

ARIC Manuscript Proposal # 855

PC Reviewed: 01/03/02
SC Reviewed: 01/07/02

Status: A
Status: A

Priority: 2
Priority: 2

1.a. Full Title: Retinal Microvascular Abnormalities and Congestive Heart Failure

b. Abbreviated Title (Length 26 characters): Retinal abnormalities and CHF

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:

This analysis is part of overall objective to investigate the cardiovascular associations of retinal microvascular abnormalities, based on photographic grading during the ARIC visit 3. Specifically, our proposed study will investigate whether retinal microvascular disease at visit 3 is related to prevalent hospitalized congestive heart failure (CHF), and incident hospitalized CHF between visits 3 and 1999. After approval, the initial analyses and writing is anticipated to begin *after* the main descriptive paper on incident CHF in the ARIC study. Initial analyses will likely begin in June 2002, with final analysis and writing Dec 2002.

4. Rationale:

CHF is a leading cause of morbidity, hospitalization and mortality in the United States.¹ Data on the risk factors and natural history for CHF are limited,² although identification and treatment of patients with early CHF may be expected to improve their outcome.^{3,4}

Microvascular processes have long been hypothesized to contribute to the risk of left ventricular dysfunction and overt CHF after a myocardial infarction (MI), particularly in people with hypertension and diabetes.⁵⁻¹⁰ In people angina and angiographically normal coronary arteries (syndrome X), microvascular disease has been further suggested to contribute to exercise-induced LV dysfunction.¹¹ However, whether microvascular disease is related to CHF in the general population (i.e. persons without a history of MI, diabetes, or hypertension) is uncertain. Few population-based data are available, largely because available methods to evaluate the coronary microcirculation are invasive (e.g., endomyocardial biopsy), difficult to interpret (e.g., pharmacological stimulation of coronary flow), and are mainly applicable in experimental settings.¹²

In ARIC, we have previously shown that retinal arteriolar narrowing, quantified from a computer-assisted measurement of retinal arteriolar diameters, were related to incident MI and fatal coronary heart disease (CHD) in women but not men.¹³ These findings provide evidence that microvascular diseases may play a more prominent role in the development of CHD in women.¹⁴ It is uncertain if microvascular disease may also play a greater role in the risk of CHF in women than men, although women have higher mortality rates after a MI than men.¹⁵

In the proposed study, we will investigate the relation of retinal microvascular disease to prevalent hospitalized CHF in men and women and, in persons free of prevalent CHF, incident CHF. We will examine if these associations differ in people with and without previous MI, hypertension and diabetes. Findings will lead to a clearer understanding of the pathogenesis and natural history of CHF.

5. Main Hypothesis/Study Questions:

- (1) After controlling for age, sex, race, blood pressure, dyslipidemia, smoking, diabetes and other risk factors, retinal arteriolar narrowing and other microvascular abnormalities are associated with increased risk of prevalent and incident CHF.
- (2) The associations are stronger in women than men, and in persons with compared to without a previous history of MI and CHD, hypertension and diabetes.

6. Data (variables, time window, source, inclusions/exclusions):

- (1) Retinal variables: Focal retinal microvascular changes include arteriovenous nicking, focal arteriolar narrowing, any retinopathy, retinal hemorrhage and type of hemorrhage (flame-shaped and blot hemorrhage), microaneurysms and soft exudates. Generalized arteriolar narrowing quantified as retinal arteriole-to-venule ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent.
- (2) Prevalent hospitalized CHF variables up to visit 3 and incident hospitalized CHF variables from visit 3 to 1999.
- (3) Demographic variables: age, sex, race, center, education, occupation
- (4) Other CVD risk factors/potential confounders: Cardiovascular history status (prevalent CHD and MI), hypertension status, diabetes status, BP at visits 1 to 3, serum lipids (total, HDL and LDL cholesterol, TG), fasting glucose levels, hemostatic function (von Willebrand factor, factor VIIIc, fibrinogen, WBC), cigarette smoking (ever/never, current/former/never, pack-years), alcohol consumption, hypertensive medications, body mass index, waist to hip ratio, sports/leisure/work activity index (variables from ARIC visit 1-3, except for von Willebrand factor, factor VIIIc, available ARIC visit 1 only)
- (5) Exclusion criteria: From participants at ARIC visit 3 (n=12,887), exclude persons who did not participate in visit 2, whose race is not black/white, with no retinal photographs or upgradeable photographs or no CHF data at any visit.

7.a. Will the data be used for non-CVD analysis in this manuscript? ☐ Yes ☒ No

b. If Yes, is the author aware that the file ICTDER01 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ☐ Yes ☐ No

(This file ICTDER01 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ☐ Yes ☒ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? _____ Yes _____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://bios.unc.edu/units/csc/ARIC/stdy/studymem.html> _____X_____ Yes _____ No

References

1. Ghali JK, Cooper R, Ford E. Trends in hospitalization rates for heart failure in the United States, 1973-1986. Evidence for increasing population prevalence. Arch Intern Med 1990; 150: 769-773
2. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive cardiac failure: the Framingham study. N Engl J Med 1971; 285: 1441-1446.
3. The SOLVD Investigators. The effects of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991; 325: 293-302.
4. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992; 327: 685-691.
5. Devereux RB, Roman MJ. Inter-relationships between hypertension, left ventricular hypertrophy and coronary heart disease. J Hypertens Suppl 1993;11:S3-9.
6. Sampson MJ, Chambers JB, Sprigings DC, Drury PL. Abnormal diastolic function in patients with type 1 diabetes and early nephropathy. Br Heart J 1990;64:266-71.
7. Vered A, Battler A, Segal P, et al. Exercise-induced left ventricular dysfunction in young men with asymptomatic diabetes mellitus (diabetic cardiomyopathy). Am J Cardiol. 1984 Sep 1;54:633-7.
8. Watschinger B, Brunner C, Wagner A, et al. Left ventricular diastolic impairment in type 1 diabetic patients with microalbuminuria. Nephron 1993;63:145-51.
9. Sato A, Tarnow L, Parving HH. Prevalence of left ventricular hypertrophy in Type I diabetic patients with diabetic nephropathy. Diabetologia. 1999;42:76-80.
10. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. 1974;34:29-34.
11. Berger HJ, Sands MJ, Davies RA, et al. Exercise left ventricular performance in patients with chest pain, ischemic-appearing exercise electrocardiograms, and angiographically normal coronary arteries. Ann Intern Med 1981;94:186-91.
12. Mosseri M, Yarom R, Gotsman MS, Hasin Y. Histologic evidence for small-vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. Circulation 1986;74:964-72.
13. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar diameter is related to incident coronary heart disease in women, but not men: The Atherosclerosis Risk in the Communities Study. JAMA (Submitted)
14. Cannon RO 3rd, Balaban RS. Chest pain in women with normal coronary angiograms. N Engl J Med. 2000;342:885-7.
15. Karlson BW, Herlitz J, Hartford M. Prognosis in myocardial infarction in relation to gender. Am Heart J. 1994;128:477-83.