Retinopathy and the Risk of Cardiovascular Disease in Patients With Chronic Kidney Disease (from the Chronic Renal Insufficiency Cohort Study)

Juan E. Grunwald, MD[a,*], Maxwell Pistilli, MS[a], Gui-Shuang Ying, PhD[a], Maureen Maguire, PhD[a], Ebenezer Daniel, PhD[a], Revell Whittock-Martin, MS[a], Candace Parker-Ostroff, MS[a], Emile Mohler, MD[a], Joan C. Lo, MD[b], Raymond R. Townsend, MD[a], Crystal Ann Gadegbeku, MD[c], James Phillip Lash, MD[d], Jeffrey Craig Fink, MD[e], Mahboob Rahman, MD, MS[f], Harold Feldman, MD, MSCE[a], John W. Kusek, PhD[g], and Dawei Xie, PhD[a], the CRIC Study Investigators[1]

Patients with chronic kidney disease (CKD) experience other diseases such as cardiovascular disease (CVD) and retinopathy. The purpose of this study was to assess whether retinopathy predicts future CVD events in a subgroup of the participants of the Chronic Renal Insufficiency Cohort (CRIC) study. In this ancillary investigation, 2,605 participants of the CRIC study were invited to participate, and nonmydriatic fundus photographs were obtained in 1,936 subjects. Using standard protocols, presence and severity of retinopathy (diabetic, hypertensive, or other) and vessel diameter caliber were assessed at a central photograph reading center by trained graders masked to study participant's information. Patients with a self-reported history of cardiovascular disease were excluded. Incident CVD events were adjudicated using medical records. Kidney function measurements, traditional and nontraditional risk factors, for CVD were obtained. Presence and severity of retinopathy were associated with increased risk of development of any CVD in this population of CKD patients, and these associations persisted after adjustment for traditional risk factors for CVD. We also found a direct relation between increased venular diameter and risk of development of CVD; however, the relation was not statistically significant after adjustment for traditional risk factors. In conclusion, the presence of retinopathy was associated with future CVD events, suggesting that retinovascular pathology may be indicative of macrovascular disease even after adjustment for renal dysfunction and traditional CVD risk factors. Assessment of retinal morphology may be valuable in assessing risk of CVD in patients with CKD, both clinically and in research settings. **© 2015 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2015;116:1527−1533)**

Patients with chronic kidney disease (CKD) experience high rates of comorbid illnesses including cardiovascular disease (CVD) and retinopathy.[1] We have previously reported the results of the Retinopathy in Chronic Renal Insufficiency Cohort (RCRIC) study on the cross-sectional association between retinopathy and cardiovascular disease (CVD)[1] in a group of patients with chronic kidney disease (CKD) enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study.[2,3] In this cohort, the prevalence of CVD was higher in patients with retinopathy and in patients with retinal venular dilation, and this association remained significant after controlling for traditional risk factors for CVD.[1] This

[a]Perelman School of Medicine, University of Pennsylvania Philadelphia, Pennsylvania; [b]Kaiser Permanente Northern California, Oakland, California; [c]Department of Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania; [d]University of Illinois, Chicago, Illinois; [e]University of Maryland, Baltimore, Maryland; [f]Maryland Case Western University, Cleveland, Ohio; and [g]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland. Manuscript received May 20, 2015; revised manuscript received and accepted August 18, 2015.

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*Corresponding author: Tel: (215) 662 8039; fax: (215) 662 8025.
E-mail address: juangrun@mail.med.upenn.edu (J.E. Grunwald).

[1] Alan S. Go, MD, Jiang He, MD, PhD, Akinlolu Ojo, MD, PhD.

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present report evaluates the association between retinopathy and venular dilatation and the risk of subsequent CVD events.

Methods

The CRIC study design and methods have been reported previously.[2,3] Participants for the RCRIC study, an ancillary investigation of the CRIC study, were recruited at 6 of the 7 CRIC clinical centers. All 2,605 participants of the CRIC study from these 6 sites were invited to participate in the RCRIC study. From June 2006 to May 2008, 1936 participants enrolled in the RCRIC study, and eye fundus photography were obtained at median time of 2 years after the CRIC baseline. The protocol was approved by an institutional review board at each of the participating institutions, and all participants provided written informed consent.

Trained nonophthalmic personnel obtained all photographs. To induce a physiologic, nonpharmacologic dilatation of the pupils, participants were seated in a darkened room for 5 minutes. Forty-five degree digital, color fundus photographs were obtained using a Canon CR-DGI, Non-Mydriatic Retinal Camera (Canon Inc, Tokyo, Japan). Two photographs, one centered on the macula and the other on the optic disc, were obtained from each eye. A participant was included in the analysis if either the disc or macula photographs of 1 eye were of sufficient quality for classification by fundus reading center staff.

Trained graders and a retinal specialist, without knowledge of the participant's clinical and demographic information, assessed all digital fundus photographs at the RCRIC Fundus Photograph Reading Center at the University of Pennsylvania. Fundus pathology including presence and severity of retinopathy of any cause (diabetic, hypertensive, or other) and measurement of the diameter of the major retinal vessels were assessed. Because the readers were unaware of the diabetic or hypertensive status of the participants, retinopathy was evaluated without assumption of cause.

The Atherosclerosis Risk in Communities (ARIC) fundus photographic[4] and the Early Treatment of Diabetic Retinopathy (ETDRS) grading protocols[5] were used to grade retinopathy due to diabetes mellitus, systemic hypertension, and other conditions. The Multi-Ethnic Study of Atherosclerosis protocol was used for the evaluation of macular edema.[6] These grading protocols have been previously validated in diabetic and nondiabetic populations. A single masked reader, using standard protocols with standardized photographic field definitions, evaluated digital fundus photographs displayed on color-calibrated monitors.

Retinal abnormalities were graded by comparing participant images to standard photographs. An ETDRS severity score was assigned for each eye.[5] The ETDRS severity score is on an ordinal scale instead of a continuous scale. Scores were classified as normal (<14), very mild nonproliferative retinopathy (NPR 14 to 20), nonproliferative retinopathy (35 to 53), and proliferative retinopathy (PR >60). The score of the eye with more advanced retinopathy or the score from a single eye, if only 1 eye was available, was used as the score of the participant. A total of 116 participants (6%) had photographs in which neither eye could be assessed. Among them, 38 participants had photographs in which retinopathy features could not be assessed because of poor image quality. The remaining 78 participants had photographs that were blurry or dark, and although some mild retinopathy features could be assessed, an accurate grading could not be assigned because more advanced and subtle retinopathy features were not discernible.

As previously reported,[7] grade−regrade reliability was assessed in 200 RCRIC participants. Weighted Kappa for participant's ETDRS score was 0.77 (95% confidence interval [CI] 0.67 to 0.88), a value consistent with the reproducibility assessment reported by the ETDRS study.[5]

Image measurements of vascular arteriolar and venular calibers were performed according to the ARIC protocol, using interactive vessel analysis software (IVAN) developed at the University of Wisconsin.[4] Vessels were measured within an annulus spanning 0.5 to 1 disc diameter from the edge of the disc. Graders identified major arterioles and venules and chose segments most suitable for measurement. The diameter of up to 6 arterioles and 6 venules were averaged.[4]

The participants of CRIC study were queried about any cardiovascular events at the time of enrollment to the CRIC study. This information was not ascertained by investigating patient's medical records. Subsequently, during semiannual CRIC study visits, participants were queried again about possible cardiovascular events, onset of end-stage renal disease (ESRD), all hospitalizations, and a selected set of diagnostic tests or procedures. *International Classification of Diseases, Ninth Revision,* discharge codes were recorded for all hospitalizations. When codes included any from a preselected list suggesting a cardiovascular event (congestive heart failure [CHF], myocardial infraction [MI], stroke, atrial fibrillation [AF], and peripheral arterial disease [PAD]) or participants died during a hospitalization, medical records were retrieved for detailed review using event-specific criteria. Two physicians performed these reviews and classified each hospitalization with respect to the probability of the events of CHF, MI, stroke, and AF. Trained study staff reviewed medical records classified with *International Classification of Diseases, Ninth Revision,* codes that suggested PAD and abstracted data onto a study form.

The criteria used for adjudication of CHF were based on clinical symptoms, radiographic evidence of pulmonary congestion, physical examination of the heart and lungs, central venous hemodynamic monitoring data, and echocardiographic imaging. The criteria for MI were based on symptoms of angina, cardiac biomarkers, and electrocardiographic data. The criteria for AF were based on electrocardiographic data, rhythm strips, and selected medical record notes. Two neurologists reviewed all hospitalizations suggestive of stroke. The criteria for stroke were based on neurologic symptoms, tests/procedures including magnetic resonance imaging of the brain, computerized axial tomography of the brain, transthoracic echocardiographic and transesophageal echocardiographic imaging, and any history of previous stroke. The guidelines for MI were based on symptoms of angina, cardiac biomarkers, and electrocardiographic data. The guidelines for AF were based on electrocardiographic data, rhythm strips, and selected

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