CLINICAL RESEARCH STUDY

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Post-Discharge Worsening Renal Function in Patients with Type 2 Diabetes and Recent Acute Coronary Syndrome

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ABSTRACT

BACKGROUND: Worsening renal function during hospitalization for an acute coronary syndrome is strongly predictive of in-hospital and long-term outcome. However, the role of post-discharge worsening renal function has never been investigated in this setting.

METHODS: We considered the placebo cohort of the AleCardio trial comparing aleglitazar with standard medical therapy among patients with type 2 diabetes mellitus and a recent acute coronary syndrome. Patients who had died or had been admitted to hospital for heart failure before the 6-month follow-up, as well as patients without complete renal function data, were excluded, leaving 2776 patients for the analysis. Worsening renal function was defined as a >20% reduction in estimated glomerular filtration rate from discharge to 6 months, or progression to macroalbuminuria. The Cox regression analysis was used to determine the prognostic impact of 6-month renal deterioration on the composite of all-cause death and hospitalization for heart failure.

RESULTS: Worsening renal function occurred in 204 patients (7.34%). At a median follow-up of 2 years the estimated rates of death and hospitalization for heart failure per 100 person-years were 3.45 (95% confidence interval [CI], 2.46-6.36) for those with worsening renal function, versus 1.43 (95% CI, 1.14-1.79) for patients with stable renal function. At the adjusted analysis worsening renal function was associated with the composite endpoint (hazard ratio 2.65; 95% CI, 1.57-4.49; $P < .001$).

CONCLUSIONS: Post-discharge worsening renal function is not infrequent among patients with type 2 diabetes and acute coronary syndromes with normal or mildly depressed renal function, and is a strong predictor of adverse cardiovascular events.

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Chronic kidney disease and worsening renal function during hospitalization are established risk factors for long-term adverse outcome in patients with acute coronary syndromes.[1-3] This association has been reported for any degree of renal dysfunction and ascribed to several factors, including comorbidities, activation of the neurohormonal system during the acute coronary syndrome event, and adverse effects of pharmacologic and interventional treatments.[4-6] Indeed, a progressive loss in renal function has been demonstrated both in the early phase and during the first year of follow-up after an acute coronary syndrome event.[7] Previous studies have demonstrated the association of post-discharge worsening renal function with mortality and increased rates of hospitalization in patients with chronic heart failure,[8] but data in acute coronary syndrome patients, especially in those with type 2 diabetes, are lacking.

CLINICAL SIGNIFICANCE

- Post-discharge worsening renal function is a relatively common condition in patients with type 2 diabetes, recent acute coronary syndrome, and preserved renal function.
- Factors that portend a more advanced diabetic status are associated with a higher risk of worsening renal function.
- Post-discharge worsening renal function is associated with mortality and increased rates of hospitalization. Careful selection of drug therapy and a more strict follow-up should be recommended in these patients.

Because of the well-known negative effect of glitazones on renal function, serum creatinine levels were carefully monitored in the AleCardio (Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus) study by using central laboratory measurements, thus offering a unique opportunity to reliably assess changes in renal function in patients with diabetes and recent acute coronary syndrome.[9,10]

Therefore, the aim of the present study was to investigate predictors of post-discharge worsening renal function and to determine the association of post-discharge worsening renal function with the long-term composite outcome of all-cause death and hospitalization for heart failure in a cohort of patients with type 2 diabetes discharged after an acute coronary syndrome.

METHODS

Study Cohort

The AleCardio trial was a randomized, double-blind, placebo-controlled, multicenter trial [NCT01042769] testing the safety and efficacy of aleglitazar (a potent dual peroxisome proliferator–activated receptors agonist), added to standard medical therapy, in improving cardiovascular outcomes in patients with type 2 diabetes mellitus and a recent acute coronary syndrome event.[9,10] In total, 7226 patients were enrolled from 720 sites in 26 countries between February 2010 and May 2012. Eligible were patients with known or recently diagnosed diabetes mellitus who were randomized at hospital discharge from a recent acute coronary syndrome or after a screening period of no longer than 12 weeks to allow stabilization of their clinical condition, completion of planned revascularization procedures, and achievement of steady-state renal function. An estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m^2 at baseline was among the exclusion criteria of the trial. Patients with symptomatic heart failure or hospitalization with heart failure within the previous 12 months were also excluded. At a median follow-up period of 24 months (interquartile range [IQR], 19-30 months), aleglitazar did not decrease the primary efficacy endpoint of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke, whereas it was significantly associated with the safety renal endpoint (defined as development of end-stage renal disease, doubling of serum creatinine, or ≥50% increase in creatinine leading to study drug discontinuation). A detailed account of the methodology of the study and of the results of the main analysis is described elsewhere.[9,10] In view of the results of the AleCardio trial, the present analysis was limited to the placebo cohort of 3610 patients. Patients with eGFR of <45 mL/min/1.73 m^2, those who had died or had been admitted to hospital for heart failure before the 6-month follow-up, as well as those without data on worsening renal function were excluded from the analysis, resulting in a study cohort of 2776 patients (**Figure 1**). The appropriate national and institutional regulatory and ethics boards approved the original AleCardio protocol, and all patients provided written, informed consent.

Definitions

Worsening renal function was defined as 1) a decrease in eGFR ≥20% from discharge to 6-month follow-up; 2) progression to macroalbuminuria; or 3) the combination of both criteria.[11,12] Serum biochemistry and urinalysis were measured using an analytical corelab; eGFR was calculated using the Modification of Diet in Renal Disease Study equation.[13] Progression to macroalbuminuria was defined as urinary albumin-to-creatinine ratio >300 mg albumin/g creatinine at 6 months in patients with baseline urinary albumin-to-creatinine ratio values <30 mg albumin/g creatinine. This definition reflects the evidence that an accurate evaluation and staging of chronic kidney disease and its relative clinical risk should take into account the combination of eGFR and albuminuria.[14-19]

Hospitalization for heart failure was defined as signs or symptoms of congestive heart failure not present at