Impact of severe chronic kidney disease on outcomes of infrainguinal peripheral arterial intervention

Virendra I. Patel, MD, MPH, Shankha Mukhopadhyay, MS, Julie M. Guest, BS, Mark F. Conrad, MD, MSSc, Michael T. Watkins, MD, Christopher J. Kwolek, MD, Glenn M. LaMuraglia, MD, and **Richard P. Cambria, MD,** *Boston, Mass*

Objective: **Patients with severe chronic kidney disease (CKD) and peripheral vascular disease are at increased risk of major adverse limb events (MALEs) and death; however, patients with end-stage renal disease have been excluded in current objective performance goals. We evaluated the effect of severe (class 4 and 5) CKD on outcomes after infrainguinal endovascular arterial interventions.**

Methods: **All primary peripheral vascular interventions (PVIs) performed at a single institution (January 2002 through December 2009) were included. End points were defined by Society for Vascular Surgery objective performance goals for critical limb ischemia (CLI), which include all-cause mortality, reintervention, and composite end points of death or amputation and MALEs (reintervention or amputation). Univariate and multivariable analysis was used to examine the effect of severe CKD on study end points.**

Results: **A total of 879 PVIs were performed, with severe CKD in 125 (14%). Severe CKD patients were significantly ($P < .05$) more likely to have diabetes (64% vs 46%), CLI (72% vs 11%), and need a multilevel PVI (34% vs 19%) or tibial intervention (35% vs 20%) compared with the remainder of the cohort. Distribution of TransAtlantic Inter-Society Consensus C and D lesions were similar (19% severe CKD vs 15%; $P = .2$). Severe CKD predicted perioperative (30-day) reintervention (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.5-4; $P = .05$), amputation or death (OR, 3.1; 95% CI, 1.1-9; $P = .04$), and MALEs (OR, 2.8; 95% CI, 1.3-6.1; $P = .04$), which was independent of CLI in multivariable regression analysis. On Kaplan-Meier analysis, severe CKD was significantly (log-rank $P < .05$) associated with death (31% ± 4% vs 7% ± 1%), amputation (14% ± 3% vs 3% ± 1%), and MALEs (40% ± 5% vs 26% ± 2%) at 1 year. Freedom from reintervention was similar at 1 year (70% ± 5% severe CKD vs 75% ± 2%; $P = .23$). Risk-adjusted (age, CLI, diabetes, coronary artery disease) Cox proportional hazards regression showed that severe CKD increased the risk of late mortality (hazard ratio [HR], 2.4; 95% CI, 1.8-3.2; $P < .01$), amputation (HR, 2.1; 95% CI, 1.1-3.9; $P = .02$), and death or amputation (HR, 1.8; 95% CI, 1.3-2.4; $P = .04$), without increasing the risk of late reinterventions or MALEs.**

Conclusions: **CKD independently predicts early and late adverse events after a PVI, in particular, excessive mortality. CKD should figure prominently in clinical decision making for patients with peripheral vascular disease. (J Vasc Surg 2014;59:368-75.)**

Likely related to minimal morbidity and a lower threshold to recommend intervention, there has been an exponential growth in peripheral vascular interventions (PVIs),[1,2] yet performance standards for PVIs are lacking. The Society for Vascular Surgery (SVS) recently established objective performance goals (OPGs) for critical limb ischemia (CLI) as benchmarks for clinical outcomes in PVI trials for new devices.[3] These OPGs were derived based on expected outcomes for lower extremity arterial revascularization using open surgical controls from three contemporary surgical bypass trials (Edifoligide for the Prevention of Infrainguinal Vein Graft Failure [PREVENT III],[4] CIRCULASE,[5] and Bypass vs Angioplasty in Severe Ischemia of the Leg [BASIL][6]). Although initially developed as benchmarks for single-arm endovascular device trials, these OPGs have and will continue to serve as important clinical quality measures for patients undergoing lower extremity revascularizations, whether open or endovascular.

Several high-risk factors were identified by the OPG document. These high-risk clinical (age >80 years and tissue loss), anatomic (distal to below-knee popliteal outflow), and conduit (lack of adequate length or diameter [>3 mm] saphenous vein) features were associated with reduced limb salvage or survival and therefore merit careful consideration in clinical practice. However, the SVS OPGs excluded patients with end-stage renal disease (ESRD), which previous investigators have shown confers a significant survival disadvantage in patients with peripheral vascular disease (PVD) and associated comorbidities.[7-11] The goal of this study therefore was to evaluate

From the Division of Vascular and Endovascular Surgery, Massachusetts General Hospital, Harvard Medical School.

Author conflict of interest: none.

Presented at the Thirty-ninth Annual Meeting of the New England Society for Vascular Surgery, Boston, Mass, September 21-23, 2012.

Reprint requests: Virendra I. Patel, MD, MPH, Massachusetts General Hospital, 15 Parkman St, Wang ACC 440, Boston, MA 02114 (e-mail: vpatel4@partners.org).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214/$36.00

http://dx.doi.org/10.1016/j.jvs.2013.09.006

the effect of severe chronic kidney disease (CKD) on perioperative and late outcomes after infrainguinal PVIs.

METHODS

Study design. This is a retrospective cohort study of patients who underwent infrainguinal PVIs for PVD at Massachusetts General Hospital from January 2002 through December 2009. The study outcome measures included perioperative (30-day) and late death as the primary end point. Secondary end points were amputation, reintervention, and the composite OPG end points of death or amputation and major adverse limb events (MALEs) of reintervention or amputation. These end points were chosen because the OPG investigators identified them as key outcome measures to ensure durable clinical efficacy.

The composite end points emphasize consideration of limb-specific and survival-related end points after PVIs. Amputation was defined as a below-knee or above-knee amputation (loss of foot amputations) and therefore excluded isolated toe amputations or partial foot amputations. Reinterventions were defined as any open or endovascular reintervention in the index limb independent of the lesion treated. This definition varies from the OPG guidelines, which define reinterventions as specific open procedures for graft failure. Therefore, the threshold for defining a MALE by way of reintervention was markedly lower in our study compared with the OPG guidelines, thus increasing the risk of MALEs in our cohort.

Study population. Eligibility criteria for this study were any adult patient undergoing primary percutaneous intervention for infrainguinal PVD; patients undergoing aortoiliac interventions were excluded. The specifics of the percutaneous intervention regarding primary angioplasty or angioplasty and stenting were at the discretion of the attending vascular surgeon or cardiologist. Patients with clinically and radiologically confirmed PVD were enrolled and consented before the procedure.

Demographics, clinical features, and medical history details recorded included indication for procedure (claudication, rest pain, or tissue loss), extent of arterial disease (femoral-popliteal disease, tibial disease), medications (Coumadin [Bristol-Myers Squibb, Princeton, NJ], lipid-lowering agents, β-blockers) smoking history, hypertension, diabetes, and history of coronary artery disease (CAD). CLI was defined by indication as rest pain or tissue loss (ulcer or gangrene) derived from patient presentation or from operative notes. The extent of PVD was assessed angiographically at the time of the intervention and categorized using TransAtlantic Inter-Society Consensus (TASC) Class[12] A (focal disease) to D (extensive). The technical procedural details were recorded.

The exposure variable of interest, severe CKD, defined as patients with CKD class 4 or 5, was derived from a preliminary sensitivity analysis. The estimated glomerular filtration rate (eGFR) was calculated for each patient using the Modified Diet in Renal Disease (MDRD) equation [GFR = 186.3 × serum creatinine$^{1.154}$ × age$^{-0.203}$ × 1.212 (if black) × 0.742 (if female)]. Patients were assigned to standard CKD classes[13] based on eGFR values: CKD 1, GFR >90 mL/min/1.73 m^2; CKD 2 (mild), GFR of 60 to 89 mL/min/1.73 m^2; CKD 3 (moderate), GFR of 30 to 59 mL/min/1.73 m^2; CKD 4 (severe), GFR of 15 to 29 mL/min/1.73 m^2; and CKD 5 (kidney failure), GFR <15 mL/min/1.73 m^2.

Baseline preoperative creatinine, age, sex, and race were used to calculated eGFR and establish a CKD class for all patients in our study. Patients were then stratified, based on preliminary analysis, into two groups for comparative analysis: those with severe CKD (class 4 and 5; eGFR <30 mL/min/1.73 m^2) vs those with lesser degrees of CKD (eGFR ≥30 mL/min/1.73 m^2).

Statistical analysis. Univariate analysis was performed to compare baseline clinical and demographic features, operative details, and perioperative outcomes. Continuous variables are presented as mean value and 95% confidence intervals (CIs). Discrete variables are presented as number of events and population percentages. Differences between the CKD categories were evaluated using the Fisher exact test for binomial outcome variables and the χ^2 test for ordinal data. A Kaplan-Meier product limit estimator curve was plotted to compare survival functions between patients with severe CKD and those without severe CKD. Observations were censored if patients survived or did not require amputation at the last documented follow-up.

A multivariable risk-adjusted Cox proportional hazards model was used to obtain hazard ratios (HRs), 95% CIs, and *P* values for primary and secondary end points. The proportional hazards assumption was assessed using Schoenfeld residuals. Statistical analysis was performed with SAS 9.2 software (SAS Institute, Cary, NC), and significance was defined as a two-tailed *P* value of <.05.

RESULTS

We identified 879 patients (54% male), who were a mean ± standard deviation age of 71 ± 11 years. CKD was mild or normal (class 1 or 2) in 48% of the patients, moderate (class 3) in 38%, and severe (class 4 or 5) in 14%. Sensitivity analysis to evaluate for a dose-dependent effect of CKD showed an incremental increase in outcome measures for patients with severe CKD compared with patients with normal renal function, mild CKD, or moderate CKD (Fig 1); therefore, severe CKD was chosen as the exposure variable for our study.

Baseline characteristics of patients with and without severe CKD are presented in Table I. By univariate analysis, severe CKD was associated with a significantly ($P < .05$) higher proportion of diabetes, insulin use, and hemodialysis dependence, and patients were more likely to present with CLI (Table I). Patients with severe CKD had a similar distribution of SVS high-risk criteria (age >80 years and tissue loss) compared with patients without severe CKD (14% severe CKD vs 11%; $P = .26$).

Procedural details are presented in Table II. Patients with severe CKD were more likely to undergo multilevel interventions, which were driven by an increased frequency