Soluble Urokinase Plasminogen Activator Receptor and Outcomes in Patients with Diabetes on Hemodialysis

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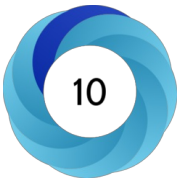

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Abstract

Background and objectives Soluble urokinase plasminogen activator receptor is a novel biomarker strongly predictive of cardiovascular outcomes implicated in the pathogenesis of kidney disease. Soluble urokinase plasminogen activator receptor levels, however, correlate with declining kidney function. It is unclear whether soluble urokinase plasminogen activator receptor levels remain associated with outcomes in patients with ESRD.

Design, setting, participants, & measurements We measured plasma soluble urokinase plasminogen activator receptor levels in 1175 patients (mean age =66±8 years old, 54% men) with type 2 diabetes mellitus on hemodialysis participating in the German Diabetes and Dialysis Study followed for a median of 4 years for outcomes including all-cause death, cardiovascular events, and infection-related mortality. Survival analysis was performed using stepwise Cox proportional hazards models adjusted for potential confounders. Also, adjustments were made for inflammatory markers (C-reactive protein and leukocyte count) and the oxidative stress marker asymmetric dimethyl arginine to investigate potential mediators of the relationship between soluble urokinase plasminogen activator receptor and outcomes.

Results Median soluble urokinase plasminogen activator receptor levels were 10,521 pg/ml (interquartile range, 9105–12,543 pg/ml). When stratified by tertiles, patients with soluble urokinase plasminogen activator receptor >11,633 pg/ml (third tertile) had adjusted 1.6-fold higher mortality (hazard ratio, 1.60; 95% confidence interval, 1.27 to 2.03) compared with those with low soluble urokinase plasminogen activator receptor <9599 pg/ml (first tertile). Risks of sudden death and stroke were higher (adjusted hazard ratio, 1.98; 95% confidence interval, 1.27 to 3.09 and adjusted hazard ratio, 1.74; 95% confidence interval, 1.05 to 2.90, respectively), together accounting for higher incidence of cardiovascular events (adjusted hazard ratio, 1.48; 95% confidence interval, 1.15 to 1.89). Associations with outcomes persisted after adjusting for C-reactive protein, leukocyte count, and asymmetric dimethyl arginine. Addition of soluble urokinase plasminogen activator receptor to a risk factor model modestly improved risk discrimination for all-cause death (ΔC statistic, 0.02; 95% confidence interval, 0.00 to 0.03) and cardiovascular events (ΔC statistic, 0.02; 95% confidence interval, 0.00 to 0.05).

Conclusions The association of soluble urokinase plasminogen activator receptor levels with outcomes persists in patients on hemodialysis. Additional study is warranted to characterize the underlying pathways of that association, which may yield opportunities to develop new therapeutic strategies.

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