THE ASSOCIATION OF SUBCLINICAL ATHEROSCLEROSIS WITH INCIDENT HEART FAILURE: THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY

By

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ABI	Ankle-brachial index
ACC	American College of Cardiology
AHA	American Heart Association
ARIC	Atherosclerosis Risk In Communities
BART	Brachial artery reactivity testing
BMI	Body mass index
CAC	Coronary artery calium
CAPS	Carotid Atherosclerosis Progression Study
CARDIA	Coronary Artery Risk Development in Young Adults
CHD	Coronary heart disease
CHS	Cardiovascular Health Study
CI	Confidence interval
CPTS	Clinical and Population Translational Sciences
CT	Computed tomography
CVD	Cardiovascular disease
DART	Direct analysis in real time
DM	Diabetes mellitus
ECG	Electrocardiogram
FRS	Framingham risk score
HbA_{1c}	Hemoglobin A_{1c}
HDL	High density lipoprotein

HF	Heart failure
HF MMCC	Heart failure mortality and morbidity classification committee
HOPE	Heart Outcomes Prevention Evaluation
HR	Hazards ratio
hs-CRP	High-sensitivity C-reactive protein
ICD	International classification of diseases
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IMT	Intima-media thickness
LDL	Low density lipoprotein
LV	Left ventricular
LVH	Left ventricular hypertrophy
MESA	Multi-Ethnic Study of Atherosclerosis
MI	Myocardial infarction
NFG	Normal fasting glucose
NHANES	National Health and Nutrition Epidemiologic Survey
PH	Proportional hazard
SD	Standard deviation

ABSTRACT

Background: Atherosclerosis plays a central role in the pathophysiology of coronary heart disease (CHD), which is believed to be the most common etiology for heart failure (HF). Greater carotid intima-media thickness (IMT), a measure of subclinical atherosclerosis, is associated with left ventricular myocardial dysfunction, a subclinical marker of HF. We investigated the association of carotid IMT with incident HF among middle-aged whites and blacks, controlling for major cardiovascular disease (CVD) risk factors.

Methods and Results: We included 13,590 participants from the ARIC cohort aged 45 – 64 years in our analysis. Excluded were participants with HF at baseline, those with missing IMT measurements and criteria to define diabetes. The mean carotid IMT of six far walls, measured by B-mode ultrasound, was used in our analyses. HF was defined using ICD-9 and ICD-10 codes from hospitalization records and death certificates. There were 2,008 incident HF hospitalizations or death over a median follow-up period 20.6 years. Baseline mean carotid IMT was significantly higher for subjects with incident HF than those without HF (0.81±0.23 vs 0.71±0.17; $p<0.0001$). Carotid IMT was significantly associated with incident HF, after adjustment for demographic and CVD risk factors and CHD (HR 1.20 per unit SD increase; 95% CI: 1.16-1.25). After accouting for major CVD risk factors and CHD, only the fourth quartile of IMT remained significantly associated with HF relative to the first quartile (HR 1.60; 95% CI: 1.37-1.87, $p<0.0001$). Also, after accounting for major CVD risk factors and CHD, the association was greater in subjects with normal fasting glucose (NFG) than those with abnormal glucose metabolism (HR 1.25 per unit SD increase, 95% CI: 1.19-1.32 for NFG; HR 1.19, 95% CI: 1.11-1.27 for impaired fasting glucose; and HR 1.14, 95% CI: 1.05-1.23 for diabetes

mellitus). The p-value for IMT*glucose status interaction term in the fully adjusted model was 0.0149.

Conclusions: Carotid IMT is strongly associated with HF in middle-aged whites and blacks after adjusting for major CVD risk factors and CHD.

Keywords: subclinical atherosclerosis, carotid intima-media thickness, heart failure, diabetes mellitus

CHAPTER I – INTRODUCTION

Heart failure (HF) represents an ever-increasing clinical and public health burden in the United States as its prevalence and incidence continue to rise,[1-3] especially among elderly Americans.[4-5] Incidence rates for HF for persons aged 45-65 years range between 7.7 to 17.4 per 1000 person-years.[6] These rates are approximately four times greater among the elderly (>65 years) than in the middle-aged.[7] HF has emerged as the single leading cause of hospitalization in the elderly and hospitalization rates are higher among blacks than whites; 83% of HF patients hospitalized at least once and 43% hospitalized at least 4 times over a mean duration of 4.7 years.[8-9] This burden of HF is likely to increase because of increasing age of the American population, a progressive increase in the age of onset of HF and improved treatment and survival from CVD, including myocardial infarction (MI) and hypertension.[10-11]

Carotid IMT is a well-established marker of subclinical atherosclerosis which indicates early manifestation of atherosclerosis in the carotid arteries[12-13], and is associated with future cardiovascular events[14-16], asymptomatic myocardial ischemia[17], coronary risk factors[18], and changes in risk factors induced by therapeutic interventions.[19] There is evidence of a direct relationship between increased carotid IMT and prevalent reduced left ventricular (LV) systolic and diastolic function in asymptomatic individuals without previous clincial CVD.[20] Elderly patients with HF differ from younger patients with HF in terms of several biologic characteristics, including the relatively large proportion of elderly patients with HF who have preserved systolic function.[21-24] Using data from the Cardiovascular Health Study which included subjects 65 years or older, atherosclerosis as measured by carotid IMT was shown to predict overt systolic and diastolic HF.[25] The association of carotid IMT with incident HF in a younger

population, which is at a lower risk of HF than an elderly population, has not been studied. Also, it is known that the cause of HF differs between blacks and whites;[26-27] CHD is the main cause of HF in whites whereas hypertension is primarily responsible in blacks. Knowledge of the association between IMT and HF in blacks and whites may help in risk stratification. Previous cross-sectional analysis using data from the ARIC cohort shows that participants with HF had a higher mean carotid IMT than participants without HF.[6]

Patients with diabetes mellitus are at an increased risk for HF than those without diabetes,[28-29] and the difference is much greater in younger age groups.[28] Diabetic cardiomyopathy has been described as a distinct clinical entity leading to HF among subjects with diabetes, and different pathophysiologic mechanisms have been postulated.[30] Because of an increasing prevalence of diabetes in the U.S., knowledge of the association of carotid IMT with HF in these patients could be beneficial in HF prevention in this high-risk group.

In the present study, we investigated the association of carotid IMT with incident cases of HF over approximately 20 years of follow-up and after adjusting for major CVD risk factors and CHD. Data from the ARIC study cohort, comprised of individuals aged 45-64 years at the time of baseline examination, was used.

The significance of this contribution stems from the fact that the burden of HF increases as a result of increasing age, a progressive increase in the age of onset of HF and improved treatment and survival from CVD.[10-11] This suggests that detection of high-risk groups for HF at a younger age and an earlier stage of the disease course could be beneficial in reducing the morbidity and mortality associated with HF, as well as its related health care costs. Also, understanding the association of subclinical atherosclerosis with HF across glucose categories in a younger cohort will be important for the differential use of carotid IMT in risk stratification.

The lack of radiation exposure, relatively low cost, ease of performing the procedure in an out-patient setting, reproducibility, and ability to detect early-stage atherosclerosis suggest that carotid ultrasound for IMT measurement should continue to be explored as a primary tool for CVD risk stratification in young to middle-aged adults.

Carotid IMT associations with incident HF in this middle-aged population could enhance our understanding of the role of subclinical atherosclerosis in the occurrence of HF. This may significantly improve early identification of individuals at high risk for the development of HF, and subsequently reduce the burden of morbidity and mortality associated with this condition.

1. Heart failure

1.1 Prevalence and incidence

Heart failure represents an ever-increasing clinical and public health burden in the United States;[31-36] its prevalence and incidence continue to rise despite a decline in the overall CVD morbidity and mortality.[31, 34] In 2010 an estimated 6.6 million US adults aged 18 and above (2.8% of total population) had HF.[37] It is estimated that by 2030, an additional 3 million people will have HF, a 25% increase in prevalence from 2010.[37]

There is a modest male predominance attributable to the higher CHD rates in males,[7] and differences in the incidence of HF by race.[38] Using data from the ARIC study, Loehr et al. showed that the age-adjusted incidence rate per 1000 person-years was 3.4 for white women, less than for all other groups; i.e. white men (6.0), black women (8.1) and black men (9.1).[6] Similarly, in the Multi-Ethnic Study of Atherosclerosis (MESA), blacks had the highest incidence rate of HF (4.6 cases per 1000 person-years) during a median follow-up of 4.0 years, followed by Hispanics, white and Chinese (3.5, 2.4, and 1.0 per 1000 person-years respectively).[38] Most cases of HF in blacks were not preceded by clinical MI. The higher rates of hypertension and diabetes associated with a low socio-economic status largely explain the ethnic differences in the risk of developing HF.[38]

The incidence of HF is higher for older individuals. For white men, the incidence rates are 15.2, 31.7, and 65.2 per 1000 population for those aged 65-74, 75-84, and above 85 years of age, respectively. For white women in the same age groups, the rates are 8.2, 19.8, and 45.6, respectively.[39-41]

1.2 Risk factors

The relative contribution of various risk factors to the development of HF remains controversial.[25, 42-44] The population attributable risk of the various risk factors for HF are summarised in Table 1 below. These important findings were derived from Framingham Heart Study and National Health and Nutrition Epidemiologic Survey (NHANES).

Table I-1: Population attributable risk of various HF risk factors.[45]

Risk factor	Framingham Heart Study	NHANES-I
Hypertension	39%-59%	10%
Coronary heart disease		62%
Myocardial infarction	13%-34%	
Angina pectoris	5%	
Obesity	11%-14%	8%
Diabetes	6%-12%	3%
Valve disease	7%-8%	2%
Echocardiographic LVH	4%-5%	NA
Smoking	NA	17%
Low physical activity	NA	9%
Male sex	NA	9%
Less than high school education	NA	9%

Abbreviations: NA, not available; NHANES-I, first National Health and Nutrition Examination Survey; LVH, left ventricular hypertrophy

In the Framingham Heart Study, hypertension was the greatest contributor to the incidence of HF in the population, followed by antecedent MI.[46-47] Hypertension alone accounted for 39% of the HF cases in men and 59% in women.[46] However, data from NHANES suggested

that CHD had the largest association with HF and might be responsible for more than 60% of cases. This could be partially related to differences in the definitions of these risk factors.

Hypertension, diabetes, or obesity generally precede HF by an average of more than 10 years, although the condition occurs more rapidly after CHD.[48] For CHD, sudden cardiac events such as MI may lead quickly to cardiac dysfunction[49] and HF. Conversely, hypertension, diabetes, and obesity can lead to HF over longer durations via hypertensive heart disease, LVH, myocardial metabolic dysfunction,[50] oxidative stress,[51] and endothelial dysfunction,[52] leading to LV remodeling[53-54] and cardiac dysfunction.

Among 20,900 male physicians in the Physicians Health Study, the lifetime risk of HF was higher in those with hypertension. A healthy lifestyle (normal weight, not smoking, moderate alcohol intake, consumption of breakfast cereals, and consumption of fruits and vegetables) was associated with a lower risk of HF.[55]

In the ARIC study, increased albuminuria, hemoglobin A_{1c} (HbA_{1c}) among individuals without diabetes, cardiac troponin measured by sensitive assay, and socioeconomic position over the life course of participants were all identified as risk factors for HF.[56-59] In the Heart Outcomes Prevention Evaluation (HOPE) study in which the efficacy of ramipril was evaluated in subjects with high cardiovascular risk, but free of HF at baseline, every 0.4-mg/mmol increase in the albumin/creatinine ratio was associated with a 10.6% increase in the risk of hospitalization for HF, and microalbuminuria (albumin/creatinine ratio of 2 mg/mmol or more) at baseline was associated with a threefold increase in the risk of hospitalization for HF.[60]

Other factors associated with the development of HF are low physical activity[43] and biomarkers such as N-terminal pro B-type natriuretic peptide,[47, 61] interleukin-6, tumor necrosis factor-α,[62] and resistin.[63]

1.3 Mortality, morbidity and prognosis

The survival of patients diagnosed with HF has improved over time, but the death rate still remains high: overall, the one-year and five-year mortality rates are estimated at 30% and 50%, respectively.[56, 64-65] Mortality rates significantly differ between the New York Heart Association (NYHA) classes; there's an estimated 8.3% one-year mortality for patients in NYHA class IV compared to 3.1% for those in NHYA class II.[66] The 30-day, 1-year, and 5-year case fatality rates after hospitalization with diagnosis of HF were 10.4%, 22% and 42.3%, respectively.[6] At all ages, the death rate from HF is greater in blacks than whites.[67-68] This may be related to the increased prevalence of hypertension and early CHD in the black population,[69] as well as poorer access to health care.[70]

HF treatment costs exceed those for both CHD and cancer combined and require about 5.4% of the total US health care cost.[40, 71] In 2004, the estimated direct and indirect cost of HF in the US was $28.8 billion USD,[72-73] and it is estimated to double (US $57.0 billion) by 2020 and reach US $97.0 billion by 2030.[40] Only 14% of the Medicare population has HF, but they account for over 43% of Medicare expenditures.[74-75]

Figure 1 illustrates the stages in the evolution of HF based on guidelines published by the American College of Cardiology (ACC) and the American Heart Association (AHA).[76]

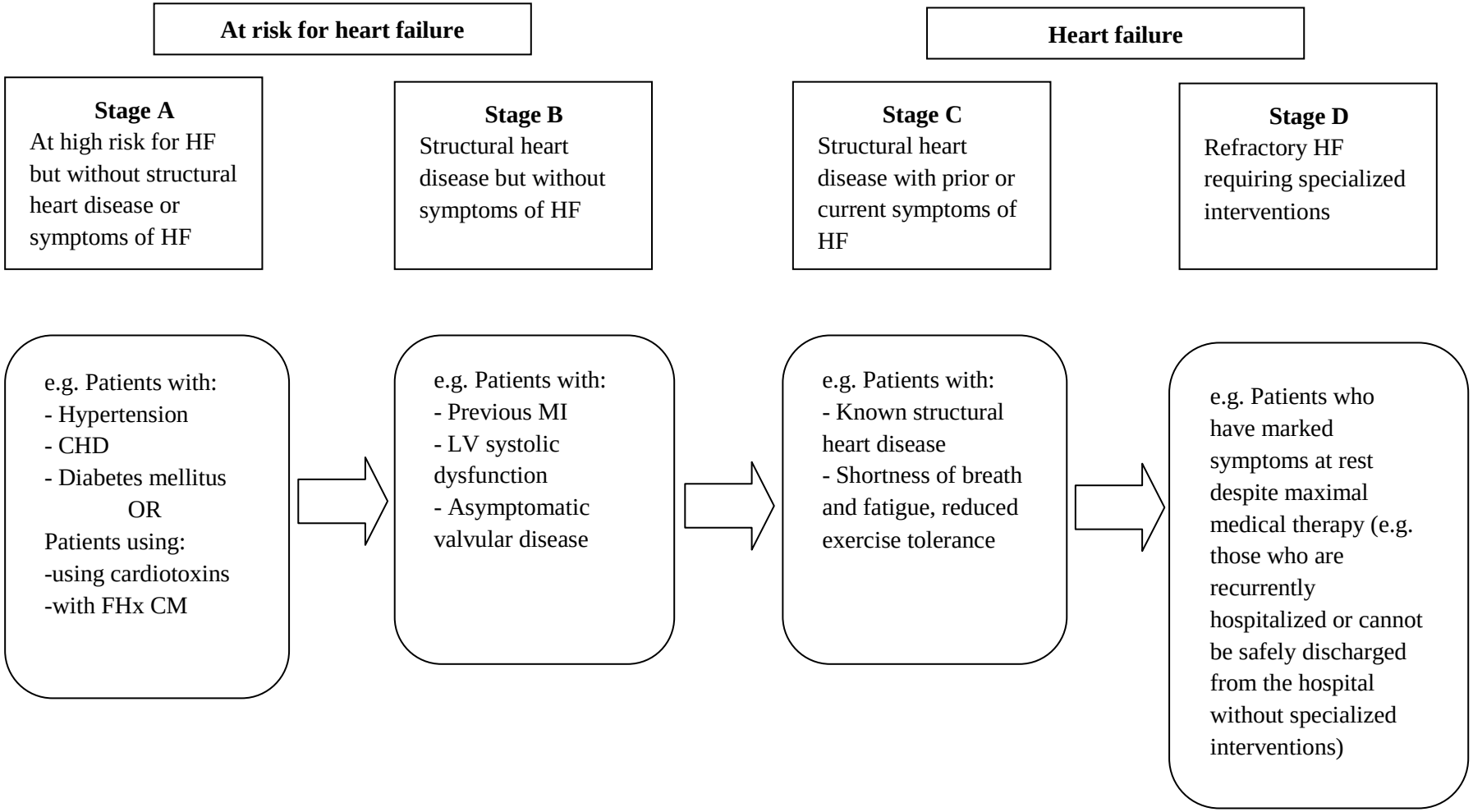

Figure I-1: Stages in the evolution of heart failure. CHD indicates coronary heart disease; FHx CM, family history of cardiomyopathy; HF, heart failure; MI, myocardial infarction; and LV, left ventricular. (Modified from Hunt et al, ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult. 2005)[76]

2. Atherosclerosis

2.1 Pathogenesis

Atherosclerosis, a systemic condition associated with inflammation, and in which fat deposits, cells, and scar tissue build up within the walls of some arteries, is the underlying cause of a majority of clinical CVD. The development of atherosclerosis is a slow process with a long silent phase before the clinical manifestations of disease become apparent. The main arteries affected are the aorta, coronary, cerebral and popliteal arteries.[77] This dynamic process is characterized by arterial wall remodelling that may go undiagnosed throughout life, but acute vascular events may become clinically manifest with significant disease process.[78]

A number of hypotheses have been proposed to identify the triggering factors for atherosclerosis; among these are the response to injury hypothesis[77, 79-82] and the oxidation hypothesis.[77, 80, 82] According to the injury hypothesis, damage to the endothelium generates abnormal intracellular signaling mechanisms that cause platelets to adhere and aggregate at the site of damage, and monocyte invasion and proliferation within the intima-media junction, all of which are precursors for atherogenic changes within arteries. In the oxidation hypothesis, lipid peroxidation contributes to the damage of the lipid layer of the plasma membrane and enhances the release of fatty acids. Oxidized LDL uses the macrophage as a scavenger molecule; it binds onto and internalizes LDL, forming what is referred to as the foam cell.

2.2 Risk factors

Atherosclerosis is a multifactorial, multistep condition that involves chronic inflammation at every step, and all risk factors contribute to its pathogenesis by aggravating the underlying inflammatory process.[83-84] The impact of traditional risk factors such as age, gender,

hypertension, smoking, family history of premature MI, diabetes mellitus, increased LDL-cholesterol and triglyceride levels, low HDL-cholesterol levels, and increased lipoprotein(a) levels on CHD risk has long been demonstrated in large observational studies and trials.[85-90]

Novel biomarkers have been under scrutiny over the last decade in a number of studies and clinical trials. Hyperhomocysteinemia has been linked with CHD risk; homocysteine levels were found to be higher in adults with CHD in the ARIC Study,[91] Framingham Heart Study,[92] and a nested case-control study of 21,826 subjects in Norway.[93] Elevated high – sensitivity C-reactive protein (hs-CRP) constitutes an independent predictor of advanced carotid plaques in dyslipidemic subjects,[94] and early-onset carotid atherosclerosis is associated with increased IMT and elevated serum levels of inflammatory markers.[95] Hs-CRP has an additive value in the prediction of future CHD risk, beyond traditional risk factors.[96] Men and women with increased baseline levels of hs-CRP are at increased risk for future CHD,[97] and hs-CRP is significantly ($p \leq 0.005$) elevated in patients dying suddenly with severe CHD.[98]

3. Subclinical atherosclerosis and non-invasive imaging

In recent decades, advances in imaging technology have allowed for improved ability to detect and quantify atherosclerosis at all stages, and in multiple different vascular beds. Noninvasive measures of atherosclerosis have emerged as adjuncts to standard CVD risk factors in an attempt to refine risk stratification and the need for more aggressive preventive strategies. The two of the most commonly used modalities in large-scale population-based studies with outcomes data are the computed tomography (CT) of the chest for evaluation of coronary artery calcification (CAC) and B-mode ultrasound of the neck region for evaluation of carotid artery intima-media

thickness (IMT). These techniques may help to define the burden of atherosclerosis in individuals before they develop clinical endpoints such as stroke, CHD, or HF.

3.1 Carotid artery ultrasonography

Carotid IMT is thought to be an earlier manifestation of atherosclerosis than CAC because thickening of the vessel wall precedes the development of frank atherosclerotic plaque.[40] As a measure of subclinical atherosclerotic burden, changes in carotid IMT have been associated with adverse cardiovascular events,[14-16, 99-101] asymptomatic myocardial ischemia,[17] and both the presence of coronary risk factors[18, 102] and the reduction in risk factors induced by therapeutic interventions.[19, 103]

B-mode ultrasound is noninvasive, thus its IMT measurements can be used in observational studies in healthy populations and also in atherosclerosis regression trials to assess medication efficacy.[13] Several observational studies[99-100, 104-108] and intervention trials[19, 109-113] have used carotid IMT as a surrogate end-point to assess the effects of various interventions on atherosclerotic burden.

Results from the Rotterdam study documented associations between carotid IMT and stroke, angina, MI, intermittent claudication and essential hypertension,[99, 107] as supported by other studies.[16, 18] Recent work using data from 500 asymptomatic participants from MESA has also associated increased carotid IMT values with reduced regional myocardial systolic function in specific myocardial territories even after adjustment for traditional and non-traditional CHD risk factors.[20] In this study, greater carotid IMT was also associated with impaired diastolic performance in specific LV wall segments. These IMT-associated alterations of regional LV function reported may represent early signs of myocardial dysfunction along the HF continuum.

Asymptomatic global LV dysfunction is considered to be a subclinical form of HF due to its frequent progression to symptomatic HF.[114-115] Accordingly, the Cardiovascular Health Study, a community-based prospective study of 5888 adults aged 65 years and older, showed that greater IMT values were independently predictive of incident systolic as well as diastolic HF.[25]

In the ARIC Study[100, 106, 108, 116] in 15,800 subjects, high – resolution B – mode ultrasound was used to assess all stages of atherosclerosis. The procedure showed a high level of reproducibility, was inexpensive and well established as a noninvasive independent predictor of CHD and stroke; a 0.2 mm increase in carotid IMT was associated with a 28% increase in the risk for stroke and a 33% increase in the risk for MI. In addition, carotid IMT has been found to modify the risk score of intermediate risk (FRS of 6%-20%)[117] and low-intermediate risk individuals.[118]

Although ultrasound is commonly used to diagnose plaque in the carotid arteries in people who have had a stroke or who have a bruit, guidelines are limited as to screening of asymptomatic people with carotid IMT to quantify atherosclerosis or to predict risk. However, some organizations have recognised that carotid IMT measurement by B-mode ultrasound may provide an independent assessment of coronary risk.[119]

3.2 Other techniques

The contribution of coronary artery calcification (CAC) to CVD risk prediction has been observed in a number of population-based studies.[120-124] In MESA, CAC was most strongly asociated with CHD (HR, 2.3 per 1 SD; 95% CI, 1.9 to 2.8) and all CVD events (HR, 1.7; 95% CI, 1.5 to 1.9).[125]

High-resolution magnetic resonance imaging (MRI),[126] brachial artery reactivity testing (BART),[127] and the ankle-brachial index (ABI) are other techniques for measuring subclinical atherosclerosis.[127] The application of BART is substantially more challenging that is carotid IMT and it is largely a research technique.[128] Carotid IMT may be more useful in determining coronary artery atherosclerosis than the ABI.[129]

3.3 Comparison between carotid IMT and CAC scoring

There is no consensus on the relative usefulness of carotid IMT compared with CAC score for evaluating subclinical atherosclerosis. Using data from the MESA cohort, Folsom et al. showed that both CAC score and carotid IMT predicted incident CHD events; CAC score was a better overall predictor of CHD events, and carotid IMT was a better predictor of strokes.[130] Similar CHD prediction values were found in the Cardiovascular Health Study involving older patients.[131] Carotid IMT evaluation detected subclinical disease in a study of young to middle-aged patients with a low FRS and a CAC score of zero.[132] Some studies have reported a moderate correlation between carotid IMT and calcified plaque in the coronary arteries.[133]

Carotid IMT may have some important advantages over the CAC score. It does not involve the exposure to ionizing radiation, which is an important consideration when imaging healthy young and middle-aged adults.[134-136] CAC score may have a limited discriminatory power to detect carotid atherosclerosis in blacks, where a high proportion of the population has no detectable CAC.[137] Carotid IMT is a continuous measure and has been suggested by the American Society of Echocardiography consensus statement to be beneficial in risk stratification in women, young men and blacks.[127, 136]

4. Subclinical atherosclerosis and association with incident cardiovascular events

4.1 Subclinical atherosclerosis and CVD events in non diabetic subjects

A number of studies have shown that carotid IMT is associated with the incidence of acute coronary events and stroke even after adjustments for hypertension and other atherosclerotic risk factors.[16, 116, 138-141] Mean carotid IMT values vary depending on the segment of the carotid artery used in a given analysis (common carotid, internal carotid, or bulb). Data from MESA showed that blacks had the highest common carotid artery IMT, compared with whites and Hispanics. Carotid IMT values obtained from the internal carotid artery were similar among blacks, whites and Hispanics.[137] In the Cardiovascular Health Study, after a mean follow-up of 6.2 years, persons aged 65 years or more with maximal combined carotid IMT in the highest quintile had a 4- to 5-fold greater risk for incident heart attack or stroke than those in the lowest quintile.[16] In the Coronary Artery Risk Development in Young Adults (CARDIA) Study involving relatively young white and black men and women, a greater proportion of the variability in common carotid IMT was explained by traditional cardiovascular risk factors than for the carotid artery bulb and internal carotid arteries.[142]

There is conflicting data on the additional value of carotid IMT in reclassifying individuals at risk of CHD events, in the absence or presence of plaque. Eleid et al. demonstrated that in a population of adults aged 65 years and below, and without diabetes, hyperlipidemia, or CHD, 42% had high-risk carotid ultrasound findings (carotid IMT $\geq 75^{th}$ percentile adjusted for age, gender, race or presence of plaque). Thirty-eight percent (38%) of asymptomatic individuals with low FRS ($\leq$ 5%) had abnormal carotid ultrasound findings associated with increased risk for CVD events.[143] Data from a 10-year follow-up of 4904 subjects from the Carotid Atherosclerosis

Progression Study (CAPS) showed that carotid IMT did not consistently improve the risk classification of individuals when added to a model with traditional risk factors, despite it being predictive of cardiovascular endpoints.[144] Two meta-analyses of large observational studies have shown carotid IMT to be a strong predictor of future cardiovascular events[145] and associated with small improvement (3.6%) in the 10-year risk prediction of first-time MI or stroke, beyond that of the FRS.[117]

There is however very limited data on the role of carotid IMT in the prediction of heart failure, of which CHD is considered one of the most important causes.

4.2 Subclinical atherosclerosis and CVD events in people with type 2 diabetes, impaired glucose tolerance and impaired fasting glucose

A number of studies haven shown that fasting glucose levels and established diabetes status are significantly and independently associated with carotid IMT, suggesting that chronic hyperglycemia may lead to an increased risk of atherosclerosis;[146-148] when compared with normal individuals, persons with already established type 2 diabetes had considerably higher IMT values than those with impaired glucose tolerance (IGT).[147]

Increased carotid IMT may be a reliable marker of higher risk of CHD in patients with type 2 diabetes.[149] Lee et al.[150] found that in a study of 1528 type 2 diabetes patients and 439 nondiabetic controls with or without CHD, high IMT ($\geq$ 1.30 mm) had significant odds ratios for concurrent CHD (2.205, $p < 0.001$). A meta-analysis showed that patients with carotid IMT higher than the cut-off level of 0.97 – 1.18 mm had significant year-incident rates of 1.21% – 1.64%.[151]

5. Subclinical atherosclerosis, diabetes status and heart failure

Epidemiological studies have shown that patients with type 2 diabetes and glucose intolerance are at increased risk of CHD. In the Framingham Heart Study, the incidence of cardiovascular events among men and women with diabetes was 2 and 3 times that among men and women without diabetes, respectively.[152] The Framingham Offspring Study has evaluated the impact of IGT, impaired fasting glucose (IFG) and type 2 diabetes versus normal glucose tolerance (NGT) on the process of atherosclerosis. Compared with NFG, subjects with IFG/IGT were more likely – and those with diabetes were significantly more likely – to have subclinical atherosclerosis, defined by CAC scores.[153] Subjects with previously diagnosed diabetes had a 3 times greater risk than subjects with newly diagnosed diabetes, and subjects with insulin resistance had a two-fold risk of subclinical atherosclerosis than subjects without.

Carotid IMT, with or without plaque, is associated with the incidence of acute coronary events and stroke, even after adjusting for atherosclerotic risk factors, but it remains largely unknown whether carotid IMT is an independent risk factor for clinical HF. Using data from MESA, Fernandes et al. showed that a greater carotid IMT was associated with reductions in both systolic and diastolic myocardial function, in almost all walls of the myocardium that were studied.[20] In this same cohort, regional myocardial dysfunction was linked to an increase in the incidence of HF and atherosclerotic cardiovascular events.[154]

In a sample of 4,691 individuals living in Malmö, Sweden, and followed up for a mean duration of 13 years, 75 subjects were hospitalized with a primary diagnosis of HF. The hazards ratio for HF after adjustments for age, gender, and risk factors was 2.7 (CI: 1.1 – 6.2) for the 4th quartile of IMT relative to the 1st quartile (p for trend = 0.003).[155]

SPECIFIC AIMS

Each year about 500,000 people are newly diagnosed with HF in the United States.[156] The median survival from HF is only 1.7 years for men and 3.2 years for women, with only 25% of men and 38% of women surviving 5 years. This mortality rate is 4-8 times that of the general population of the same age.[7]

Recent work has associated greater carotid IMT, a marker of subclinical atherosclerotic burden, with alterations of myocardial strain parameters reflecting reduced systolic and diastolic myocardial functions, even after adjustment for established CHD risk factors.[20] Because asymptomatic LV dysfunction is considered to be a subclinical marker of HF[114], carotid IMT associations with LV function could represent an earlier marker of myocardial dysfunction along the HF continuum. Whether these changes in LV function translate directly to HF in middle-aged adults remains uncertain. A better understanding of the association between carotid IMT and HF could help in the stratification of asymptomatic individuals at risk for HF for more intensive prevention therapies.

A few studies have examined the relationship between glucose categories and incident HF. Thrainsdottir et al – in a study involving 19,381 subjects aged 33-84 years – showed a strong association between HF and glucose status; HF was diagnosed in 3.2% of subjects with NGT, compared with 6.0% and 11.8% in subjects with IFG and diabetes, respectively.[157] In a sample of 9,591 individuals with diabetes, age- and sex-matched with a control group without diabetes, incident cases of HF were observed in 7.7% of diabetic subjects free of HF at baseline and in 3.4% of control subjects.[158] In the Strong Heart Study, subjects with diabetes were shown to have a 2.8-fold greater risk of HF than those with NGT (95%CI: 2.0–3.8, $p<0.0001$), independently of established risk factors; no differences were observed between subjects with NGT and IFG.[159]

The ARIC Study is a multicenter cohort study of 15,792 people aged 45-64 years at baseline and has detailed longitudinal data on carotid IMT measures, with more than 1,727 cases of incident HF hospitalization or death over 20 years, as well as data on CVD risk factors.[160] We used data from this cohort to investigate the importance of atherosclerosis on the occurrence of HF, and determine whether this association was modified by glucose status. We addressed the following aims:

Aim 1: To determine whether a previously reported cross-sectional association of carotid IMT, defined as the mean of six far wall measures, with incident HF among middle-aged white and black ARIC participants free of HF symptoms at baseline, persists over approximately 20 years of follow-up and after controlling for major CVD risk factors.

Aim 2: To determine if the relationship of carotid IMT with incident HF differs across categories of glucose metabolism (NFG, IFG, and DM) in this cohort.

Aim 3: To investigate the relationship of change in carotid IMT over an interval of approximately 3 years with incident HF following the baseline examination.

METHODS

1. Study Population

The Atherosclerosis Risk In Communities (ARIC) study recruited 15,792 participants aged 45-64 years at the time of their baseline assessment (1987-1989) from four U.S. communities: Forsyth County, North Carolina; suburban Minneapolis, Minnesota; Washington County, Maryland; and Jackson, Mississippi.[161]

Excluded from the analyses were: i) participants with missing all far wall values of carotid IMT at baseline (n = 607);[162] ii) racial groups other than black or white because of their limited numbers (n = 48); iii) participants with missing criteria needed to define baseline glucose status (n = 148); iv) participants with missing data needed to define HF at baseline (n = 287); v) prevalent cases of HF at baseline, either by self-reported current intake of HF medication, or those with stage 3 or manifest HF by Gothenburg criteria (n = 752).[6, 163] The Gothenburg criteria (Table I-2) is composed of 3 scores, i) cardiac, (ii) pulmonary, and (iii) therapy. To have stage 3 or manifest HF, the participant must have a point from each category. All current medications (taken within the last 2 weeks) were brought into the clinic and documented. Use of digoxin and diuretics was determined from these medication lists.[6] Atrial fibrillation was diagnosed by visual inspection of a 2-minute rhythm strip from leads V1, II, and V5 using standardized methodology.[164] All other components were determined by participant self-report. Our final sample size was 13,590 participants.

For analysis of change in IMT I limited the analysis to participants with complete data on IMT measurement (all six far wall measurements) at the baseline exam (1987-1989) and at the

first follow-up visit (1990-1992), approximately 3 years apart, and those participants who were free of HF at the second follow-up visit. The remaining sample was comprised of a total of 10,729 participants for this analysis, with 1,378 cases of incident HF. Adjustment for CVD risk factors was done using baseline values for covariates.

Table I-2: Description of the Gothenburg Score

Category	Gothenburg Components	Score
Cardiac	Coronary heart disease	1 point if ever, 2 points if within the last year
	Angina	1 point if ever, 2 points if within the last year
	Leg edema	1 point
	Shortness of breath at night	1 point
	Rales on lung exam	1 point
	Atrial fibrillation on ECG	1 point
Pulmonary	History of bronchitis	1 point
	History of asthma	1 point
	Cough, phlegm, or wheezing	1 point
	Rhonchi on lung exam	1 point
Therapy	Treatment with digoxin	1 point
	Treatment with diuretics	1 point

Modified from Loehr et al. Heart failure incidence and survival. Am J Cardiol. 2008 Apr 1;101(7):1016-22.

Data Collection and study variables

ARIC study participants provided information on demographic and behavioral variables and medical history to a trained interviewer at each visit. Race, gender, educational level, current alcohol use, and smoking status were determined by self-report at baseline. Medication use for dyslipidemia and hypertension were coded by trained personnel.

Measurement of carotid IMT

Evidence of atherosclerosis of the common carotid arteries was determined by non-invasive high resolution B-mode ultrasound.[161] In this study, technicians scanned three specified segments of

the extracranial carotid arteries bilaterally: the common carotid, the bifurcation and the internal carotid. The common carotid intima and media was assessed in a 1-cm segment proximal to the dilatation of the carotid bulb. The intima and media of the bifurcation and internal carotid were assessed over the 1-cm segments proximal and distal to the flow divider, respectively.[165] A total of 6 sites were examined, 3 measurements in each carotid. The mean intimal-medial thickness of the far wall of the 6 segments was used as a general indicator of atherosclerosis in the carotid artery.

The ultrasound examinations were performed according to a detailed standardized protocol by trained, certified sonographers subject to semiannual evaluation.[166] Ultrasound images were recorded on a videotape and forwarded to a central reading center for interpretation. The ultrasound readers were blinded from patient characteristics. For each of the 6 images, attempts were made to measure the IMT over a 1-cm segment at 1-mm increments (total of 11 measurements). A mean wall thickness for each segment was then calculated. A mean carotid IMT adjusted for reader differences and reading date was then calculated. This protocol produces a single index of atherosclerosis with improved precision provided by the averaging of multiple IMT measurements.[165]

In a randomly selected subset of 855 participants, the between-reader reliability coefficients ranged from 0.78 to 0.93 and coefficients of variation ranged from 13.1 to 18.3% (80% or more of duplicate scans differed by less than 0.267 mm).[166-167]

Ascertainment of Heart Failure

Incident HF was defined as the first occurrence of either i) a HF hospitalization which included an International Classification of Diseases (ICD), 9th revision, discharge code of 428.x (428.0 to 428.9) in any position (n = 1,206), or ii) a death certificate with a 428 (HF) or ICD, 10th

revision, code I50 (HF) in any position (n = 76). All hospitalizations occuring in cohort participants were identified either through generated computer programs, or review of hospital discharge indexes or information elicited during the annual follow-up interview. Hospitalizations eligible based on set criteria (discharge codes, discharge dates, race sex, and age) but were found upon review to have been hospitalized for less than 24hrs were not abstracted. Abstractors made copies of sections of the medical record (discharge summary, history and physical report, admission note, and imaging reports) for use by the ARIC Heart Failure Mortality and Morbidity Classification Committee (HF MMCC). The inter-abstractor agreement rate for determining whether or not to conduct detailed abstraction in a quality control sample was 99%. The ARIC community surveillance database was also searched for possible HF events occuring among cohort participants that were not reported at the annual follow-up visit or may be otherwise missed.

Beginning in 2005, the ARIC Study conducted continuous, retrospective surveillance of hospital discharges for HF for all residents aged 55 and above in the 4 ARIC communities via annual electronic discharge indices. Each hospitalization eligible for full abstraction was independently reviewed by two centrally trained and certified physicians on the ARIC HF MMCC. The reviewers were provided a report of the abstracted data as well as the copied materials noted above. Each reviewer was provided a summary of the abstracted data noted above (including measurement of ejection fraction and biomarkers) and the copied portions of medical records, and classified each hospitalization into 1 of 5 categories: definite ADHF, possible ADHF, chronic stable HF, HF unlikely, or unclassifiable.[168] Differences between these reviewers are adjudicated by a Chair of the HF MMCC. The adjudicated classification becomes the event's final classification. HF cases occuring prior to 2005 were not adjudicated. The %

agreement between HF events adjudicated by the HF MMCC and ICD-9 code 428.x at any position was 73%, similar to that with the Framingham HF criteria (70%)[168].

Follow-up time for those with incident HF events was defined by the time from their baseline exam (visit 1) until the incident event. The end of follow-up time for those without HF was i) December 31, 2009, ii) date of last contact for those lost to follow-up, or iii) date of death, whichever occurred first.

Measurement of other study variables

Prevalent CHD was defined as a history of myocardial infarction (MI), MI from adjudicated baseline ECG data, a history of physician-diagnosed MI, a prior coronary reperfusion procedure. Incident CHD was defined as any case of hospitalized MI, fatal CHD or ECG-diagnosed MI by the end of the study period.

Three (3) systolic and diastolic blood pressures were taken with participants in the sitting position after 5 minutes of rest using a random-zero sphygmomanometer. The average of the second and third readings was recorded. Certified technicians measured height, weight and waist circumference. Body mass index was calculated as weight (in kilograms) divided by the square of the height (in meters). Waist circumference was measured at the umbilicus.

Fasting serum glucose was measured by the optimized direct analysis in real time (DART) GLUCOSE reagent method. Diabetes mellitus was defined according to measured fasting glucose level of ≥ 7.0 mmol/l (≥ 126 mg/dl), self-reported previous physician diagnosis, or use of diabetes medication (oral hypoglycemic agents and/or insulin), or a non-fasting glucose of ≥ 11 mmol/l (≥ 200 mg/dl). Impaired fasting glucose was defined by a fasting glucose level between 5.6 and 6.9 mmol/l (100-125 mg/dl) in accordance with the 2004 American Diabetes Association definition. Normal fasting glucose was defined as any other participant who does not

meet the criteria for DM and IFG. Triglycerides and HDL cholesterol were determined using enzymatic methods. LDL cholesterol was calculated using the Friedewald equation.[169] Serum creatinine concentration was measured using a modified kinetic Jaffe method.

2. Power Calculations and Data Analysis

We obtained data for our analyses from the ARIC Coordinating Center and signed a data distribution agreement in concordance with the ARIC protocol.

Aim 1: *To determine whether a previously reported cross-sectional association of carotid IMT, defined as the mean of six far wall measures, with incident HF among middle-aged white and black ARIC participants free of HF symptoms at baseline, persists over approximately 20 years of follow-up and after controlling for major CVD risk factors.*

Cene et al. reported that among 14,348 participants of the ARIC cohort after a median follow-up of 16.9 years (excluding incident HF cases between visits 1 and 2, and with racial groups other than Black or Caucasian), 1,727 went on to develop HF.[160]

Power calculations:

We used the formula derived by Latouche et al,[170] given below:

$$Z_{1-\beta} = \sqrt{\frac{D\ x(\log_e HR)^2}{4}} - Z_{1-\alpha/2}$$

where *D* is the total number of events (incident HF), logHR is the natural log hazards ratio associated with a one-unit change in the predictor, and $Z_{1-\alpha/2}$ and $Z_{1-\beta}$ are standard normal deviates at the desired two-sided significance level α and power $1 - \beta$, respectively.

In the ARIC Study, between 1990 and December 31st, 2008, there were 1,727 incident HF cases. Based on our exclusion criteria outlined in section 3.3 above, and under the assumption that we excluded approximately 11.7% of the total cohort sample from our analyses (1,842 of 15,792 participants), we estimated having 1,526 incident HF cases to investigate. Based on the above information, we calculated power as follows:

Number of events	Power		
	HR = 1.15	HR = 1.20	HR = 1.25
1,526	78%	95%	99%

Using data from ARIC, Chambless et al. estimated the HR for MI per 1 SD (0.19 mm) increase in common carotid IMT, adjusted for age and sex, to be 1.22.[100, 138] We thus had sufficient power to detect a much lower HR (1.15 or greater) than that estimated in the above study.

Statistical Analyses:

For this aim, we investigated the association between baseline carotid IMT data and new-onset (incident) cases of HF using a Cox proportional hazards regression. The hazard ratios (and 95% confidence intervals) per unit increase in standard deviation of carotid IMT were estimated. Data on covariates were used in the multivariable regression analysis to better understand the independent association of carotid IMT with incident HF. Four sets of models were derived:

- *Model 1*: unadjusted for covariates
- *Model 2 (demographic model)*: adjusted for age, gender, race, and level of education
- *Model 3 (clinical and biologic model):* adjusted for covariates in model 2, plus systolic and diastolic blood pressures, BMI, waist circumference, HDL-cholesterol, LDL-

cholesterol, triglycerides, hypertension and lipid-lowering medications, smoking status and amount in pack-years, alcohol consumption, and serum creatinine.

- *Model 4 (CHD model)*: adjusted for covariates in model 3, plus prevalent and incident CHD.

Incident CHD was modeled as a time-varying covariate. We further categorized carotid IMT into quartiles and estimate the hazard ratios for incident HF (events) using the first quartile as reference.

Aim 2: *To determine if the relationship of carotid IMT with incident HF differs across categories of glucose metabolism (NFG, IFG, and DM) in this cohort.*

Data from the ARIC study website on the characteristics of the cohort[171] indicate that at baseline approximately 12% of the study population had T2DM (N = 1,895). Also Chamberlain et al. showed that the prevalence of IFG at baseline in the ARIC cohort was 48% (N = 7,245).[172]

Statistical Analyses:

To address this aim, we tested for an effect-modifying property of diabetes status by including a two-way interaction term (IMT*glucose status) in the model. In the event of a significant interaction ($p<0.05$), we specified four (4) separate models each for a glucose metabolism status and calculate hazard ratios with the IMT-glucose status interaction term in the model. We used Cox regression to calculate hazard ratios for the different glucose status, while progressively adjusting the models.

Aim 3: *To investigate the relationship of change in carotid IMT over an interval of approximately 3 years with incident HF following the baseline examination.*

Statistical Analyses:

Follow-up carotid IMT measurements were done during the second visit, approximately 3 years after the baseline visit. For this follow-up measurement, an adjustment was made for method drift during study visits and systematic differences between readers. Change in carotid IMT was assessed by estimating the average annualized change between the baseline and second visit (approximately 3 years interval). Participants with prevalent HF at the time of the second visit were excluded from this analysis, as well as those lacking IMT measurement at the second visit. The estimate of annualized change in IMT was modeled as time-constant variable in Cox regression models with adjustments for CVD risk factors and CHD. The four models described in the first aim were used.

3. Human Subjects Research

The ARIC study protocol was approved by the Institutional Review Boards of all participating institutions. Written informed consent was obtained from all participants in accordance with guidelines for human experimentation of the US Department of Health and Human Services (DHHS).

We performed secondary data analysis using a de-identified dataset from this cohort. Our study did not involve contact with any study participant to collect new data or perform new procedures, and analysis of any stored sample.

Based on Title 45 of the Code of Federal Regulations (CFR), DHHS Part 46 (Protection of Human Subjects), Section 46.101, paragraph (b), our analysis met the criteria for exemption.

45 CFR 46.101(b)(4): Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.[173]

4. Inclusion of Women and Minorities

Women and minorities were included as outlined in the ARIC Study protocol.[161] ARIC study participants were recruited from four US communities and comprised 27.2% Blacks (n = 4266), 72.5% Whites (n = 11478) and less than 1% of other minority groups (n = 48). The baseline study population was made up of 55% women. Our study sample was a good representation of the ARIC population; 24.8% Blacks and 75.2% Whites, and 55% women.

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CHAPTER II - MANUSCRIPT

The Association of Subclinical Atherosclerosis with incident Heart Failure: The Atherosclerosis Risk in Communities Study

Effoe et al: Atherosclerosis and Heart Failure

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ABSTRACT

Background: Atherosclerosis plays a central role in the pathophysiology of coronary heart disease (CHD), which is believed to be the most common etiology for heart failure (HF). Greater carotid intima-media thickness (IMT), a measure of subclinical atherosclerosis, is associated with left ventricular myocardial dysfunction, a subclinical marker of HF. We investigated the association of carotid IMT with incident HF among middle-aged whites and blacks, controlling for major cardiovascular disease (CVD) risk factors.

Methods and Results: We included 13,590 participants from the ARIC cohort aged 45 – 64 years in our analysis. Excluded were participants with HF at baseline, those with missing IMT measurements and criteria to define diabetes. The mean carotid IMT of six far walls, measured by B-mode ultrasound, was used in our analyses. HF was defined using ICD-9 and ICD-10 codes from hospitalization records and death certificates. There were 2,008 incident HF hospitalizations or death over a median follow-up period 20.6 years. Baseline mean carotid IMT was significantly higher for subjects with incident HF than those without HF (0.81±0.23 vs 0.71±0.17; $p<0.0001$). Carotid IMT was significantly associated with incident HF, after adjustment for demographic and CVD risk factors and CHD (HR 1.20 per unit SD increase; 95% CI: 1.16-1.25). After accouting for major CVD risk factors and CHD, only the fourth quartile of IMT remained significantly associated with HF relative to the first quartile (HR 1.60; 95% CI: 1.37-1.87, $p<0.0001$). Also, after accounting for major CVD risk factors and CHD, the association was greater in subjects with normal fasting glucose (NFG) than those with abnormal glucose metabolism (HR 1.25 per unit SD increase, 95% CI: 1.19-1.32 for NFG; HR 1.19, 95% CI: 1.11-1.27 for impaired fasting glucose; and HR 1.14, 95% CI: 1.05-1.23 for diabetes

mellitus). The p-value for IMT*glucose status interaction term in the fully adjusted model was 0.0149.

Conclusions: Carotid IMT is strongly associated with HF in middle-aged whites and blacks after adjusting for major CVD risk factors and CHD.

Keywords: subclinical atherosclerosis, carotid intima-media thickness, heart failure, diabetes mellitus

INTRODUCTION

Heart failure (HF) represents an increasing clinical and public health burden in the United States as its prevalence and incidence continue to rise,[1-3] especially among elderly Americans.[4-5] HF has emerged as the single leading diagnosis for hospitalization in the elderly and hospitalization rates are higher among blacks than whites, with 83% of HF patients hospitalized at least once and 43% hospitalized at least 4 times over a mean duration of 4.7 years.[6-7] This burden of HF is likely to increase because of increasing age of the American population, a progressive increase in the age of onset of HF and improved treatment and survival from cardiovascular (CV) diseases, including myocardial infarction (MI) and hypertension.[8-9]

Carotid IMT is a well-established marker of subclinical atherosclerosis which indicates early manifestation of atherosclerosis in the carotid arteries,[10-11] and is associated with future CV events,[12-13] asymptomatic myocardial ischemia,[14] and changes in risk factors induced by therapeutic interventions.[15] There is evidence of a direct relationship between increased carotid IMT and reduced left ventricular (LV) systolic and diastolic function in asymptomatic individuals without previous clincial CV disease.[16] Elderly patients with HF differ from younger patients with HF in terms of several biologic characteristics, including the relatively large proportion of elderly patients with HF who have preserved systolic function.[17-18] Using data from the Cardiovascular Health Study which included subjects 65 years or older, atherosclerosis as measured by carotid IMT was shown to predict overt systolic and diastolic HF.[13] The association of carotid IMT with incident HF in middle-aged adults, who are at a lower risk of HF than older adults, is not well known. Previous cross-sectional analysis using data from the ARIC cohort showed that participants with HF had a higher mean carotid IMT than participants without HF.[19] These findings were not adjusted for CVD risk factors.

Patients with diabetes mellitus are at an increased risk for HF than those without diabetes,[20-21] and the difference is much greater in younger age groups.[20] Diabetic cardiomyopathy has been described as a distinct clinical entity leading to HF among subjects with diabetes, and different pathophysiologic mechanisms have been postulated.[22] Because of an increasing prevalence of diabetes in the U.S., knowledge of the association of carotid IMT with HF in these patients could be beneficial in HF prevention in this high-risk group.

Subclinical vascular disease as determined by an increasing carotid IMT may be a determinant of risk for future HF, but this has not been studied. In the present study, we examine the hypothesis that subclinical atherosclerosis assessed by the mean carotid IMT is associated with incident HF, beyond what is explained by major CV disease risk factors in middle-aged whites and blacks. To test this hypothesis, we used data from the ARIC cohort. Secondly, we examined if this association differed in persons with normal fasting glucose, impaired fasting glucose, and diabetes mellitus.

METHODS

Study Population

The Atherosclerosis Risk In Communities (ARIC) study is community-based prospective study which enroled 15,792 participants aged 45-64 years at the time of their baseline assessment (1987-1989) from four communities: Forsyth County, North Carolina; suburban Minneapolis, Minnesota; Washington County, Maryland; and Jackson, Mississippi.[23] In the cohort, response rates at baseline were 46% in Jackson and 65-67% for the other communities. Successful contact with living cohort members through an annual phone interview was above 93%. The institutional review boards from each site approved the ARIC study.

Our analysis involved the use of data from the baseline examination. Excluded from the sample were: i) participants with missing all far wall values of carotid IMT at baseline (n = 607);[24] ii) racial groups other than black or white because of their limited numbers (n = 48); iii) participants with missing criteria needed to define baseline glucose status (n = 148); iv) participants with missing data needed to define HF at baseline (n = 287); v) prevalent cases of HF at baseline, either by self-reported current intake of HF medication, or those with stage 3 or manifest HF by Gothenburg criteria (n = 752).[19, 25] The Gothenburg criterion (Table I-2) is composed of 3 scores, i) cardiac, (ii) pulmonary, and (iii) therapy. To have stage 3 or manifest HF, the participant must have a point from each category. All current medications (taken within the last 2 weeks) were brought into the clinic and documented. Use of digoxin and diuretics was determined from these medication lists.[19] Atrial fibrillation was diagnosed by visual inspection of a 2-minute rhythm strip from leads V1, II, and V5 using standardized methodology.[26] All other components were determined by participant self-report. Our final sample size was 13,590 participants.

Data Collection and study variables

ARIC study participants provided information on demographic and behavioral variables and medical history to a trained interviewer at each visit. Race, gender, educational level, current alcohol use, and smoking status were determined by self-report at baseline. Medication use for dyslipidemia and hypertension were coded by trained personnel.

Measurement of carotid IMT

Evidence of atherosclerosis of the common carotid arteries was determined by non-invasive high resolution B-mode ultrasound.[23] In this study, technicians scanned three specified segments of the extracranial carotid arteries bilaterally: the common carotid, the bifurcation and the internal

carotid. The common carotid intima and media was assessed in a 1-cm segment proximal to the dilatation of the carotid bulb. The intima and media of the bifurcation and internal carotid were assessed over the 1-cm segments proximal and distal to the flow divider, respectively.[27] A total of 6 sites were examined, 3 measurements in each carotid. The mean intimal-medial thickness of the far wall of the 6 segments was used as a general indicator of atherosclerosis in the carotid artery.

The ultrasound examinations were performed according to a detailed standardized protocol by trained, certified sonographers subject to semiannual evaluation.[28] Ultrasound images were recorded on a videotape and forwarded to a central reading center for interpretation. The ultrasound readers were blinded from patient characteristics. For each of the 6 images, attempts were made to measure the IMT over a 1-cm segment at 1-mm increments (total of 11 measurements). A mean wall thickness for each segment was then calculated. A mean carotid IMT adjusted for reader differences and reading date was then calculated. This protocol produces a single index of atherosclerosis with improved precision provided by the averaging of multiple IMT measurements.[27]

In a randomly selected subset of 855 participants, the between-reader reliability coefficients ranged from 0.78 to 0.93 and coefficients of variation ranged from 13.1 to 18.3% (80% or more of duplicate scans differed by less than 0.267 mm).[28-29]

Ascertainment of Heart Failure

Incident HF was defined as the first occurrence of either i) a HF hospitalization which included an International Classification of Diseases (ICD), 9th revision, discharge code of 428.x (428.0 to 428.9) in any position (n = 1,206), or ii) a death certificate with a 428 (HF) or ICD, 10th revision, code I50 (HF) in any position (n = 76). All hospitalizations occuring in cohort

participants were identified either through generated computer programs, or review of hospital discharge indexes or information elicited during the annual follow-up interview. Hospitalizations eligible based on set criteria (discharge codes, discharge dates, race sex, and age) but were found upon review to have been hospitalized for less than 24hrs were not abstracted. Abstractors made copies of sections of the medical record (discharge summary, history and physical report, admission note, and imaging reports) for use by the ARIC Heart Failure Mortality and Morbidity Classification Committee (HF MMCC). The inter-abstractor agreement rate for determining whether or not to conduct detailed abstraction in a quality control sample was 99%. The ARIC community surveillance database was also searched for possible HF events occuring among cohort participants that were not reported at the annual follow-up visit or may be otherwise missed.

Beginning in 2005, the ARIC Study conducted continuous, retrospective surveillance of hospital discharges for HF for all residents aged 55 and above in the 4 ARIC communities via annual electronic discharge indices. Each hospitalization eligible for full abstraction was independently reviewed by two centrally trained and certified physicians on the ARIC HF MMCC. The reviewers were provided a report of the abstracted data as well as the copied materials noted above. Each reviewer was provided a summary of the abstracted data noted above (including measurement of ejection fraction and biomarkers) and the copied portions of medical records, and classified each hospitalization into 1 of 5 categories: definite ADHF, possible ADHF, chronic stable HF, HF unlikely, or unclassifiable.[30] Differences between these reviewers are adjudicated by the Chair of the HF MMCC. The adjudicated classification becomes the event's final classification. HF cases occuring prior to 2005 were not adjudicated.

The % agreement between HF events adjudicated by the HF MMCC and ICD-9 code 428.x at any position was 73%, similar to that with the Framingham HF criteria (70%)[30].

Follow-up time for those with incident HF events was defined by the time from their baseline exam (visit 1) until the incident event. The end of follow-up time for those without HF was i) December 31, 2009, ii) date of last contact for those lost to follow-up, or iii) date of death, whichever occurred first.

Measurement of other study variables

Prevalent CHD at baseline was defined as a history of myocardial infarction (MI), MI from adjudicated baseline ECG data, a history of physician-diagnosed MI, a prior coronary reperfusion procedure. Incident CHD was defined as any case of hospitalized MI, fatal CHD or ECG-diagnosed MI by the end of the study period.

Three (3) systolic and diastolic blood pressures were taken with participants in the sitting position after 5 minutes of rest using a random-zero sphygmomanometer. The average of the second and third readings was recorded. Certified technicians measured height, weight and waist circumference. Body mass index was calculated as weight (in kilograms) divided by the square of the height (in meters). Waist circumference was measured at the umbilicus.

Fasting serum glucose was measured by the optimized direct analysis in real time (DART) GLUCOSE reagent method. Diabetes mellitus was defined according to measured fasting glucose level of ≥ 7.0 mmol/l (≥ 126 mg/dl), self-reported previous physician diagnosis, or use of diabetes medication (oral hypoglycemic agents and/or insulin), or a non-fasting glucose of ≥ 11 mmol/l (≥ 200 mg/dl). Impaired fasting glucose was defined by a fasting glucose level between 5.6 and 6.9 mmol/l (100-125 mg/dl) in accordance with the 2004 American Diabetes Association definition. Normal fasting glucose was defined as any other participant who does not

meet the criteria for DM and IFG. Triglycerides and HDL cholesterol were determined using enzymatic methods. LDL cholesterol was calculated using the Friedewald equation.[31] Serum creatinine concentration was measured using a modified kinetic Jaffe method.

Statistical Analysis

Results of analyses are presented as mean ± SD, for continuous variables and as frequencies (percentages) for categorical variables, unless otherwise stated. Unadjusted differences in baseline characteristics between participants with and without HF were assessed using the Student's t-test (for continuous variables) and Chi-square test (for categorical variables). The independent association of carotid IMT with incident heart failure was assessed using Cox proportional hazard models with progressive adjustment for covariates. Hazard ratios and 95% confidence intervals for Cox regression analysis are presented per unit standard deviation increase and by quartiles of IMT. The base model was an unadjusted model.

In multivariable analysis, the base model (unadjusted model) was progressively adjusted for covariates of interest. A second model was adjusted for age, gender, race, and level of education (demographic model). A third model was further adjusted for systolic and diastolic blood pressures, BMI, waist circumference, HDL-cholesterol, LDL-cholesterol, triglycerides, smoking status and amount in pack-years, alcohol consumption, serum creatinine, and medications for hypertension and dyslipidemia (clinical and biologic model). Finally, a fourth model was finally adjusted for prevalent and incident CHD (CHD model). For the fourth model, incident CHD was modeled as a time-varying covariate. Covariates were chosen based on their associations in the present cohort and in prior published studies.[13, 32]

Effect modification between race, gender and glucos metabolism status, and carotid IMT was examined using two-way interaction. This was achieved by including the product the

IMT*race, IMT*gender, and IMT*glucose status terms in the model. In the presence of a significant interaction (p for interaction <0.05), we performed a stratified analysis for the covariate in question.

Separate Cox regression models included carotid IMT as a continuous variable (Z-scores) and as a categorical variable (quartiles). The proportional hazard assumption was assessed by visually examining the log (-log survival) plots and time-covariate interaction terms. Kaplan-Meier plots were used to illustrate the overall survival probabilty and cumulative incidence of HF by subgroups, and group comparison was done using the log-rank test. All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). Statistical significance was inferred at two-sided p<0.05.

Role of the funding source

The ARIC study is sponsored by the National Heart, Lung, and Blood Institute (NHLBI) of the NIH. The sponsor had no role in the design, analysis and interpretation of the results of this study.

RESULTS

Baseline characteristics

Among the 13,590 participants in this study, there were 2,008 (14.8% of total cohort) incident cases of HF over a median follow-up period of 20.6 years. Table II-1 compares the unadjusted baseline demographic and clinical characteristics of participants with and without HF. Compared to participants without HF, participants with HF were older (56.6 vs 53.7 years), more likely to be male (52.5% vs 44.1%), and more likely to be hypertensive (50.3% vs 28.6%). Participants who developed HF over the course of follow-up were also more likely to have an abnormal lipid

profile, were current smokers but less likely to be current drinkers and to have completed a college education. The prevalence and incidence of CHD were higher among subjects with HF ($p<0.0001$), as well as the prevalence of diabetes mellitus (26.3% vs 7.8%; $p<0.0001$).

Association of carotid IMT with incident HF

Mean carotid IMT was significantly higher for subjects with HF (0.81±0.23 vs 0.71±0.17; $p<0.0001$), Table II-1. In this sample, the overall unadjusted incidence rate of HF was 8.07 cases per 1,000 person-years. Compared with subjects in the 1st quartile of carotid IMT (IMT≤0.61 mm), the unadjusted incidence rates of HF increased across the 2nd, 3rd, and 4th quartiles (Table 2). The rate in the highest quartile of carotid IMT was 15.42 cases per 1,000 person-years (about four times the rate in the 1st quartile, and twice the rate in the 3rd quartile). Figure II-1 shows a Kaplan-Meier plot of the overall survival probability of HF over time as a function of carotid IMT quartiles. There was a significant difference in survival from HF between quartiles of IMT ($p<0.0001$). Of note, participants in the 4th quartile had a significantly lower survival.

In the multivariable analysis, we estimated the HR of HF across quartiles of carotid IMT (Table II-2). After adjustment for demographic factors, the 2nd, 3rd and 4th quartiles of carotid IMT were significantly associated with HF compared to the first quartile of IMT (HR for 4th quartile 2.59, 95% CI: 2.23-2.99). The strength of this association was reduced, but significantly persisted only for the 4th quartile of carotid IMT after further adjustments for CV disease risk factors (HR 1.65, 95%CI: 1.42, 1.93, <0.0001) and CHD (HR 1.60, 95%CI: 1.37-1.87, $p<0.0001$).

Similar results were observed when modeling carotid IMT as a continuous variable. The hazard ratios (HRs) and 95% confidence intervals of HF per unit SD (0.18 mm) increase in IMT are given in Table II-3. No interactions were observed by gender or race.

Association of carotid IMT with incident HF across status of glucose metabolism

The association of carotid IMT with incident HF was modified by glucose metabolism status (p for interaction <0.0001 in the unadjusted model). Therefore we performed stratified analyses. Compared to participants with normal and impaired fasting glucose, participants with diabetes mellitus had a higher mean systolic blood pressure, mean waist circumference, mean BMI, and mean carotid IMT (0.70±0.17 for NFG, 0.75±0.19 for IFG vs 0.79±0.20 for DM, P<0.0001). Participants with diabetes had an adverse lipid profile and a higher prevalence of CHD. Thirty-seven percent (37%) of individuals with diabetes developed HF, compared with a much lower proportion of participants with IFG and NFG (14% and 11% respectively).

The unadjusted incidence rate per 1,000 person-yrs of HF was at least three times higher among participants with diabetes (24.7; 95%CI: 22.68-26.90) than among participants with IFG (7.75; 95%CI: 7.17-8.37) and NFG (5.79; 95%CI: 5.41-6.19), Table II-4. When compared across quartiles of carotid IMT, the rates of HF increased progressively from the 1st to 4th quartile in all strata of glucose metabolism (Figure II-2). Regardless of carotid IMT quartile, the rates of incident HF among participants with diabetes were significantly higher (at least twice as high) than rates for participants with IFG and NFG. The rates in the highest quartile for NFG (12.38; 95%CI: 11.11-13.80) and IFG (13.12; 95%CI: 11.70-14.70) were lower than that in the lowest quartile for DM (14.83; 95%CI: 11.18-19.68).

Table II-4 also displays hazard ratios for HF per unit SD (0.18 mm) increase in carotid IMT, stratified by glucose metabolism status. Overall, participants with NFG had a higher HR of

HF, than participants with IFG and DM. In the unadjusted model, the HR was 1.56 (95% CI, 1.50-1.62) for those with NFG, 1.48 (95% CI, 1.40-1.57) for those with IFG, and 1.41 (95% CI, 1.31-1.51) for those with DM (all P<0.001). The strength of this association decreased with progressive addition of CV disease risk factors and CHD into the model. In the fully adjusted model, the HR was 1.25 (95% CI: 1.19-1.32, p<0.001) for participants with NFG, 1.19 (95% CI, 1.11-1.27, p<0.001) for those with IFG, and 1.14 (95% CI, 1.05-1.23, p=0.0014) for those with DM.

Proportionality hazard assumption

The proportionality hazard assumption, checked graphically and using time-interaction terms in a model, was met for all study variables.

DISCUSSION

Our results demonstrate that carotid IMT is significantly associated with incident HF among middle-aged whites and blacks, independent of demographic and major CV risk factors, and CHD. This relationship was present in both blacks and whites, as well as in diabetic and non-diabetic individuals.

Carotid IMT is a well validated measure of pre-clinical atherosclerotic lesions[10-11]. In this population-based study, we found mean far wall carotid IMT to be 0.72±0.18 mm. Similar mean far wall estimates have been reported in other populations of similar age groups; in the Carotid Atherosclerosis Progression Study[33] and Malmo Diet and Cancer Study[34], mean far wall IMT was 0.73±0.16 mm and 0.77±0.15 mm, respectively. The present study has shown that the association of carotid IMT with incident HF, with IMT modeled as both a continuous and

categorical variable, was significant after taking into account age, gender, race, blood pressure, BMI, waist circumference, HDL-cholesterol, LDL-cholesterol, triglycerides, cigarette smoking, alcohol, and serum creatinine, as well as medications for dyslipidemia and hypertension. Our result is consistent with that described by Engstrom et al.[32], who reported a significant association of increased IMT and HF hospitalizations in a sample of 4,691 subjects with 75 cases of HF. Moreover, our results remained significant even after adjustment for prevalent and incident cases of CHD, which has been reported to be a major cause of HF.

The finding, in our study, that the association of carotid IMT with HF remained significant after adjustment for prevalent and incident CHD, as well as blood pressure, and other traditional CV risk factors suggests that carotid IMT mediates HF through a mechanism that is different from that causing discrete clinical episodes of myocardial ischemia or infarction. There are a number of potential mechanisms that could explain this association. First, increasing carotid IMT leads to structural changes of the artery wall which result in the deposition of collagen in the intracellular matrix[35] and a decrease in arterial distensibility, causing increased pressure afterload, pressure wave propagation, and diastolic dysfunction.[35-36] A second potential mechanism relates to the finding from prior studies that increasing common carotid IMT was associated with reduced myocardial flow reserve in adults with[37] and without[38] CHD. Indeed some prospective and cross-sectional studies have established an association between increasing carotid IMT and regional LV myocardial systolic and diastolic dysfunction,[16, 39] a subclinical marker and strong predictor of HF.[40] However, further characterization of HF cases (systolic vs diastolic dysfunction) in their relation to increasing carotid IMT may be necessary to fully understand the different mechanisms that could contribute to HF in subjects with increased carotid IMT.

Carotid IMT was significantly increased in participants with diabetes than those with IFG and NFG. This finding is consistent with results from previously published studies.[41-43] The increased IMT in diabetic individuals may be explained by either a direct effect of chronic hyperglycemia on the carotid artery walls or an indirect effect of diabetes-related metabolic abnormalities. Chronic hyperglycemia contributes through a nonenzymatic glycosylation effect of proteins in the arterial wall,[44] the acceleration of lipoprotein oxidation,[45] and the stimulation of smooth muscle cell proliferation.[46] Diabetes is also associated with CHD risk factors, including dyslipidemia and hypertension[42] which have been linked to increasing carotid IMT.

To the best of our knowledge, no prior study has addressed whether the association of carotid IMT with incident HF is the same among participants with NFG and those with abnormal glucose metabolism (IFG and DM). Interestingly and contrary to our hypothesis, we demonstrated that the strength of this relationship (as measured by the hazard ratio) was lowest among participants with diabetes, after controlling for demographic and CV risk factors. The association was significant in all three categories of glucose metabolism. Despite a much higher difference in absolute risk of HF between the first and fourth quartiles of IMT among subjects with DM (17.65/1000 pyrs) than those with IFG (9.75/1000 pyrs) and NFG (8.15/1000 pyrs), each unit SD increase in carotid IMT was associated a 14% increase in the risk of HF for participants with DM, 19% for those with IFG, and 25% for those with NFG. This suggests the presence of other significant mechanisms, other than atherosclerosis, in the occurrence of HF in diabetic subjects. In these subjects, hyperglycaemia, hyperlipidemia and increased reactive oxygen species induce alterations in downstream transcription factors which result in changes in gene expression, myocardial substrate utilization, myocyte growth, endothelial function and myocardial compliance.[22] Also, carotid IMT may have a lower predictive value for CV

endpoints in persons with abnormal glucose metabolism than in normal subjects. In persons with DM and IFG, a larger association between IMT and CV outcomes at the femoral than at the carotid sites has been described.[47-48] This may suggest the usefulness of femoral IMT in assessing CV outcomes in this population. It would be interesting, in future studies, to investigate the relationship of IMT to incident HF in additional vascular beds (e.g. femoral artery).

To the best of our knowledge, our study is the first to investigate the association of carotid IMT with incident HF in a large cohort with over two decades of follow-up and more than 2,000 cases of incident HF. The use of a middle-aged population, than the elderly, who are at a lower risk of HF is particularly important. There are nonetheless a number of limitations to this study that should be mentioned. First, we did not adjust our analyses for novel biomarkers that could potentially influence the relationship between carotid IMT and HF, such as NT-proBNP and hs-CRP. However, in a prior published study, the association of carotid IMT with HF remained significant, even after adjustment for these markers[32]. Second, the use of hospital discharge codes and death registers to recruit HF cases may have underestimated HF incidence in the population. Also, these may have been severe cases of HF with complications. The fact that increased carotid IMT is associated with reduced LV systolic and diastolic function in asymptomatic individuals[16] suggests an association of carotid IMT with less severe cases of HF. Our analyses included both adjudicated and non-adjudicated cases of HF. Third, our cohort comprised of only blacks and whites, so caution should be made when generalizing these results to other race groups. Finally, in our study, carotid IMT estimates used were based on far wall measurements.

CONCLUSIONS

In this cohort of middle-aged blacks and whites, we have demonstrated that increasing carotid IMT is strongly associated with the development of HF even beyond the risks accounted for by traditional CV risk factors and CHD. Carotid IMT may be better in discriminating persons at risk of HF in non-diabetics than in diabetic subjects.

CLINICAL IMPLICATIONS

Carotid IMT is particularly appealing because it has been shown in several population-based studies to predict future CV outcomes, and this study takes it further to include HF. Carotid IMT is a reliable, low cost, low risk indicator of early atherosclerosis currently used in cardiovascular research. Measurement of carotid IMT can be quickly and easily accomplished in a clinical setting, and with modern ultrasound scanners this procedure becomes more efficient and reproducible.

Findings from this study indicate that carotid IMT may be a useful tool in the differential classification of individuals at risk for HF in middle-aged blacks and whites.

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DISCLOSURES

The authors have no financial disclosures.

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TABLES AND FIGURES

Table II-1: Baseline Demographic and Clinical Characteristics and Incident Heart Failure Status of ARIC Participants.

Characteristic	Overall	Incident Heart Failure Status	
	N = 13,590	Subjects with HF (N = 2,008)	Subjects without HF (N = 11,582)
Age, years	54.1 ± 5.8	56.6 ± 5.5	53.7 ± 5.7
Males, n (%)	6,166 (45.3)	1,057 (52.5)	5,109 (44.1)
White, n (%)	10,227 (75.2)	1,378 (68.5)	8,849 (76.4)
Hypertension, n (%)	4,320 (31.8)	1,010 (50.3)	3,310 (28.6)
Systolic blood pressure, mmHg	120.8 ± 18.6	128.0 ± 20.6	119.5 ± 18.0
Diastolic blood pressure, mmHg	73.5 ± 11.2	74.9 ± 12.7	73.2 ± 10.9
Blood pressure medication, n (%)	3,619 (26.6)	893 (44.4)	2,726 (23.54)
BMI, Kgm^{-2}	27.3 ± 5.0	29.1 ± 5.7	27.0 ± 4.8
Waist circumference, cm	96.1 ± 13.4	101.7 ± 14.1	95.1 ± 13.0
Education level			
Less than college education	8,688 (64.0)	1,512 (75.3)	7,176 (62.0)
Completed at least college	4,894 (36.0)	497 (24.7)	4,397 (38.0)
Smoking status, %			
Never	5,669 (41.7)	605 (30.1)	5,064 (43.7)
Former smoker	4,381 (32.2)	677 (33.7)	3,704 (32.0)
Current smoker	3,542 (26.1)	728 (36.2)	2,814 (24.3)
Alcohol consumption, %			
Never	3,315 (24.5)	546 (27.3)	2,769 (24.0)
Former drinker	2,472 (18.2)	521 (26.0)	1,951 (16.9)
Current drinker	7,761 (57.3)	932 (46.6)	6,829 (59.1)
Total Cholesterol, mmol/l	5.6 ± 1.1	5.7 ± 1.2	5.5 ± 1.1
LDL Cholesterol, mmol/l	3.6 ± 1.0	3.7 ± 1.1	3.5 ± 1.0
HDL Cholesterol, mmol/l	1.3 ± 0.4	1.2 ± 0.4	1.4 ± 0.5
Triglycerides, mmol/l †	1.3 ± 0.2	1.4 (1.0)	1.2 (0.8)
Lipid-lowering medication, n (%)	2,937 (21.7)	728 (36.5)	2,209 (19.2)
Fasting glucose level, mmol/l	5.96 ± 2.11	5.7 (1.4)	5.5 (0.8)
Blood glucose category, n (%)			
Normal fasting glucose	7,594 (55.8)	835 (41.5)	6,759 (58.3)
Impaired fasting glucose	4,574 (33.6)	648 (32.2)	3,926 (33.9)
Diabetes mellitus	1,431 (10.5)	529 (26.3)	902 (7.8)
Prevalent CHD, n (%)	555 (4.1)	240 (12.1)	315 (2.7)
Carotid IMT, mm	0.72 ± 0.18	0.81 ± 0.23	0.71 ± 0.17
Incident CHD, n (%)	1,727 (12.7)	827 (41.1)	900 (7.8)

Data are mean ± SD, or number (percentages). All comparisons were significant at P<0.0001.
† Data for triglycerides is presented as geometric mean ± SD

Table II-2: Unadjusted and Adjusted HRs (95% CI) for Incident Heart Failure across Quartiles of Carotid IMT

Models	Quartiles of IMT (mm)			
	Q1 (< 0.62)	Q2 (0.62 – 0.69)	Q3 (0.70 – 0.79)	Q4 (> 0.79)
Number of HF events	268	389	482	869
Rate/1000 pyrs (95%CI)	3.9 (3.4, 4.4)	6.0 (5.4, 6.6)	8.3 (7.6, 9.0)	15.4 (14.4, 16.5)
Model 1, HR (95%CI)	1.0 (ref.)	1.57 (1.35, 1.84)*	2.20 (1.89, 2.55)*	4.26 (3.71, 4.88)*
Model 2, HR (95%CI)	1.0 (ref.)	1.30 (1.11, 1.52)†	1.59 (1.37, 1.85)*	2.59 (2.23, 2.99)*
Model 3, HR (95%CI)	1.0 (ref.)	1.10 (0.93, 1.29)	1.14 (0.98, 1.34)	1.65 (1.42, 1.93)*
Model 4, HR (95%CI)	1.0 (ref.)	1.09 (0.92, 1.28)	1.14 (0.97, 1.33)	1.60 (1.37, 1.87)*

*p<0.0001; †p=0.001; Model 1: unadjusted; Model 2: adjusted for age, gender, race, education; Model 3: model 2 plus systolic and diastolic blood pressure, BMI, waist circumference, LDL, HDL, triglycerides, smoking, alcohol, hypertension and cholesterol medication, serum creatinine; Model 4: model 3 plus prevalent and incident CHD

Table II-3: Unadjusted and Adjusted HRs (95% CI) for Incident Heart Failure per 1 SD (0.18 mm) increase in Carotid IMT.

Clinical outcome: Heart Failure	HR	95% CI	p-value
Model 1 (unadjusted)	1.54	1.50, 1.58	< 0.0001
Model 2	1.38	1.33, 1.42	< 0.0001
Model 3	1.21	1.16, 1.25	< 0.0001
Model 4	1.20	1.16, 1.25	< 0.0001

Model 2: adjusted for age, gender, race, education; Model 3: model 2 plus systolic and diastolic blood pressure, BMI, waist circumference, LDL, HDL, triglycerides, smoking, alcohol, hypertension and cholesterol medication, serum creatinine; Model 4: model 3 plus prevalent and incident CHD

Table II-4: Unadjusted and Adjusted HRs (95% CI) for Incident Heart Failure per unit SD (0.18 mm) Increase in Carotid IMT, Stratified by Categories of Glucose Metabolism.

Models		**Categories of Glucose Metabolism**		
		NFG	IFG	DM
Number of HF cases		834	646	528
Rate/1000 person-years (95% CI)		5.79 (5.41, 6.19)	7.75 (7.17, 8.37)	24.70 (22.68, 26.90)
Model 1 (unadjusted)	HR (95% CI)	1.56 (1.50, 1.62)	1.48 (1.40, 1.57)	1.41 (1.31, 1.51)
Model 2	HR (95% CI)	1.42 (1.35, 1.49)	1.34 (1.26, 1.42)	1.25 (1.16, 1.35)
Model 3	HR (95% CI)	1.26 (1.19, 1.32)	1.20 (1.12, 1.28)	1.13 (1.05, 1.22)
Model 4	HR (95% CI)	1.25 (1.19, 1.32)	1.19 (1.11, 1.27)	1.14 (1.05, 1.23)

Model 2: adjusted for age, gender, race, level of education. Model 3: adjusted for covariates in model 2 and hypertension medication, systolic and diastolic blood pressure, BMI, waist circumference, HDL-cholesterol, LDL-cholesterol, triglycerides, lipid-lowering medication, smoking status and amount in pack-years, alcohol consumption, and serum creatinine. Model 4: adjusted for covariates in model 3, prevalent and incident CHD. All results are significant at $p < 0.001$, except for the effect of carotid IMT for DM in model 3 ($p=0.0020$) and model 4 ($p=0.0014$)

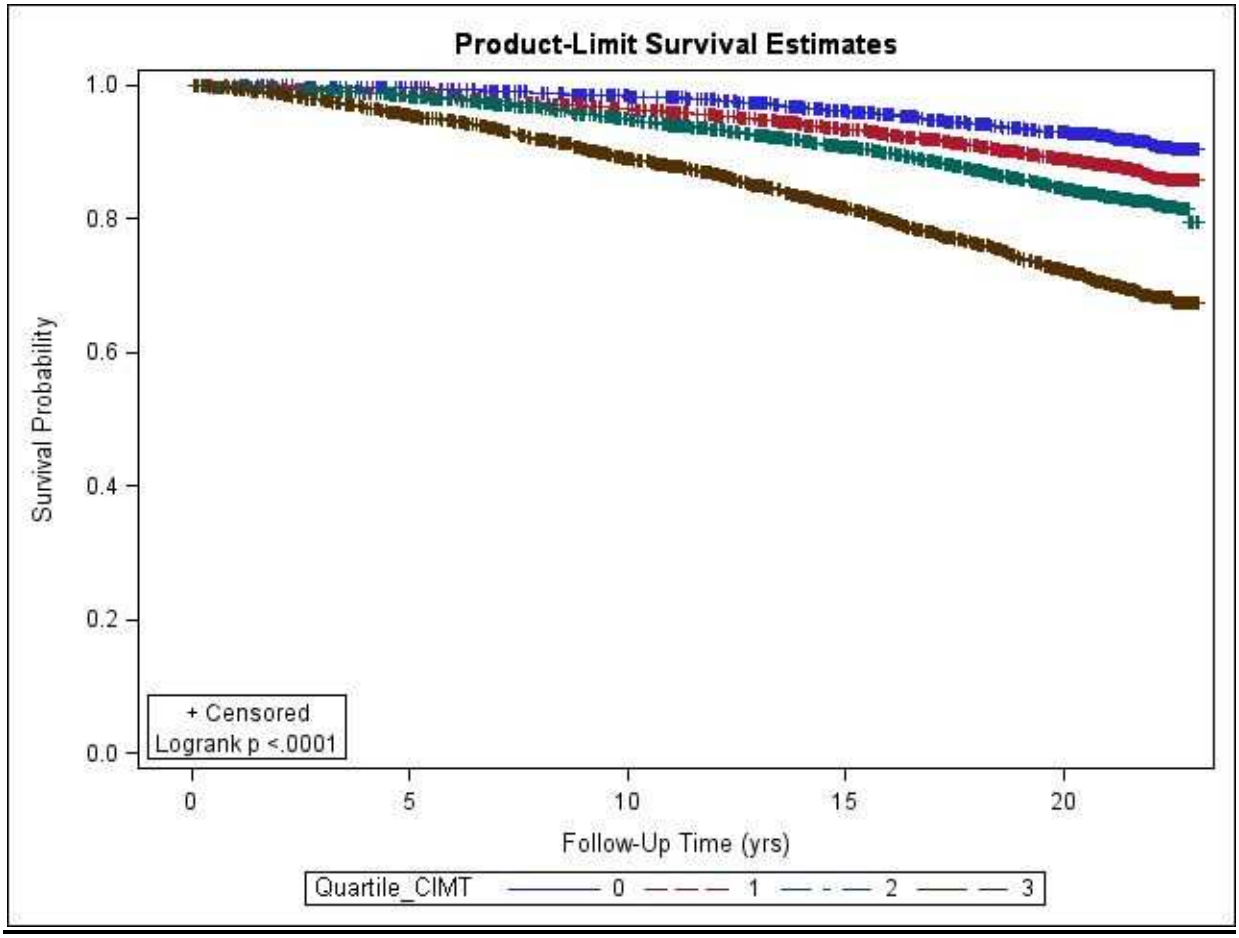

Figure II-1: Kaplan-Meier curves illustrating the overall survival probability of HF over time as a function of quartiles of carotid IMT. Quartile_CIMT indicates quartiles of carotid IMT; 0 (blue), 1st quartile; 1 (red), 2nd quartile; 2 (green), 3rd quartile; 3 (brown), 4th quartile.

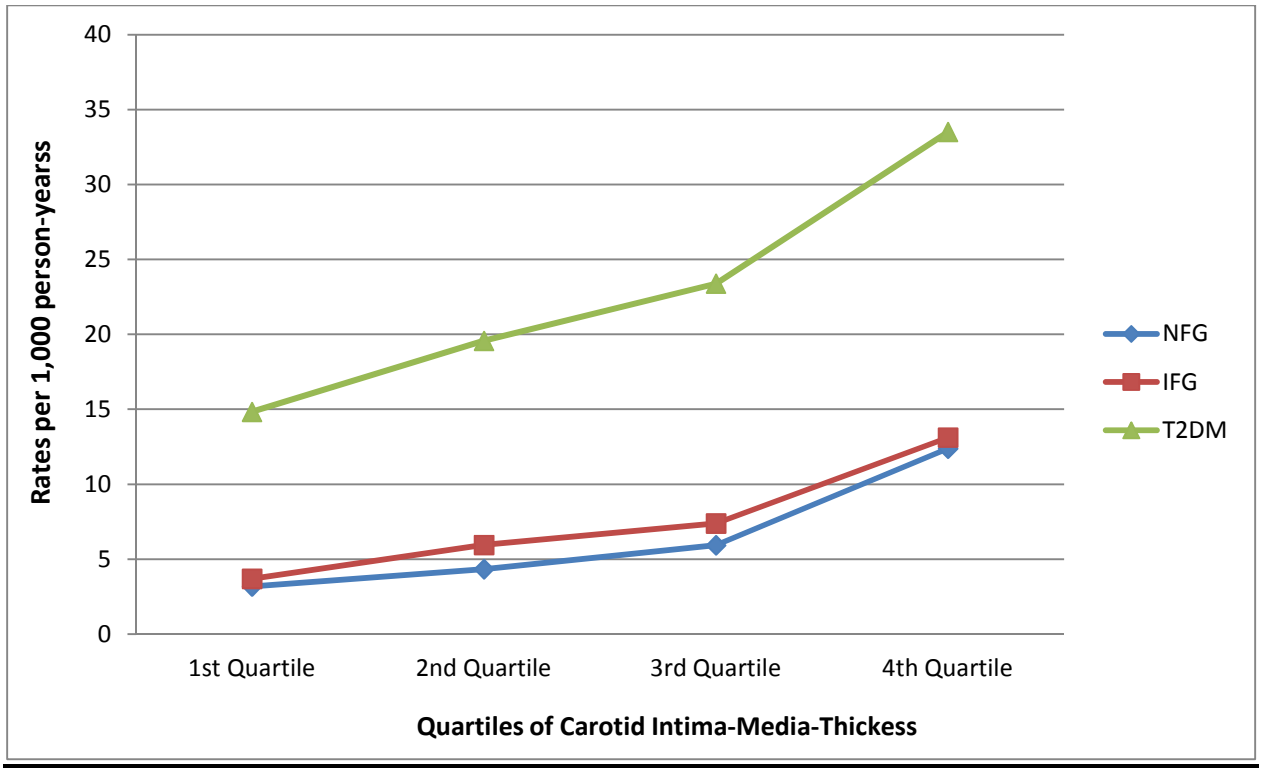

Figure II-2: Unadjusted incidence rates per 1,000 person-yrs of HF by Quartiles of Carotid IMT and by Glucose Status. NFG indicates normal fasting glucose; IFG, impaired fasting glucose; DM, diabetes mellitus.

CHAPTER III – ANCILLARY ANALYSES AND FUTURE DIRECTIONS

In this chapter I present supplemental data analyses, not primarily intended for publication with the manuscript, as well as future directions in this area of research. In the previous chapter, an association between baseline carotid IMT and incident HF was shown. In this chapter, I further investigated the relationship of change in IMT with incident HF. Also, it is known that the etiology of HF differs between blacks and whites;[1-2] ischemic heart disease is the main cause of HF in whites whereas hypertension is primarily responsible in blacks. I investigated the association of IMT with incident HF in both blacks and whites. Due to the finding, in the previous chapter, that glucose metabolism status modifies the relationship between carotid IMT and incident HF, I take a further look at this relationship across the three categories of glucose metabolism (NFG, IFG, and DM).

METHODS

Follow-up carotid IMT measurement for ARIC participants was done during the second examination (1990-1992), approximately 3 years from baseline. For this measurement, adjustments were made for method drift during study visits and systematic differences between readers. For analysis of change in IMT I limited the analysis to participants with complete data on IMT measurement (all six far wall measurements) at the baseline exam (1987-1989) and at the first follow-up visit (1990-1992), and those participants who were free of HF at the second examination.

Change in carotid IMT was assessed by estimating the average annualized change between baseline and the second examination. These estimates were then modeled as time-constant covariates in Cox regression models with adjustments for CVD risk factors and CHD. The four-model approach for covariate adjustment was used.

Details on the measurement of carotid IMT, ascertainment of HF events, as well as measurement of covariates have been given in chapters I and II. I also assessed two-way interactions between carotid IMT and race.

RESULTS

Table III-1 shows the differences in baseline demographic and clinical characteristics of study participants by quartiles of carotid IMT. Compared to participants in the lowest quartile, those in the highest quartile were older, more likely to be male, hypertensive, overweight, current smokers, and have an adverse lipid profile. The prevalence of diabetes was three times higher in the fourth quartile of baseline IMT compared to the first (16.2% vs 5.2%). There was a graded relationship of incident HF across quartiles of baseline IMT ($p<0.0001$).

Overall mean carotid IMT was not significantly different between blacks and whites (0.73 mm ± 0.16 vs 0.72 mm ± 0.19 respectively, $p=0.16$). This was true of mean IMT between diabetic blacks and whites ($p=0.23$). However, significant differences were noted between blacks and whites for subjects with NFG ($p=0.009$) and IFG ($p=0.002$).

Association of baseline carotid IMT with incident HF by Race

The unadjusted incidence rate of HF was higher for blacks than whites (10.8 vs 7.22 cases per 1000 person-years) (Table III-2). In multivariable analysis using Cox PH models, baseline

carotid IMT was associated with incident HF in both blacks and whites. The strength of the association decreased progressively in both blacks and whites; for example, in blacks the HR was 1.54 per unit SD increase in IMT (95% CI, 1.45-1.65) for the unadjusted model to 1.22 (95% CI, 1.12-1.32) after adjustment for CV disease risk factors and CHD (model 4). The p-value for carotid IMT*race interaction in the unadjusted model was 0.97.

Further analysis on the association of baseline carotid IMT with incident HF across categories of glucose metabolism

The overall unadjusted incidence rate of HF was 5.79 (95%CI: 5.14-6.19) cases per 1000 person-years for subjects with NFG, 7.75 (95%CI: 7.17-8.37) for those with IFG, and 24.69 (95%CI: 22.69-26.89) for those with DM.

Figure III-1 illustrates a plot of the cumulative hazard for incident HF by glucose metabolism status. The baseline cumulative hazard was comparable for subjects with NFG and IFG, but was higher for those with diabetes. This risk disproportionately increased with time for subjects with diabetes, compared to those with NFG and IFG.

Table III-3 shows the hazard ratios of HF by glucose metabolism status-specific quartiles of carotid IMT. For each category of glucose metabolism, specific carotid IMT quartiles were obtained. In each category, there was a graded relationship in the incident rates of HF across quartiles of carotid IMT. Furthermore, rates in the lowest quartile for participants with diabetes were higher than rates in the fourth quartile for the other two groups.

In multivariable analysis, after adjusting for demographic and CV risk factors, and interim CHD, only the fourth quartile was significantly associated with an increase in HF among subjects with NFG (HR 1.42; 95%CI: 1.12-1.81, p=0.004) and IFG (HR 1.53; 95%CI: 1.16-2.01,

p=0.002) relative to the first quartile. Among those with DM, the third (HR 1.33; 95%CI: 1.01-1.76, p=0.045) and fourth (HR 1.50; 95%CI: 1.12-2.01, p=0.007) quartiles of carotid IMT were significantly associated with an increase in HF relative to the first quartile.

Association of change in carotid IMT with HF

The overall rate of change of carotid IMT for study participants was 7.22 µm per year (Table 4). This was higher among participants who experienced a HF (9.22 µm/yr, SD 69.44) than those who did not (6.93 µm/yr, SD 51.64). Change in carotid IMT between baseline and the second examination was not associated with incident HF; in the unadjusted model, the HR was 1.04 (95%CI: 0.99–1.10, p=0.15) per unit SD increase in mean carotid IMT change.

SUPPLEMENTAL DISCUSSION

The etiology of HF differs by race;[1-2] CHD is the leading cause of HF among white adults whereas hypertension is the principal cause in blacks. Despite this known difference, this study found carotid IMT to be significantly associated with HF in both blacks and whites. Hypertension is a major determinant of carotid IMT[3-4] via thickening of the arterial wall.[5] This may lead to an increase in the afterload, and subsequently HF. On the other hand, increased IMT may cause discrete myocardial insults, and consequently regional LV myocardial dysfunction.[6]

Our study demonstrates that change in carotid IMT over a median follow-up period of 2.9 years is not associated with incident HF in this population of middle-aged adults. Data on carotid IMT change and its association with incident CV events is very limited. In the European Lacidipine Study on Atherosclerosis[7], it was shown that baseline IMT, but not treatment-induced

changes in IMT, predicted CV events. This study involved very well controlled hypertensive patients followed up for 3.7 years with low rates of CV outcomes. However, using data from MESA, Polak et al. showed that changes in IMT were predictive of incident stroke over a median follow-up of 3.0 years.[8] Our literature search didn't yield any published results addressing IMT rate of change as a risk factor for incident HF. Our finding suggests that change in an individual's carotid IMT over a short period of time (approximately 3 years) may not add further value to the baseline IMT measure in assessing HF risk.

Our approach to this analysis was to use the average annualized change in carotid IMT in the Cox model as a time-varying covariate. The use of time-varying covariates may provide additional predictive or prognostic information beyond the baseline data.[9]

CONCLUSIONS AND FUTURE RESEARCH

Our study has shown that baseline IMT, but not change in IMT, is strongly associated with incidence of HF in middle-aged whites and blacks. The role of carotid IMT in the occurrence of HF was unknown. This analysis now demonstrates that the role of IMT is independent of major CV risk factors and CHD, suggesting a mechanism different from myocardial ischemia or infarction.

There are still a lot of unknowns regarding IMT as it relates to HF incidence. In future studies, a further characterization of HF cases (systolic vs diastolic) in their associations with IMT may provide additional insights on the mechanisms through which IMT mediates HF. It would be interesting to investigate the effect of change in IMT on incident HF over a longer duration (more than 3 years) of follow-up. Also, it is important in the future to investigate the

significance of adding carotid IMT to a HF predictive model including other novel risk factors like NT-pro BNP.

In individuals with abnormal glucose metabolism (impaired fasting glucose, impaired glucose tolerance and diabetes), it would be important to investigate the associations of IMT with incident HF using additional vascular beds (e.g. femoral artery) which have been shown to have larger associations for CVD outcomes in this population.

Finally, regarding the clinical use of carotid IMT, it would be necessary to carry out a randomized, controlled trial studying the effectiveness of this procedure as a tool to modify current preventive therapies and improve HF outcomes.

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TABLES AND FIGURES

Table III-1: Baseline Demographic and Clinical Characteristics of ARIC Participants by Quartiles of Carotid IMT

Characteristic	Categories of carotid IMT (mm)			
	1st quartile (≤ 0.61)	2nd quartile (0.62 – 0.69)	3rd quartile (0.70 – 0.79)	4th quartile (>0.79)
N	3,399	3,401	3,400	3,399
Age, yrs	51.6 ± 5.2	53.4 ± 5.5	54.7 ± 5.7	56.8 ± 5.4
Women, n (%)	2,519 (74.1)	2,068 (60.8)	1,603 (47.2)	1,243 (36.6)
White, n (%)	2,712 (79.8)	2,495 (73.4)	2,472 (72.7)	2,548 (75.0)
Hypertension, n (%)	678 (20.0)	981 (28.9)	1,170 (34.4)	1,491 (44.0)
Systolic blood pressure, mmHg	114.6 ± 16.2	119.2 ± 17.2	122.4 ± 18.8	126.7 ± 20.0
Diastolic blood pressure, mmHg	71.3 ± 10.4	73.6 ± 10.7	74.2 ± 11.4	74.7 ± 12.0
Blood pressure medication, n (%)	642 (18.9)	846 (24.9)	963 (28.3)	1,168 (34.4)
BMI, Kgm^{-2}	26.1 ± 4.9	27.3 ± 5.0	28.0 ± 5.1	28.0 ± 4.9
Waist circumference, cm	91.5 ± 13.1	95.4 ± 13.2	98.2 ± 13.2	99.3 ± 12.7
Education level				
Less than college education	2001 (58.9)	2,143 (63.2)	2,201 (64.8)	2,343 (69.0)
Completed at least college	1,398 (41.1)	1,249 (36.8)	1,193 (35.2)	1,054 (31.0)
Smoking status				
Never, n (%)	1,693 (49.8)	1,591 (46.8)	1,394 (41.0)	991 (29.2)
Former smoker, n (%)	920 (27.1)	1,004 (29.5)	1,117 (32.9)	1,340 (39.4)
Current smoker, n (%)	784 (23.1)	804 (23.7)	888 (26.1)	1,066 (31.4)
Alcohol consumption				
Never, n (%)	876 (25.8)	903 (26.6)	837 (24.7)	699 (20.7)
Former drinker, n (%)	496 (14.6)	580 (17.1)	643 (19.0)	753 (22.3)
Current drinker, n (%)	2,020 (59.5)	1,905 (56.2)	1,906 (56.3)	1,930 (57.0)
Total Cholesterol, mmol/l	5.4 ± 1.1	5.5 ± 1.1	5.6 ± 1.0	5.8 ± 1.1
LDL Cholesterol, mmol/l	3.3 ± 1.0	3.5 ± 1.0	3.6 ± 1.0	3.8 ± 1.0
HDL Cholesterol, mmol/l	1.5 ± 0.5	1.4 ± 0.5	1.3 ± 0.4	1.2 ± 0.4
Triglycerides, mmol/l	1.1 (0.7)	1.2 (0.8)	1.3 (0.9)	1.3 (0.9)
Lipid-lowering medication, n (%)	537 (15.9)	688 (20.4)	760 (22.5)	952 (28.2)
Diabetes mellitus, n (%)	178 (5.2)	289 (8.5)	413 (12.2)	551 (16.2)
Incident HF, n (%)	256 (7.5)	384 (11.3)	506 (14.9)	866 (25.5)
Prevalent CHD, n (%)	42 (1.3)	94 (2.8)	148 (4.4)	271 (8.1)
Incident CHD, n (%)	203 (6.0)	305 (9.0)	462 (13.6)	757 (22.3)

Data are mean ± SD or number (percentages). All comparisons were significant at P<0.0001.

Table III-2: Unadjusted and Adjusted HRs (95% CI) for Incident Heart Failure per 1 SD (0.18 mm) Increase in Carotid IMT by Race.

Models		**Race**	
		Whites	**Blacks**
Number of HF cases		1,376	632
Rate/1000 person-years (95% CI)		7.22 (6.86, 7.62)	10.80 (9.99, 11.67)
Model 1 (unadjusted)	HR (95% CI)	1.56 (1.51, 1.61)	1.54 (1.45, 1.65)
Model 2	HR (95% CI)	1.38 (1.33, 1.43)	1.35 (1.25, 1.45)
Model 3	HR (95% CI)	1.19 (1.14, 1.25)	1.23 (1.14, 1.34)
Model 4	HR (95% CI)	1.20 (1.14, 1.25)	1.22 (1.12, 1.32)

Model 2: adjusted for age, gender, level of education. Model 3: adjusted for covariates in model 2 and hypertension medication, systolic and diastolic blood pressures, BMI, waist circumference, HDL cholesterol, LDL cholesterol, triglycerides, lipid lowering medication, smoking status and amount in pack-years, alcohol consumption, and serum creatinine. Model 4: adjusted for covariates in model 3, prevalent and incident CHD.

Table III-3: Adjusted HRs (95% CI) for Incident Heart Failure across Group-Specific Quartiles of cIMT, Stratified by Glucose Metabolism Status

Models		**Quartiles of Carotid Intima-Media Thickness (mm)**											
		Normal Fasting Glucose				**Impaired fasting Glucose**				**Diabetes Mellitus**			
		Q1 (≤ 0.59)	**Q2** (0.60 – 0.67)	**Q3** (0.68 – 0.76)	**Q4** (> 0.76)	**Q1** (≤ 0.62)	**Q2** (0.63 – 0.70)	**Q3** (0.71 – 0.82)	**Q4** (> 0.82)	**Q1** (≤ 0.66)	**Q2** (0.67 – 0.75)	**Q3** (0.76 – 0.86)	**Q4** (> 0.86)
Number of cases		112	153	201	368	88	137	162	259	108	117	141	162
Rate/1000 pyrs (95% CI)		2.94 (2.45, 3.54)	4.14 (3.53, 4.85)	5.60 (4.88, 6.43)	11.09 (10.01, 12.28)	3.94 (3.19, 4.85)	6.41 (5.42, 7.58)	7.81 (6.69, 9.11)	13.69 (12.13, 15.47)	18.0 (14.91, 21.74)	20.77 (17.33, 24.90)	27.11 (22.98, 31.97)	35.65 (30.57, 41.59)
Model 1	HR (95% CI); p	1.0 (ref.)	1.12 (0.88, 1.43); 0.36	1.33 (1.05, 1.68); 0.019	2.14 (1.70, 2.68); <0.0001	1.0 (ref.)	1.46 (1.12, 1.91); 0.006	1.51 (1.16, 1.97); 0.002	2.39 (1.85, 3.09); <0.0001	1.0 (ref.)	1.08 (0.83, 1.40); 0.59	1.44 (1.11, 1.86); 0.006	1.83 (1.41, 2.38); <0.0001
Model 2	HR (95% CI); p	1.0 (ref.)	1.01 (0.79, 1.29); 0.93	1.03 (0.81, 1.32); 0.80	1.44 (1.14, 1.81); 0.003	1.0 (ref.)	1.28 (0.97, 1.69); 0.079	1.14 (0.87, 1.51); 0.35	1.54 (1.18, 2.01); 0.002	1.0 (ref.)	0.97 (0.73, 1.30); 0.86	1.37 (1.04, 1.81); 0.027	1.60 (1.20, 2.14); 0.002
Model 3	HR (95% CI); p	1.0 (ref.)	1.05 (0.81, 1.35); 0.73	1.02 (0.79, 1.31); 0.88	1.42 (1.12, 1.81); 0.004	1.0 (ref.)	1.30 (0.98, 1.72); 0.065	1.15 (0.87, 1.52); 0.33	1.53 (1.16, 2.01); 0.002	1.0 (ref.)	0.94 (0.70, 1.26); 0.68	1.33 (1.01, 1.76); 0.045	1.50 (1.12, 2.01); 0.007

Table III-4: Baseline IMT and annualized change in IMT by Heart Failure Status

Characteristic	Overall	HF Status	
		With HF	Without HF
N	10,729	1,378	9,351
Baseline IMT, mean (SD), µm	720 (180)	810 (230)	700 (160)
Annualized change in IMT, mean (SD), µm/yr	7.22 (54.26)	9.22 (69.44)	6.93 (51.64)

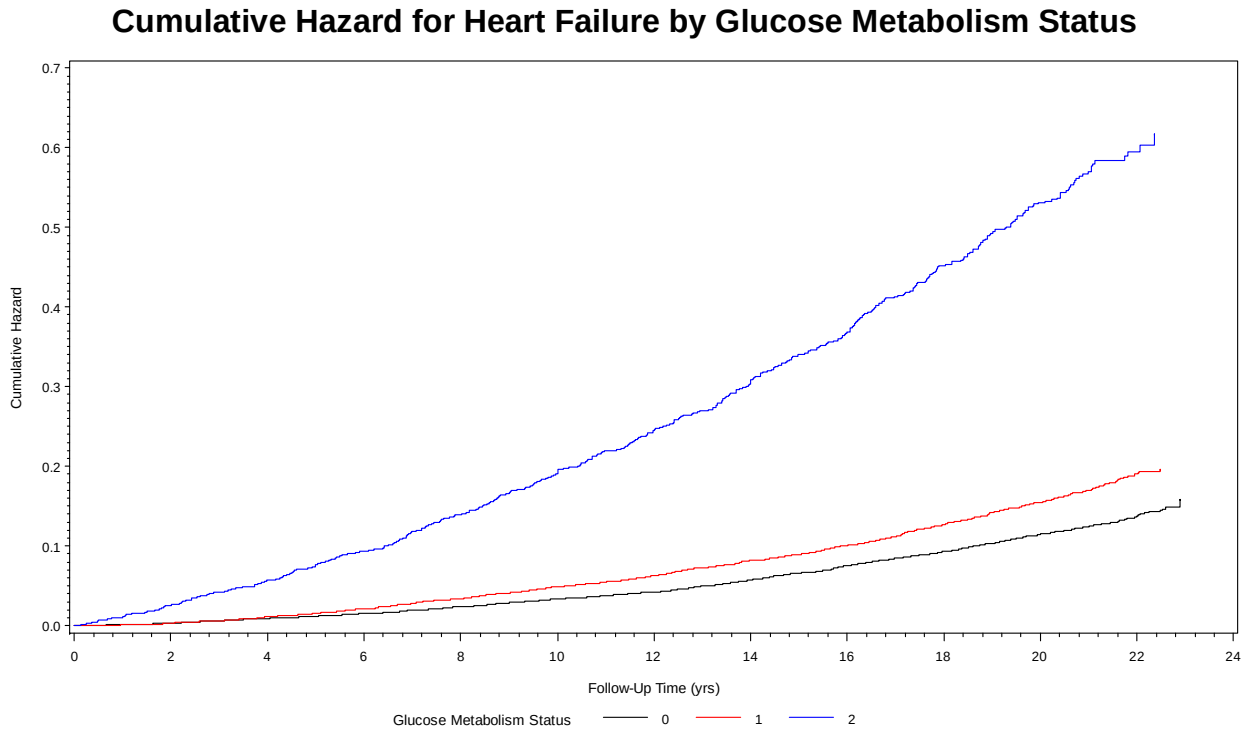

Figure III-1: Cumulative Hazard of Heart Failure Over Time as a Function of Glucose Metabolism Status. 0 (black) indicates normal fasting glucose; 1 (red), impaired fasting glucose; 2 (blue), diabetes mellitus.

APPENDIX

CURRICULUM VITAE

PERSONAL INFORMATION

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EDUCATION

2010 – 2013 M.S. Clinical and Population Translational Science,
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Thesis: The Association of Subclinical Atherosclerosis with Incident Heart Failure: The Atherosclerosis Risk In Communities Study.

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1999 – 2006 M.D. Faculty of Medicine and Biomedical Sciences, University of

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Thesis: Relationship Between Circulating Adiponectin Levels and Insulin Sensitivity in non-Diabetic Adults.

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CONFERENCES AND WORKSHOPS

2008	Research Methods Course and training in Good Clinical Practice organized by the Effective Care Research Unit and the University of Fort Hare, East London, South Africa.
2006	Invited Speaker, 19th World Diabetes Congress, Cape Town International Convention Centre, Cape Town, South Africa.
2006	Training course on Diabetes Epidemiology organized by the International Diabetes Epidemiology Group, Stellenbosch, South Africa.
2006	Training workshop on project management organized by the Cameroon Burden of Diabetes Project and the German Cooperation (GTZ), Yaounde, Cameroon.

PROFESSIONAL LICENSURE

2006	Cameroon National Medical Council (CNMC), # 5150

ACADEMIC APPOINTMENTS

2011 - current	Research Scholar, Wake Forest School of Medicine. Working on: the Association of Subclinical Atherosclerosis and Heart Failure in the ARIC cohort and Medications Database Management for the Action For Health in Diabetes (Look AHEAD) Trial.
2006 - 2008	Research Assistant, National Obesity Center, Central Hospital Yaounde, Cameroon. Worked on: multicentre trial organized by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and the International Diabetes Federation (IDF) on the comparison between HbA1c levels and mean blood glucose.

HOSPITAL APPOINTMENTS

2009 – 2010	General Physician, National Obesity Center, Central Hospital Yaounde, Cameroon.
	General Physician, Diabetes, Endocrine and Metabolic Disease Unit, Central Hospital Yaounde, Cameroon.
2006 – 2009	General Physician, Regional Hospital, Buea, Cameroon.
	Head of Diabetes and Hypertension Clinic, Regional Hospital, Buea, Cameroon.
Feb. – Oct. 2006	General Physician, Diabetes, Endocrine and Metabolic Disease Unit, Central Hospital Yaounde, Cameroon.

PROFESSIONAL INTERESTS

Research interests: Diabetes and Cardiovascular Epidemiology, Heart Failure, Prevention of Cardiovascular Diseases in Diabetes Patients.

Clinical interests: Internal Medicine/General Cardiology, Diabetes Management

Education interests: Epidemiology, General Cardiology, Diabetes Management

PROFESSIONAL ORGANIZATIONS

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HONORS AND AWARDS

2010 – 2013	Wake Forest University Graduate School Tuition Scholarship for the Masters program in Clinical and Population Translational Sciences.
2008	Wellcome Trust Grant to participate in the Research Methods Course, organized by the Effective Care Research Unit and the University of Fort Hare, South Africa.
2006	Invited Speaker, 19th World Diabetes Congress, Cape Town International Convention Centre, Cape Town, South Africa.

2006	International Diabetes Federation (IDF) Young Investigator Grant to participate in the World Diabetes Congress, South Africa.
2006	International Diabetes Epidemiology Group (IDEG) New Investigator Scholarship to participate in the IDEG Diabetes epidemiology training course.

CURRENT RESEARCH

Valery S. Effoe, Lynne E. Wagenknecht, Carlos J. Rodriguez, Patricia P. Chang, Maria C. Mirabelli, Alain G. Bertoni. Carotid Intima-Media Thickness is Associated with Incident Heart Failure Among Middle-Aged Whites and Blacks: The Atherosclerosis Risk In Communities Study. (Intended for submission to Circulation).

SKILLS

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English: fluent in both spoken and written.
French: fluent in both spoken and written.

PUBLICATIONS

1. E Sobngwi, AL Lekoubou, MY Dehayem, BE Nouthe, EV Balti, F Nwatsock, EA Akwo, VS Effoe, VT Balla, AS Mamdjokam, V Siaha, CA Tabi, A Mvom, I Djam, JC Mbanya. Evaluation of a simple management protocol for hyperglycaemic crises using intramuscular insulin in a resource-limited setting. *Diabetes and Metabolism*, 35 (2009) 404-409.

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