Heart-Kidney Interactions in Ischemic Syndromes

To the Editor:

In a recent GUSTO-IV substudy of 6809 patients with non-ST-segment–elevation acute coronary syndromes, raised serum N-terminal pro-brain natriuretic peptide (BNP) and creatinine clearance below the 25th percentile (51 mL/min) independently predicted 1-year mortality.1 The combination of creatinine clearance with BNP was the strongest predictor of death, compared with each marker alone, or to the combination of BNP with troponin T, C-reactive protein, or heart rate. Strikingly, creatinine clearance <51 mL/min, but not raised BNP, also predicted myocardial infarction (MI) at 30 days. Unexpectedly, however, the authors did not discuss the association of renal impairment with incident death and MI.

We propose that renal dysfunction may increase the risk of death and MI in these patients, at least in part, through an associated reduction of erythropoietin secretion2 and insulin-like growth factor-1 (IGF-1).3 Erythropoietin is a recognized stimulus for the mobilization of endothelial progenitor cells, which are considered mediators of vascular repair by homing to sites of endothelial injury or apoptosis, and are related to endothelial function.4 IGF-1 is emerging as a powerful cardioprotective agent, as an insulin-sensitizing vasodilator, and as a ubiquitous antiapoptotic factor.5 The reduction of IGF-1 (by promoting endothelial dysfunction and cellular apoptosis) and the lowering of erythropoietin (by hindering endothelial progenitor cell—mediated vascular repair) may thus contribute significantly to the unfavorable course of patients with ischemic syndromes and renal impairment.

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Response

We appreciate the interest of Drs Conti and Andreotti in our recently published study.1 The association between a moderately reduced creatinine clearance and the outcome in patients with non-ST-elevation acute coronary syndromes is interesting, indeed. Our results confirm the results of previous studies of patients with various types of cardiovascular diseases, showing that renal insufficiency is associated with a worse short- and long-term outcome.2 No previous study has, however, included a sufficient number of patients to enable the evaluation of the individual endpoints of mortality and myocardial infarction (MI) separately. Creatinine was analyzed and creatinine clearance calculated for 7703 patients (98.7%). The median level was 66 mL/min with interquartile limits of 51 and 84 mL/min. Mortality was increasing with increasing quartiles of reduced creatinine clearance. Thus, at 1 year, the mortality was 2.2% (43), 4.8% (93), 8.6% (162), and 17.7% (347) for the respective quartiles (P < 0.001). Also, the incidence of MI at 30 days follow-up was increasing, 3.6% (70) 4.7% (91), 5.3% (100), and 8.4% (165) (P < 0.001).

Patients with renal dysfunction are at high risk partly because of the high prevalence of multiple risk factors. In the GUSTO-IV substudy, a reduced creatinine clearance was significantly correlated with a number of predictors of a worse outcome, such as diabetes; hypertension; age; heart failure; previous MI; and elevation of C-reactive protein, troponin T, and N-terminal pro-brain natriuretic peptide.3 Still, a creatinine clearance below the 1st quartile was independently associated with mortality as well as subsequent MI in multivariate analyses.1

Smoking, hyperlipidemia (including elevated Lp[a] lipoprotein levels), the insulin resistance syndrome, and hyperhomocystinemia are other factors contributing to coronary artery disease in patients with renal dysfunction. Other specific cardiovascular risk factors contributing to the vasculopathy induced by renal disease include secondary hyperparathyroidism, elevated levels of oxidized LDL, endothelial dysfunction, and diminished vascular nitric oxide production.4 The chronic anemia and volume overload associated with severe renal dysfunction may be important contributors to an increased vascular stiffness, the development of heart failure, and subsequent mortality. Moreover, as correctly pointed out by Drs Conti and Andreotti, a reduced secretion of erythropoietin and insulin-like growth factor5 may also specifically contribute to an increased risk of thrombotic cardiovascular events by an inhibition of vascular repair.

Our results in the GUSTO-IV substudy have further enlightened the recognition of even moderate renal dysfunction in the risk assessment of patients with acute coronary syndromes. Additional studies on the actual mechanisms of the striking increase in mortality and MI may also provide information on specific treatment alternatives for these patients.

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