The Risk of Hematuria and Proteinuria with Rosuvastatin Use in Severe CKD

By Zainab Obaidi and Marco Bonilla

Statin therapy has been on the rise in patients with chronic kidney disease (CKD) following the National Kidney Foundation and American Heart Association guidelines recognizing CKD as a cardiovascular risk equivalent for atherosclerotic cardiovascular disease prevention (1, 2). Several clinical and basic sciences studies have noted the benefits of statin use, such as renovascular protection and delaying fibrosis (3–7). However, adverse effects, such as hematuria and proteinuria, have been reported with high-dose rosuvastatin use since its approval by the U.S. Food and Drug Administration (FDA) in 2003 (8, 9). The reported incidence of proteinuria was <1% and <1.5% in rosuvastatin, 5–10 mg dose versus 40 mg dose, respectively (9). A recent large observational cohort study by Shin et al. (10), published in *JASN*, examined the association of hematuria and proteinuria risk with rosuvastatin versus atorvastatin use.

The investigators compared approximately 1 million new statin users (n = 152,101 rosuvastatin and n = 795,799 atorvastatin) during a median follow-up of 3 years, using a database of 40 health care electronic medical records in the United States from 2011 to 2019. Eligibility criteria included patients with no prior hematuria or proteinuria, patients' recent labs (creatinine, glomerular filtration rate [GFR], urine albumin-to-creatinine ratio [UACR], or urine protein-to-creatinine ratio), and patients new to statin therapy (within 1 year). Patients were excluded if they had missing or no labs and/or kidney failure with replacement therapy or evidence or rhabdomyolysis.

Both groups had similar baseline characteristics with a mean age of 60 years, 82% White, 28% with diabetes, 66% with hypertension, and 10% with coronary artery disease. Hematuria (defined as dipstick hematuria ≥1+ or the presence of three or more red blood cells in urine microscopy noted at more than two separate time points) occurred in 5178 individuals (3.4%) in the rosuvastatin group versus 22,604 individuals (2.8%) in the atorvastatin group over a 3-year follow-up. The incidence rate of hematuria among patients with estimated GFR (eGFR) <30 mL/min/1.73 m^2 was twofold higher than those with eGFR >60 mL/min/1.73 m^2 (8.4 events for rosuvastatin vs 7.9 events for atorvastatin per 1000 person-years).

For the risk of proteinuria (defined as dipstick proteinuria ≥2+ or UACR ≥300 mg/g noted at more than two separate timepoints), the incidence rates were 1.2% (n = 1776) for rosuvastatin and 0.9% (n = 7495) for atorvastatin, with a ninefold greater risk for patients with eGFR <30 mL/min/1.73 m^2. Eighty percent of patients with an eGFR <30 mL/min/1.73 m^2 were started on a higher rosuvastatin dose than what is recommended as the initial dose by the FDA (5 mg). There was a greater risk of proteinuria and hematuria noted with higher rosuvastatin dosing and kidney failure with replacement therapy risk (inverse probability of treatment weighting [IPTW] hazard ratio, 1.15; 95% CI, 1.02–1.30) when compared with atorvastatin.

This study had several strengths. It used the IPTW within each of the 40 study cohorts to minimize confounders between the two treatment groups. This is one of the first studies that examined the risk of hematuria and proteinuria with high-intensity statins in a large CKD population. The authors noted some limitations to the study relating to the study population, as most individuals were insured, and <1% were with eGFR <30 mL/min/1.73 m^2, which limits its generalizability. In addition, other causes of proteinuria should be carefully examined, as approximately 60% of the study population had hypertension and diabetes, 30% were on angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and 1% was on sodium glucose co-transporter 2 inhibitors. Kidney biopsy was not performed to determine the cause of proteinuria or whether proteinuria resolved on discontinuation of the statins.

The association of rosuvastatin with proteinuria can also be related to its renal clearance (10%–25%) when compared with other statins that are hepatically metabolized (8, 11). In vitro studies' proposed mechanisms for proteinuria with statin use included a dose-dependent impaired albumin tubular absorption via receptor-mediated endocytosis in proximal tubules due to β-hydroxy β-methylglutaryl-coenzyme A reductase inhibition (12, 13). Another study noted oxidative stress leading to mitochondrial dysfunction due to reduced ubiquinone synthesis (14). van Zyl-Smit and colleagues (15) reported that a case of proteinuria and hematuria that resolved upon rosuvastatin discontinuation and kidney biopsy findings was notable for tubular casts and chronic tubulointerstitial kidney disease.

In conclusion, pharmacovigilance of rosuvastatin used in patients with severe CKD is of importance. The initial rosuvastatin dose should be reduced to 5 mg daily to a maximum dose of 10 mg daily in patients with severe CKD (eGFR <30 mL/min per 1.73 m^2). Adequate follow-up and patient education are required to monitor for adverse effects, such as proteinuria, hematuria, or acute kidney injury, during drug initiation. Nonetheless, further studies are needed to elucidate the effect of statins in severe kidney diseases. ■

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The authors report no conflicts of interest.

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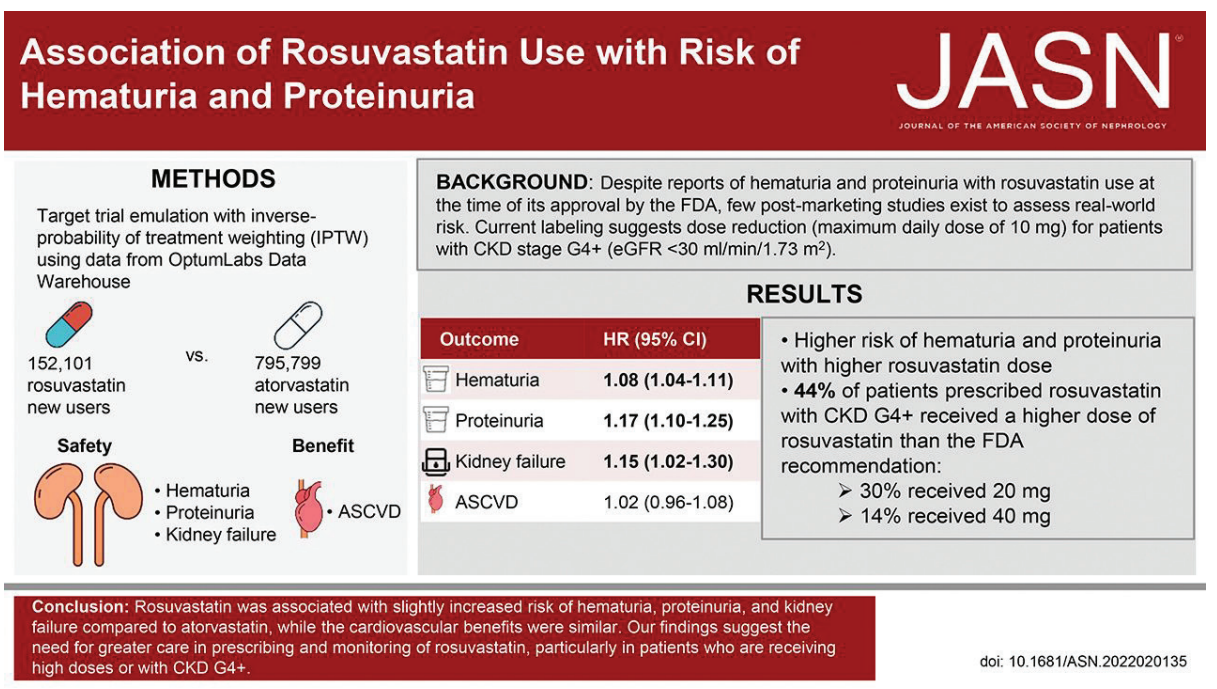

ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval. Reprinted from Shin et al. (10).