Longitudinal Assessment of Estimated Glomerular Filtration Rate in Apparently Healthy Adults: A Post hoc Analysis from the JUPITER Study (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin)

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ABSTRACT

Background: Serum creatinine–based estimates of glomerular filtration rate (eGFR) are frequently used to identify patients with chronic kidney disease and assess cardiovascular risk both in clinical trials and in clinical practice. Although change in eGFR may be useful to assess change in renal function in patients with chronic kidney disease, the utility of serum creatinine–based eGFR is uncertain, particularly among individuals with normal or only mildly impaired renal function.

Objective: The goal of this study was to examine the relationship between baseline serum creatinine and eGFR, as well as changes in these parameters, in apparently healthy adults in a post hoc analysis of data obtained in participants in the JUPITER study (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin).

Methods: JUPITER was a randomized study of rosuvastatin 20 mg versus placebo in apparently healthy adults with high-sensitivity C-reactive protein levels ≥2.0 mg/L, LDL-C <130 mg/dL, and serum creatinine ≤2.0 mg/dL. Changes from baseline in serum creatinine and eGFR, based on the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, were assessed in the entire population and in subsets classified according to baseline eGFR status.

Results: Baseline characteristics of the 16,279 JUPITER study participants (mean age, 66 years; 62% men; 72% white; and 58% with a history of hypertension) who had both a baseline and ≥1 postbaseline serum creatinine measurement were similar to the entire population of 17,802 patients who entered the trial. The mean age of the study population was 66 years, 62% were men, 72% were white, and 58% had a history of hypertension. Mean (SD) serum creatinine increased from baseline by 0.08 (0.16) mg/dL and 0.09 (0.14) mg/dL in the rosuvastatin and placebo groups, respectively ($P = 0.001$) at year 1 and by 0.09 (0.18) and 0.10 (0.16) mg/dL ($P = 0.0045$) at the final visit. Reductions in MDRD and CKD-EPI eGFR were ~0.5 mL/min/1.73 m^2 greater with placebo than with rosuvastatin ($P < 0.004$) at year 1 and the final visit. The magnitude of eGFR change was closely related to baseline eGFR, with greater reductions among subjects with eGFR ≥60 mL/min/1.73 m^2 in both the rosuvastatin and placebo groups. Among those with an eGFR ≥90 mL/min/1.73 m^2 , mean changes at year 1 and final visit ranged from –16 to –23 mL/min/1.73 m^2 with MDRD and CKD-EPI, respectively; in contrast, mean changes were <1 mL/min/1.73 m^2 in subjects with eGFR <60 mL/min/1.73 m^2 .

Conclusions: In JUPITER, reductions in MDRD or CKD-EPI eGFR levels were greater in study participants with higher baseline eGFR levels but less in the rosuvastatin than in the placebo group. Future studies are required to assess the reliability of serum creatinine–based estimates of GFR to assess change in renal function, particularly among individuals with normal serum creatinine levels. ClinicalTrials.gov identifier: NCT00239681. (*Clin Ther.* 2011;33:717–725)

Key words: CKD-EPI equation, eGFR, MDRD equation, serum creatinine.

INTRODUCTION

Serum creatinine is the most commonly used laboratory measurement to assess renal function in clinical

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practice because it reflects, albeit imperfectly, glomerular filtration rate (GFR). More accurate and precise estimates of GFR can be obtained using equations that control for factors other than GFR that also affect serum creatinine. The most frequently used equation for estimates of GFR (eGFR) is based on data obtained from the Modification of Diet in Renal Disease (MDRD) study.[1] This equation incorporates age, sex, and race, in addition to serum creatinine levels. More recently, an eGFR equation was developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) research group that included measurements of serum creatinine and GFR from apparently healthy individuals as well as from patients with CKD in its validation data set.[2]

Although these equations unquestionably improve identification of patients with at least moderately impaired renal function when compared with serum creatinine alone, their utility in assessing change in renal function over time is less clear, particularly among individuals with normal or only mildly impaired renal function (60–89 mL/min/1.73 m^2).[3] Changes in eGFR based on the MDRD or CKD-EPI equations depend almost entirely on changes in serum creatinine levels when assessed over a relatively short period of time (eg, ≤1 year) because gender and race are unchanged and the age-related decline in renal function is small (~1 mL/min/1.73 m^2 per year after the age of 30 years).[4,5] For this reason, only a small change in eGFR during a 1-year period would be expected among individuals with normal renal function during a relatively brief duration of follow-up. However, data obtained from the previously reported JUPITER study (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) were assessed. The study determined the effects of rosuvastatin 20 mg/d versus placebo on the risk of major cardiovascular events among 17,802 apparently healthy men and women with LDL-C levels <130 mg/dL and high-sensitivity C-reactive protein (hsCRP) levels ≥2.0 mg/L. A median MDRD eGFR was reported that was ~7 mL/min/1.73 m^2 lower when compared with baseline after a 1-year follow-up of both rosuvastatin-treated study participants and those receiving placebo.[6] This magnitude of change was considered surprising when viewed within the context of data reported from other cardiovascular disease prevention trials.[7] For this reason, we performed an analysis of eGFR changes that were observed across the range of baseline serum creatinine and eGFR levels encountered in the JUPITER study population. Changes in eGFR were assessed using the MDRD and CKD-EPI equations among the entire group of study participants and among subsets classified according to their baseline eGFR levels, using data obtained at year 1 and the final visit of the trial.

SUBJECTS AND METHODS

JUPITER was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial conducted in 26 countries at 1315 sites designed to determine the effects of rosuvastatin 20 mg/d on the risk of major cardiovascular events among apparently healthy adults with an elevated hsCRP but normal LDL-C level.[6,8] The study was performed in accordance with ethical principles that have origin in the Declaration of Helsinki[9] and are consistent with International Conference on Harmonisation/Good Clinical Practice.[10] Subjects who consented to participate in the trial signed a consent form that had been approved by an institutional review board or ethics committee. Financial support for the trial was provided by AstraZeneca Pharmaceuticals LP, who collected trial data and monitored study sites.

As previously described,[8] study participants were men aged ≥50 years and women aged ≥60 years with no pre-existing history of cardiovascular disease, LDL-C levels <130 mg/dL, and hsCRP ≥2.0 mg/L. Subjects were excluded if they had serum creatinine levels >2.0 mg/dL. JUPITER was an event-driven trial designed to continue until a total of 520 study participants experienced a confirmed major cardiovascular event (cardiovascular death, stroke, myocardial infarction, unstable angina, or arterial revascularization) unless early stopping criteria were met at interim analyses. Criteria for stopping the trial, which were based on the O'Brien-Fleming method and Lan-DeMets spending function, were met at the second interim analysis and the trial was closed early due to clear evidence of a reduction in major cardiovascular events during rosuvastatin treatment. The median duration of follow-up was 1.9 years, with a maximum follow-up of 5 years.[6]

Serum creatinine levels were obtained at baseline, after 1 year, and at the final visit of the JUPITER trial. Creatinine analyses were performed in JUPITER core central laboratories using the Roche Modular Analyt-