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Diabetic Retinopathy and Risk of Heart Failure

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Objectives The purpose of this study was to examine the association of diabetic retinopathy with incident heart failure (HF).

Background Microvascular disease might play a more prominent role in the pathogenesis of diabetic cardiomyopathy, a major cause of HF in diabetes. Whether diabetic retinopathy, a microvascular complication of diabetes, predicts HF is unclear.

Methods A population-based study included 1,021 middle-aged type 2 diabetic persons with normal renal function and free of clinical coronary heart disease or HF at baseline. Diabetic retinopathy signs were graded from retinal photographs. Incident HF events were prospectively identified from hospital stay and death records.

Results There were 125 (12.8%) participants with diabetic retinopathy. After 9-year follow-up, 106 (10.1%) participants developed incident HF events. Persons with retinopathy were more likely to develop HF (cumulative incidence of 21.6%) than those without retinopathy (cumulative incidence of 8.5%). After controlling for age, gender, race, smoking, diabetes duration, insulin use, blood pressure, lipid profile, and other risk factors, participants with retinopathy had more than 2.5-fold higher risk of developing HF than those without retinopathy (hazard ratio [HR] 2.71; 95% confidence interval [CI] 1.46 to 5.05). This association remained significant after further adjustments for glycemic control, carotid atherosclerosis, and serum markers of endothelial dysfunction (HR 2.20, 95% CI 1.08 to 4.47).

Conclusions The presence of diabetic retinopathy signifies an excess risk of HF, independent of known risk factors. This further supports a contribution of microvascular disease to the development of HF in people with diabetes. (J Am Coll Cardiol 2008;51:1573–8) © 2008 by the American College of Cardiology Foundation

Heart failure (HF) is a major cause of morbidity, hospital stays, and mortality in diabetic populations (1–3). Although epicardial coronary stenosis and hypertension are strongly related to HF risk in the general population, diabetic hearts might fail even in the absence of epicardial coronary artery disease and other risk factors. This phenomenon has been attributed to diabetic cardiomyopathy, a complex and incompletely understood disease process recently linked to dysfunction of the coronary microcirculation (4,5). In support of this hypothesis, studies show that microvascular pathology is common in the diabetic myocardium, evidenced by presence of microaneurysms (6) and by quantitative demonstration of perfusion defects from radiological studies (5,7). Hyperglycemia has also been associated with disturbances in microvascular homeostasis in the myocardium (e.g., endothelial cell apoptosis) (8–10), which might lead to myocardial dysfunction in the absence of epicardial coronary disease or systemic hypertension (11,12).

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Retinopathy is the most common and specific microvascular complication of diabetes. Previous studies have reported associations of diabetic retinopathy with risks of cardiovascular diseases, such as stroke and coronary heart disease (13–17). However, there are only limited data on whether this microvascular complication is related to HF risk (18–20). In the MESA (Multi-Ethnic Study of Atherosclerosis), we reported a cross-sectional association between retinopathy signs and left ventricular concentric remodeling, a precursor of clinical HF (21). Here, we

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Abbreviations and Acronyms

CI = confidence interval

HbA1c = glycosylated hemoglobin

HR = hazard ratio

IMT = intima-media thickness

examined prospectively the association of diabetic retinopathy with incident HF in a population-based cohort of diabetic persons free of clinical heart disease.

Methods

Study population. The ARIC (Atherosclerosis Risk In Communities) study is a population-based cohort study that included 15,792 persons, ages 45 to 64 years at recruitment in 1987 to 1989 (22). Retinal photographs were first obtained at the third examination (1993 to 1995) (23). Of the 12,642 participants who returned for this examination, 1,916 had diabetes mellitus, defined as fasting serum glucose levels of ≥7.0 mmol/l, nonfasting levels of ≥11.1 mmol/l, use of diabetic medications, or physician diagnosis of diabetes (23). Of these, we excluded those whose race was neither white nor African-American (n = 8) and those with HF at the time of retinal photography (n = 162) (either taking medication for HF or with manifest HF according to the Gothenburg Criteria) (24). In addition, we also excluded participants with prevalent coronary heart disease (n = 221) (25) or renal dysfunction (n = 217) (estimated glomerular filtration rate <90 ml/min/1.73 m^2) (24), because they are 2 competing causes of HF. Of the remaining 1,308 persons, photographs were gradable for at least 1 retinopathy sign in 1,021 persons. Characteristics of participants with and without gradable retinal photographs have been described elsewhere (23). Ungradable retinal photographs were due to either no photographs or photographs of insufficient quality.

Assessment of diabetic retinopathy. One randomly selected eye was photographed with a 45-degree nonmydriatic camera and evaluated by masked graders according to standardized protocol (13,14,23). Retinopathy was graded according to the Early Treatment of Diabetic Retinopathy Study severity scale and defined for analysis as absent or present and also as absent, mild (minimal nonproliferative retinopathy), moderate (moderate nonproliferative retinopathy), and severe (severe nonproliferative or proliferative retinopathy) (23). Individual retinopathy signs and the presence of macular edema were defined separately.

Assessment of HF. Detailed description of HF ascertainment in the ARIC study and quality control procedures has been published elsewhere (18,24). In brief, an incident HF event was defined as a hospital discharge diagnosis coded as HF (ICD-9, code 428 or 518.4) (hospital stay and emergency room visits) or a death certificate with an underlying primary or secondary cause of death coded as HF (ICD-9-CM code 428 or ICD-10 code I50) from the time of retinal photography (third examination, 1993 to 1995) to December 31, 2003.

Assessment of cardiovascular risk factors. Participants underwent standardized evaluations for blood pressure and other cardiovascular risk factors at all examinations (26,27). For analysis, we used data collected from the third examination (when retinal photography was performed), except for data (glycosylated hemoglobin [HbA1c], fibrinogen, white blood cells, von Willibrand factor, factor VIII, carotid intima-media thickness [IMT]) that were only available from the second examination (1990 to 1992) (14). The mean difference in time between second and third examinations was 3.03 years (95% confidence interval [CI] 3.02 to 3.05).

Statistical analysis. We compared unadjusted survival curves by absence or presence of retinopathy. Follow-up time was defined as the number of days from retinal photography to the date of the first HF event, last contact, or December 31, 2003. We used Cox regression to determine hazard ratio (HR) and its 95% CI for HF in relation to diabetic retinopathy, initially controlling for age, gender, race, and study center (Model 1). The proportional hazard assumption was checked by plotting the "log-minus-log" plot of the estimated survival functions against log time. Our multivariate analysis included additional adjustments for traditional cardiovascular risk factors measured at the third examination when retinal photography was performed (Model 2) and further adjustments for glycemic control (HbA1c), carotid atherosclerosis (IMT), and biomarkers of endothelial dysfunction (factor VIII and von Willebrand factor) measured at the second examination (Model 3). In supplementary analysis, we performed stratified analyses by gender, race and hypertension status, adjusting for Model 2 covariates. We also tested for potential interactions for these variables.

Results

Participants with retinopathy at baseline were more likely to be women, African Americans, current smokers, insulin users, and to have hypertension and higher levels of serum HbA1c, von Willebrand factor and factor VIII than participants without retinopathy (Table 1). Over the 8.9 years (SD 2.3) of follow-up, there were 106 incident HF cases identified. Of the 125 participants who developed HF, 36 (34%) died. Persons with retinopathy were more likely to develop HF (cumulative incidence of 21.6%) than those without retinopathy (cumulative incidence of 8.5%), as shown in Figure 1.

Table 2 shows that after initial adjustments for age, gender, and race/center (Model 1) and further adjustments for cardiovascular risk factors (Model 2), the presence of diabetic retinopathy was significantly associated with incident HF, with higher risks seen for some specific retinopathy lesions, such as retinal microaneurysms and hard exudates. The association remained significant after further adjustments for HbA1c, carotid IMT, and biomarkers of endothelial dysfunction (Model 3).

Stratified analyses showed that the association of retinopathy with HF was present in both whites (HR 2.39, 95% CI