin 40 mg / 80 mg QD (n=2265) |
|----------------------------------------|----------------------------------------|----------------------------------------|
| Age, y (mean±SD)                       | 60.6±10.5                              | 60.2±10.9                              |
| Male                                   | 75.3%                                  | 75.8%                                  |
| White race                             | 84.7%                                  | 85.4%                                  |
| Diabetes mellitus                      | 23.8%                                  | 23.4%                                  |
| Hypertension                           | 49.6%                                  | 50.0%                                  |
| Serum creatinine (mean±SD, mg/dL)      | 1.14±0.26                              | 1.14±0.27                              |
| eGFR (mean±SD, mL/min per 1.73 m²)     | 60.1±19.5                              | 60.3±19.8                              |
| PCI for qualifying event               | 43.9%                                  | 43.2%                                  |
| ACE-I or ARB at hospital discharge     | 75.7%                                  | 74.2%                                  |

Table 2. Baseline Characteristics by Treatment Arm in the A-to-Z Trial

| Characteristic                          | Placebo/Simvastatin 20 mg QD (n=2232) | Simvastatin 40 mg / 80 mg QD (n=2265) |
|----------------------------------------|----------------------------------------|----------------------------------------|
| Age, y (mean±SD)                       | 60.6±10.5                              | 60.2±10.9                              |
| Male                                   | 75.3%                                  | 75.8%                                  |
| White race                             | 84.7%                                  | 85.4%                                  |
| Diabetes mellitus                      | 23.8%                                  | 23.4%                                  |
| Hypertension                           | 49.6%                                  | 50.0%                                  |
| Serum creatinine (mean±SD, mg/dL)      | 1.14±0.26                              | 1.14±0.27                              |
| eGFR (mean±SD, mL/min per 1.73 m²)     | 60.1±19.5                              | 60.3±19.8                              |
| PCI for qualifying event               | 43.9%                                  | 43.2%                                  |
| ACE-I or ARB at hospital discharge     | 75.7%                                  | 74.2%                                  |

Table 2. Baseline Characteristics by Treatment Arm in the A-to-Z Trial

Serum Creatinine
In the PROVE IT-TIMI 22 trial, mean serum creatinine rose across both treatment arms from randomization to month 1 and then trended downward for the duration of the trial (Figure 1A). The mean change in serum creatinine at follow-up visits, as compared with baseline, did not differ significantly for subjects randomized to atorvastatin 80 mg daily versus those randomized to pravastatin 40 mg daily (P=0.17; Figure 1A). At month 4, mean serum creatinine had decreased by 3.88% in the atorvastatin arm and by 2.88% in the pravastatin arm (P=0.07 between treatment arms), as compared with baseline. At month 16, mean serum creatinine had decreased by 5.83% in the atorvastatin arm (P=0.07 between treatment arms).

In the A-to-Z trial, the mean serum creatinine rose across both treatment arms from randomization to month 1 and then trended downward for the duration of the trial (Figure 1A). The mean change in serum creatinine at follow-up visits, as compared with baseline, did not differ significantly for subjects randomized to atorvastatin 80 mg daily versus those randomized to pravastatin 40 mg daily (P=0.17; Figure 1A). At month 4, mean serum creatinine had decreased by 3.88% in the atorvastatin arm and by 2.88% in the pravastatin arm (P=0.07 between treatment arms), as compared with baseline. At month 16, mean serum creatinine had decreased by 5.83% in the atorvastatin arm (P=0.07 between treatment arms).

In the A-to-Z trial, the mean serum creatinine rose across both treatment arms from randomization to month 1 and then trended downward for the duration of the trial (Figure 1A). The mean change in serum creatinine at follow-up visits, as compared with baseline, did not differ significantly for subjects randomized to atorvastatin 80 mg daily versus those randomized to pravastatin 40 mg daily (P=0.17; Figure 1A). At month 4, mean serum creatinine had decreased by 3.88% in the atorvastatin arm and by 2.88% in the pravastatin arm (P=0.07 between treatment arms), as compared with
baseline (Figure 1B). At month 24, mean serum creatinine had decreased by 0.87% in patients treated with a moderate-potency statin regimen and by 0.88% in patients who had been treated with a high-potency statin regimen (P = 0.87 between treatment arms).

Incidence of Kidney Injury

For subjects in the PROVE IT-TIMI 22 trial, the incidence of more than a 1.5-fold or ≥0.3-mg/dL rise, or 2.0- and 3.0-fold (or serum creatinine >4.0 mg/dL) rise, in serum creatinine from baseline at any time during follow-up was similar between treatment arms (Figure 2A). Similarly, in the A-to-Z trial, there were no differences in the incidence of kidney injury for patients randomized to either an intensive or delayed moderate-intensity statin regimen (Figure 2B). Consistent results were observed when patient follow-up was restricted to the first 4 months after randomization (data not shown). Sensitivity analyses demonstrated that the incidence of kidney injury was similar between treatment arms in patients at increased risk of kidney injury, including individuals with DM or those with a baseline eGFR <60 mL/min per 1.73 m² (Tables 3 and 4).

We subsequently examined the incidence of serious and nonserious AEs relating to AKI. When data were pooled across trials, the incidence of AKI-related AEs was similar for subjects who had been randomized to an intensive versus a moderate potency statin regimen during the first 4 months (0.48% versus 0.42%; OR, 1.15; 95% CI, 0.61 to 2.16) and through long-term follow-up (0.92% versus 0.86%; OR, 1.06; 95% CI, 0.68 to 1.67; Figure 3). All analyses were qualitatively

Figure 1. Percentage change in mean serum creatinine by treatment arm in PROVE IT-TIMI 22 (A) and A-to-Z trial (B). Baseline serum creatinine served as the referent. P values reflect (treatment×time) covariate in a linear mixed-effects repeated-measures model with serum creatinine as the outcome. Covariates in the model included time, treatment arm, time×treatment arm, and baseline serum creatinine. The analysis was restricted to those subjects with a sample available at all time points. PROVE IT-TIMI 22 indicates Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22.

Figure 2. Incidence of serum creatinine elevations, as assessed through the central lab in the PROVE IT-TIMI 22 (A) and A-to-Z trial (B), based on the KDIGO classification of kidney injury. KDIGO indicates Kidney Disease: Improving Global Outcomes; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22.
consistent when analyzed in the intention-to-treat study population.

**Discussion**

In the current analysis of 2 randomized trials of statin therapy, the use of a high-potency statin regimen did not raise serum creatinine or increase the risk of kidney injury in individuals after ACS, when compared to a moderate-potency statin regimen. Consistent results were observed in selected high-risk individuals, including those with DM and those with moderate renal dysfunction. Although these observations should be confirmed in additional randomized data sets, these findings provide reassurance to clinicians that exposure to high-potency statin regimens does not appear to cause adverse renal effects. This reassurance is perhaps even more relevant in light of the recently revised ACC/AHA lipid management guidelines that now support the use of a high-potency statin regimen in moderate- to high-risk individuals without known atherosclerotic disease.7

Several trials have demonstrated that high-potency statin regimens reduce the risk of recurrent CV events in patients after ACS.1–4 Although concerns have been raised regarding certain adverse effects of statins,8,9 the weight of the evidence continues to support the use of these medications in at-risk patients. However, more recently, data from 2 large-scale observational studies published in the British Medical Journal raised concerns that high-potency statins may increase the risk of AKI.10,11 In the first of these population-based studies, researchers examined the incidence of AEs in a database of over 2 million primary care patients in the United Kingdom aged 30 to 84 who were newly prescribed statins.10 After adjusting for potential confounders, the researchers concluded that the use of statins (in particular, simvastatin, atorvastatin, and pravastatin) was associated with an increased risk of acute renal failure (hazard ratio ranging from 1.50 to 2.19) and the effect appeared to be dose dependent. The risk emerged during the first year of therapy and continued through 5 years. In addition, the risk of acute renal failure persisted for up to 1 year after statin

| Subgroup | Rise in sCr With Baseline sCr as Referent | Atorvastatin 80 mg QD | Pravastatin 40 mg QD | P Value |
|----------|------------------------------------------|-----------------------|---------------------|---------|
| Diabetic patients (n=994) | ≥1.5-fold or ≥0.3-mg/dL rise | 12.6% | 15.0% | 0.29 |
| | ≥1.5-fold | 2.20% | 3.03% | 0.42 |
| | ≥2.0-fold | 0.40% | 0.81% | 0.45 |
| | ≥3.0-fold or sCr ≥4.0 mg/dL | 0.40% | 0.40% | 1.00 |
| Baseline eGFR <60 mL/min per 1.73 m² (n=2554) | ≥1.5-fold or ≥0.3-mg/dL rise | 10.1% | 9.8% | 0.80 |
| | ≥1.5-fold | 1.25% | 1.97% | 0.15 |
| | ≥2.0-fold | 0.31% | 0.24% | 1.00 |
| | ≥3.0-fold or sCr ≥4.0 mg/dL | 0.23% | 0.08% | 0.63 |

eGFR indicates estimated glomerular filtration rate; NA, not applicable; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22; sCr, serum creatinine.

Table 4. Incidence of Kidney Injury in Selected High-Risk Individuals by Treatment Arm in A-to-Z

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discontinuation. In a second large-scale study, investigators conducted a retrospective observational analysis of more than 2 million individuals aged 40 or older who were registered in administrative databases in Canada, the United Kingdom, and United States and who were newly prescribed statins. After accounting for the propensity to be treated with a statin, the use of a high-potency statin (defined as ≥10 mg/day rosuvastatin, ≥20 mg/day atorvastatin, and ≥40 mg/day simvastatin) was associated with an increased risk of hospitalization for AKI and the risk appeared to be highest during the first 120 days after initiation of therapy. However, because both data sets were observational, neither analysis could exclude the possibility that their findings were explained by residual confounding.

To date, randomized trials have not specifically addressed the question of whether statin therapy may increase the risk of AKI. In a report by the U.S. Food and Drug Administration, the incidence of renal-related AEs in the JUPITER (Justification of the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial was similar (albeit numerically higher) for high-risk primary prevention patients randomized to rosuvastatin 20 mg daily, as compared to those on placebo (6.0% versus 5.4%; RR, 1.19; 95% CI, 0.61 to 2.31). In the current analysis of 8659 subjects randomized to an intensive or moderate statin regimen after ACS, we did not observe any directional signal to suggest any adverse renal effects with high-potency statin regimens. Nonetheless, we acknowledge that the current analysis was relatively underpowered to detect a small safety signal.

On a biological level, there is not a clear mechanism to support the concern that statins increase the risk of AKI. It has been hypothesized that statins might increase the risk of AKI either as a result of an increased risk of rhabdomyolysis or through suppression of the antioxidant, coenzyme Q10. In contrast, accumulating evidence suggests that statins may offer a renal protective effect. To that end, randomized trials have demonstrated that statins may reduce the risk of contrast-induced nephropathy in patients undergoing cardiac catheterization.19–21 The renal protective effects of statins may be related to a variety of pleiotropic effects, including angiotensin receptor down-regulation, reduced endothelial dysfunction, reduced endothelin-1 synthesis, and increased nitric oxide bioavailability.22–24 Statins may also limit reactive oxygen species production, interfere with the inflammatory cascade, and protect against complement-mediated injury.24,25

The current analysis offers relevant advantages, when compared with earlier analyses conducted within large databases. Although observational data sets may be able to achieve a high degree of precision based on their very large sample size, such analyses are unable to exclude the possibility that their findings may be explained by residual confounding. Namely, individuals who are prescribed statins, in particular, a high-potency statin regimen, may differ profoundly from individuals who do not receive these therapies. Although the researchers attempted to take these differences into account in their analysis, they were limited by the availability and accuracy of those variables that were captured in their database. In the current analysis, the randomized allocation of statin therapy eliminated the risk of bias by indication. Another advantage of our study design was the central assessment of serum creatinine in all subjects at predefined intervals throughout follow-up. In contrast, ascertainment bias may exist within large registries, because laboratory testing is sporadic and individuals who are prescribed statin therapy may receive enhanced surveillance, thereby leading to a more frequent diagnosis of AKI. Although a very large data set will have increased power to detect an infrequent AE, we did not observe any directional signal to suggest any adverse renal effects with high-potency statin regimens. Nonetheless, we acknowledge that the current analysis was relatively underpowered to detect small changes in serum creatinine.

Figure 3. Incidence of investigator-reported serious or nonserious adverse events that were related to kidney injury across the PROVE IT-TIMI 22 and A-to-Z trials. PROVE IT-TIMI 22 indicates Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22.
or a small increase in the incidence of kidney injury events; therefore, we encourage further examination of this issue across additional randomized trials of statin therapy.

Additional limitations of the current analysis warrant consideration. Because serum creatinine was collected at prespecified time points, we cannot exclude a subclinical transient rise in creatinine that may have occurred between study visits. We are also unable to assess the rate of rise in subjects who were found to have an elevated serum creatinine level at a study visit. However, consistent results were observed when we examined the incidence of serious and nonserious AEs, including hospitalizations for AKI. Also, because subjects in the trial were enrolled in the first 2 weeks after ACS, their baseline creatinine and eGFR may not reflect their true steady state. Because individuals with a serum creatinine level >2.0 mg/dL were excluded from enrollment in the study trials, the current analysis included very few subjects with an eGFR <30 mL/min per 1.73 m². To that end, subjects enrolled in clinical trials are not always representative of the general population; however, both trials enrolled patients at moderate to high risk of a recurrent CV event and therefore had comorbidities that may place them at risk of renal dysfunction.

In conclusion, in the current analysis, there was no indication that a high-potency statin regimen raised serum creatinine or increased the risk of kidney injury in patients after ACS, when compared to a moderate-potency statin regimen. These findings may carry important prognostic implications, because AKI has been shown to be independently associated with an increased risk of death in patients after myocardial infarction.28 Because the CV benefits of high-potency statin regimens in this high-risk patient population are well established, these regimens should remain the standard of care for patients after ACS. Furthermore, these observations provide valuable safety information for a growing number of individuals who are now eligible for a high-potency statin regimen under the revised ACC/AHA guideline recommendations. Because individual trials are relatively underpowered to detect a low-frequency safety signal, additional analyses from randomized data sets of statin use should be conducted to confirm these findings.

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