Elevated serum cystatin C level is an independent predictor of contrast-induced nephropathy and adverse outcomes in patients with peripheral artery disease undergoing endovascular therapy

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Objective: **The aim of this study was to investigate the association of serum cystatin C levels with contrast-induced nephropathy (CIN) and adverse clinical events in patients with peripheral artery disease (PAD).**
Methods: **A total of 240 PAD patients who received endovascular therapy were included in this retrospective analysis. Serial serum levels of creatinine and cystatin C before and within 48 hours of endovascular therapy were evaluated for the incidence of CIN. The relationship between serum cystatin C levels and the incidence of major adverse events, defined as a composite of all-cause death, myocardial infarction, stroke, amputation, and target vessel revascularization, was investigated.**
Results: **The incidence of CIN increased from 1.7% to 27.9%, depending on the quartile of baseline cystatin C level. Baseline serum cystatin C level (area under the curve of the receiver operating characteristic curve, 0.757; 95% confidence interval [CI], 0.696-0.735) predicted the incidence of CIN better than baseline serum creatinine level (area under the curve, 0.629; 95% CI, 0.563-0.691; $P < .001$). An elevated baseline cystatin C level was an independent predictor of CIN (hazard ratio, 14.37; 95% CI, 4.11-50.19; $P < .001$) and major adverse events in patients with PAD (hazard ratio, 2.57; 95% CI, 1.28-5.17; $P = .008$).**
Conclusions: **We found elevated baseline cystatin C level to be an independent risk factor for CIN and a predictor of all-cause mortality and major adverse events in patients with PAD undergoing endovascular therapy. (J Vasc Surg 2015;61:1223-30.)**

Cystatin C is a cysteine-protease inhibitor and a low-molecular-weight protein produced by all nucleated cells at a constant rate.[1] Because of its small size, it is freely filtered by the glomerulus and fully reabsorbed and catabolized by the proximal tubules.[2] Compared with creatinine, serum cystatin C level is less affected by muscle mass, diet, age, gender, and race. Previous studies report that cystatin C is superior to creatinine in estimating glomerular filtration rate (GFR)[3] and is more sensitive to acute changes in renal function, such as contrast-induced acute kidney injury.[4,5] Furthermore, serum cystatin C level is a good predictor of cardiovascular mortality and morbidity in patients with coronary artery disease (CAD) and peripheral artery disease (PAD).[4,6,7]

Contrast-induced nephropathy (CIN) is a potentially serious complication of angiographic procedures that use contrast media. It is the third most common cause of hospital-acquired renal insufficiency and one of the most important predictive factors for short-term and long-term adverse events after such angiographic procedures.[8] The risk of CIN increases with age, chronic kidney disease, and diabetes mellitus.[9] Patients with PAD often have multiple risk factors for CIN and generally have poorer prognoses than patients with CAD.[10] However, data on the association of cystatin C levels with CIN in patients with PAD are limited. Therefore, the aim of the present study was to evaluate the role of cystatin C in predicting CIN and clinical outcomes in patients with PAD undergoing endovascular therapy.

METHODS

Study population. From the retrospective database of endovascular therapy in lower limb artery disease at Severance Cardiovascular Hospital, Yonsei University Health System, we identified a total of 472 patients with intermittent claudication or critical limb ischemia who were treated with percutaneous transluminal angioplasty (PTA) from October 2010 to September 2012. Of these, serial serum cystatin C data were available for 259 patients. Cystatin

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C was not measured in 113 patients referred from other departments for the endovascular therapy, 81 patients with end-stage renal failure requiring chronic dialysis, and 19 patients with acute embolic occlusion. After exclusion of three patients with Buerger disease and 16 patients with a failed procedure, a total of 240 patients with PAD who were treated with endovascular therapy were evaluated in this study. None of the enrolled patients had exposure to contrast dye within 7 days before the index procedure. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Institutional Review Board approved this study and waived the requirement for informed consent because of its retrospective design.

Definitions. CIN was defined as an absolute increase in serum creatinine level of ≥0.5 mg/dL or as a relative increase of ≥25% from baseline within 48 hours after exposure to iodinated contrast medium when no other cause of kidney insult was identified.[11] Major adverse events were defined as a composite of all-cause death, myocardial infarction, stroke, unplanned amputation, and target vessel revascularization.

Renal function evaluation. Fasting venous blood samples were drawn for serial measurement of serum creatinine and cystatin C concentrations before and at 24 and 48 hours after PTA. Serum cystatin C concentration was determined with use of particle-enhanced nephelometric immunoassay kits (Nephelometer II; Dade Behring, Marburg, Germany). Serum creatinine levels were analyzed by an enzymatic method with an automatic biochemical analyzer (7600 Auto Analyzer; Hitachi Inc, Tokyo, Japan). The estimated GFR (eGFR) was calculated by the re-expressed Modification of Diet in Renal Disease equation after calibration of serum creatinine (Scr) measurements to isotope dilution mass spectrometry-traceable values: GFR (mL/min/1.73 m^2) = $175 \times Scr^{-1.154} \times Age^{-0.203} \times (0.742 \text{ if female})$.[12]

Procedure and follow-up. All patients had a baseline physical evaluation, an ankle-brachial index (ABI) measurement, and at least one imaging test, such as duplex ultrasound, computed tomographic angiography, or magnetic resonance angiography, before the index procedure. In general, hydration was performed with 0.5 to 1 mL/kg/h of normal (0.9%) saline for 12 to 24 hours before percutaneous coronary intervention and 12 to 24 hours after the procedure, with the exception of patients with heart function and volume overload. All procedures were performed under local anesthesia supplemented with intravenous sedation and analgesia when required. Systemic heparin (5000 units) was administered to achieve an activated clotting time of >250 seconds. The nonionic dimeric, iso-osmolality contrast medium iodixanol (Visipaque; GE Healthcare, Princeton, NJ) was used in all patients. Endovascular therapy was performed by the femoral approach according to standard clinical practice. All patients received a combination of aspirin (100 mg/d) and clopidogrel (75 mg/d) for at least 3 months after the procedure. Patients were followed up clinically 1 month after the procedure and at 3- to 6-month intervals thereafter. Follow-up ABI was obtained before hospital discharge and subsequently at 6- to 12-month intervals or if symptoms became aggravated. At least one imaging test, such as computed tomography angiography, color duplex ultrasound, or intra-arterial angiography, was performed if a >0.15 decrement in the ABI was present or if symptoms worsened by one Rutherford category.

Statistical analysis. Continuous variables are expressed as mean (standard deviation), and categorical variables are presented as frequencies. Patients were categorized into four subgroups according to quartiles of baseline serum cystatin C levels. Baseline characteristics and renal parameters were compared across quartiles of cystatin C by χ^2 test (categorical variables) and analysis of variance (continuous variables) for linear trends. The ability of serum cystatin C and creatinine level to predict CIN was evaluated by receiver operating characteristic (ROC) curve analysis. The optimal cutoff value of cystatin C for prediction of CIN was the value providing the greatest sum of sensitivity and specificity. To identify risk factors for CIN, univariate and multivariate logistic regression analyses were performed. The cumulative incidence of clinical events was estimated by the Kaplan-Meier method. The significance of the curves was tested with the log-rank test. Univariate and multivariate Cox proportional hazards analyses were performed to identify independent predictors of clinical outcomes. Variables with $P < .15$ in the univariate analysis were entered into the multivariate analysis. Statistical significance was defined as $P < .05$. Statistical analysis was performed by SPSS version 18.0 (SPSS Inc, Chicago, Ill) and MedCalc version 13.0 (MedCalc Software, Ostend, Belgium).

RESULTS

Baseline characteristics. Baseline characteristics of the study population and patient subgroups depending on quartiles of baseline cystatin C levels are summarized in Table I. The mean age of patients was 67 years, and 80.8% of patients were male. Critical limb ischemia was present in 44.6% of patients. Patients were divided into quartiles according to baseline cystatin C levels: first quartile, 0.60 to 0.91 mg/L; second quartile, 0.92 to 1.12 mg/L; third quartile, 1.14 to 1.47 mg/L; and fourth quartile, 1.49 to 1.95 mg/L. Subgroups with higher cystatin C levels were older and showed a higher frequency of dyslipidemia, diabetes, hypertension, CAD, critical limb ischemia, left ventricular ejection fraction ≤40%, and infrapopliteal lesions than subgroups with lower cystatin C levels (P value for trend < .05). Postprocedural use of antiplatelet agents, such as aspirin and clopidogrel, was similar among subgroups. The higher cystatin C quartile subgroups had more frequent use of angiotension-converting enzyme inhibitors or angiotension receptor blockers (P value for trend = .005). The volume of contrast medium did not differ among subgroups.

Changes in renal function and CIN. Changes in creatinine and cystatin C serum levels within 48 hours after the procedure are presented in Table II. Baseline serum creatinine levels and eGFR varied significantly across quartile subgroups. Subgroups with a higher baseline