CAROTID INTIMA-MEDIA THICKNESS AND ITS RELATIONSHIP WITH INCIDENT HEART FAILURE WITH REDUCED AND PRESERVED EJECTION FRACTION: THE MULTI-ETHNIC STUDY OF ATHEROSCLERSIS (MESA)

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LIST OF ABBREVIATIONS

HF	Heart Failure
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
cIMT	Carotid intima-media thickness
CVD	Cardiovascular disease
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
MESA	Multi-Ethnic Study of Atherosclerosis
IC	Internal Carotid
CC	Common Carotid

ABSTRACT

Carotid intima-media thickness (cIMT) is associated with heart failure (HF) in previous studies, but it is unknown whether the association of cIMT differs between HF with reduced (HFrEF) versus preserved ejection fraction (HFpEF). We studied 6726 participants (mean age 62 ± 10 yrs., 47% male, 38% white) from the Multi-Ethnic Study of Atherosclerosis (MESA) with cIMT measurements at baseline. An adjudication committee ascertained HF events for a mean follow-up of 12.1 yrs. We classified HF events as HFrEF (EF <50%) or HFpEF (EF ≥ 50%) at the time of diagnosis. Cox proportional hazard regression was used to compute hazard ratios (HR), and 95% confidence intervals (CI) for the association between the IMT Z-score (measured maximum IMT of IC and CC sites as the mean of the maximum IMT of the near and far walls of right and left sides), and incident HFrEF or HFpEF. Models were adjusted for covariates and interim coronary artery disease (CAD) events. A total of 152 HFrEF and 132 HFpEF events occurred during follow-up. In multivariable analysis, each 1 standard deviation increase in the measured maximum IMT (Z-score); was associated with both HFrEF and HFpEF in the unadjusted and demographically adjusted models but not in the fully adjusted models [HRs, 95% CI 1.54 (1.37-1.73) and 1.57 (1.39-1.77); respectively].

During long-term follow-up in a large, ethnically diverse population-based cohort, cIMT is significantly associated with incident HF, but the association is partially attenuated with adjustment for demographic factors and becomes non-significant after adjustment for other traditional heart failure risk factors and interim CAD events. There was no difference in the association of IMT measures with HFrEF versus HFpEF.

CHAPTER ONE: BACKGROUND

Introduction

Heart failure (HF) is a heterogeneous disorder, which can be the result of different disease processes that reduce the cardiac function. Although HF was originally viewed as a disorder due solely to abnormalities of the cardiac function, our understanding has evolved such that HF and specifically HF with reduced ejection fraction (HFrEF) is now understood as a systemic syndrome involving multiple organ systems, and it is likely that it is triggered by inflammation and other as-yet-unidentified factors, with important contributions of aging and multiple comorbidities, features generally typical of other geriatric syndromes.[1] Coronary heart disease (CHD) is one of the most important causes. Traditional risk factors for atherosclerosis diseases (e.g., hypertension, diabetes, smoking, and overweight), have also been associated with incident HF.[2-4] HF has emerged as the single leading diagnosis for hospitalization in elderly, with 80% of HF patients hospitalized at least once and 40% hospitalized at least 4 times over a median duration of 4.7 years.[5, 6] The incidence of HF is likely to increase because of the increasing age of the American population, earlier age of onset of HF and improved treatment and survival from cardiovascular (CV) diseases, including myocardial infarction (MI) and hypertension.[7, 8] The Framingham heart study, a large cohort study from Massachusetts in the United States, reported an estimated prevalence of heart failure of 0.8% in both genders within age group of 50-59 years. The prevalence increases notably with advancing age, rising to 6.6% and 7.9% in men and women, respectively, aged 80-89 years.[9]

Carotid intima-media thickness (cIMT) is associated with cardiovascular events.[10] IMT can be measured using noninvasive ultrasound measurement in the common carotid artery (CCA) and in the carotid bulb/ proximal internal carotid artery (ICA). IMT measurements made at these two locations likely represent separate phenotypes since their patterns of associations with risk factors are different.[11, 12] cIMT is a well-established marker of subclinical atherosclerosis, which

indicates early manifestation of atherosclerosis in carotid arteries,[13, 14] and is associated with future CV events,[12, 15] asymptomatic myocardial ischemia,[16] and changes in risk factors induced by therapeutic interventions.[17] There is evidence of a direct relationship between increased cIMT and reduced left ventricular (LV) systolic and diastolic function assessed by myocardial strain in asymptomatic individuals without previous clinical CV disease.[18] Elderly patients with HF differ from younger patients with HF in terms of several biological characteristics, including the relatively large proportion of elderly patients with HF who have preserved systolic function.[19, 20] Using data from the Cardiovascular Health Study (CHS), which included subjects 65 years or older, atherosclerosis as measured by cIMT was shown to predict overt systolic and diastolic HF.[21]

Relationship of cIMT with Cardiovascular Disease

A close relationship of cIMT with a number of CV risk factors has been found. The cIMT was estimated to increase by 0.04 mm for every 10 years of age. Furthermore, cIMT is affected by lifestyle. In the monitored Atherosclerosis Regression Study (MARS)[22] cholesterol intake, body mass index and smoking were significantly related to the annual progression of cIMT.[23] The cIMT would be also useful in evaluation of new (non-classical) risk factors such as the lipoprotein(a) level, hyperhomocysteinemia and markers of thrombotic risk. Of all traditional risk factors, hypertension appears to have the greatest effect on cIMT. In one study[24] investigators reported that in female youngsters displaying initiating stages of vascular pathology, blood pressure level and numerous nontraditional risk conditions showed a significant relation to high cIMT. The study indicates that auto-immune processes, high lipoprotein(a), and environmental exposure to tobacco smoke may play a role in early atherogenesis.

cIMT is a well-established measure for assessing cardiovascular risk, the extent of atherosclerosis and end-organ damage. cIMT has proved to be an independent risk factor for MI and stroke. In a prospective study on 1257 men, the risk of acute MI increased by 11% for each

0.1mm increase in cIMT[25] and it was shown that the cIMT above 1mm was associated with two-fold greater risk of acute MI over three years. Furthermore, in the CHS an increased cIMT was associated with four-fold greater risk of combined acute MI and stroke over six years.[12] Therefore, increased cIMT is a mirror of atherosclerosis burden and predictor of subsequent events. Because of its quantitative value, cIMT is more frequently used in clinical trials to follow the harmful effects of risk factors on vessel walls in individual patients and, more importantly, the effect of treating risk factors that cause reduction or prevent the progression of cIMT, paralleled by a decrease in cardiovascular risk and events. Therefore, cIMT measurements may be used in addition to classical risk factors of individual risk assessment. cIMT is correlated with most of the major cardiovascular risk factors. ICA-IMT was correlated more than CCA-IMT with CAD and enhances the predictive power of the Framingham Risk Score (FRS) for stroke and CV events.[26] Measurement of cIMT could influence a clinician to intervene with medication and to use more aggressive treatments of risk factors in primary prevention, and in patients with atherosclerotic disease in whom there is evidence of extension of atherosclerosis on carotid arteries.

The Associations Between cIMT and Blood Pressure

High blood pressure (BP) has been recognized as an important risk factor for CV and cerebrovascular diseases. However, the associations between cIMT and different types of abnormal BP in different populations remain unknown. High BP is a major determinant of cIMT.[27] Systolic BP[28-30], diastolic BP[31, 32], higher pulse pressure[30, 33], persistently elevated BP from childhood to adulthood[34] were found to be positively associated with cIMT. Systolic BP[35] appears to be a main pathological mechanism that indirectly affects cIMT through hemodynamic pathway. The increase in cIMT in Congolese hypertensive participants was identified as a marker of arterial remodeling associated with a long history of uncontrolled hypertension rather than of early atherosclerosis.[36] In a sample of hypertensive African men, cIMT was negatively associated

with glutathione (GSH) levels[37] suggesting that cIMT might contribute to the attenuation of GSH levels in the development of subclinical atherosclerosis.

The Associations Between cIMT and Dyslipidemia, Dietary Patterns and Risk-Lowering Drug Therapy

Healthy and unhealthy life style changes during young adulthood are associated with decreased and increased risks, respectively, for subclinical atherosclerosis in middle age.[38] Dyslipidemia is an important factor for atherosclerosis that has been shown to be associated with cIMT.[27] In particular, patients with familial hypercholesterolemia (FH) are at increased risk of premature CV disease and exhibited significantly higher cIMT.[39] Circulating low-density lipoprotein (LDL-C) concentrations were associated with cIMT[40, 41], and high levels of oxidized LDL were significantly associated with progression and increased levels of cIMT.[42-44] Low levels of HDL cholesterol or relative levels of the HDL 3b subclasses and changes in the proportion of small HDL particles were significantly associated with an increased in cIMT[29, 45] and with presence of carotid plaques.[46] Furthermore, among women cIMT max was significantly negatively correlated to HDL cholesterol.[47] In the group taking statin, HDL cholesterol levels were associated with cIMT; in the combined therapy group, HDL cholesterol levels were the only significant correlate of cIMT.[48] Apolipoproteins are also important risk factors for atherosclerosis. Among them apolipoprotein B (apoB)[40] and apoB/ApoA1[49] were significantly positively associated with cIMT, and the absence or very low levels of erythrocyte-bound apoB was associated with clinical and subclinical atherosclerosis.[50] In contrast, other studies revealed that ApoE genotypes and cIMT were not associated[51] and that ApoA1 has an inverse association with cIMT.[49] Therefore, several studies have demonstrated that Mediterranean diet has a protective effect on the CV system because lower adherence to a Mediterranean diet was shown to increase the risk of subclinical atherosclerosis.[52] Additionally, 12 months of Mediterranean diet intervention caused a significant reduction in cIMT.[53] Atorvastatin[54], rosuvastatin[55] and

fluvastatin[56] treatments slowed or reduced the progression of cIMT; intensive lipid lowering and antihypertensive therapy along with a reduction in central fat[57] may be considered a mandatory treatment strategy in young patients with FH to prevent atherosclerosis and increase arterial stiffness. In men with CHD and high level of LP(a), atorvastatin uses [58] results in average 0.06 mm decrease in cIMT over 6 months. Adequate statin treatment[59] might delay carotid atherosclerosis in FH independent of LP(a) levels. Hence, cIMT was associated with dyslipidemia and dysapoliproprotein but was not associated with protein intake. Therefore, intensive lipid-lowering therapy might be used to reduce the progression of cIMT in high-risk patients.

The Associations Between cIMT and Hereditary and Certain Genotypic Indices

Most of our understanding of the factors contributing to atherosclerosis has come from epidemiologic studies and from studies of mendelian forms of the disease, such as familial hypercholesterolemia. These have revealed important roles for plasma lipoprotein, blood pressure, diabetes, and other risk factors. The elaboration of pathways and mechanisms involved in the disease has relied largely on animal models, particularly genetically engineered hypercholesterolemic mice.[60, 61] The vast majority of CAD and stroke is complex, involving multiple genetic and environmental factors which, until recently, have largely resisted genetic dissection. Clearly, a detailed mechanistic understanding of the genetic factors contributing to common forms would have important implications for prevention and treatment of atherosclerosis.[62] However, whether cIMT is associated with certain genotypic indices remains unknown. One study suggested that a different set of genes influences variation in cIMT and waist circumferences.[63] Certain genetic loci that are determinants of human lung function also influence cIMT and CAD susceptibility.[64] The strongest association was reported between the rate of telomere in adults between 53 and 60-64 years and cIMT in adults 60 to 64 years of age.[65] However, the chromosome 9p21 locus does not influence CAD risk through a mechanism that also affects cIMT or that induces early changes in flow-mediated dilatation.[66] The haptoglobin

(Hp) 2-2 genotype is a significant predictor of premature atherosclerosis and is associated with increased cIMT in children with beta-thalassemia major.[67] Single nucleotide polymorphisms (SNPs) in 7-dehydrocholestrol reductase/NAD synthetase-1 interacted with type 2 diabetes to significantly influence the progression of cIMT independent of 25 (OH)D levels and established risk factors.[68] However, no significant associations were identified between the genotype at any of the SNPs and cIMT in 846 individuals with acceptable measurements.[69] Additionally, humans with the osteopontin-66 TT genotype, particularly those without MetS, exhibit thicker cIMT.[70] Hence, the associations between cIMT and hereditary require further exploration to search for better etiological treatment.

The Associations Between cIMT and HF

The measurement of cIMT has long been regarded as a method, which can be used to evaluate the presence of generalized atherosclerotic disease.[11, 71] In some reports cIMT values have also been related to LV hypertrophy and function.[72, 73] One study of patients with carotid disease showed a possible prediction of minimal cardiovascular resistance in patients with probable CAD.[74] Ultrasound measurement of cIMT has become a valuable tool for detecting and monitoring progression of atherosclerosis.[75] The American College of Cardiology Foundation/ American Heart Association guidelines recommend cIMT measurements for patients at intermediate CVD risk.[76] The longitudinal arranged subendocardial fibers are more vulnerable to ischemia due to their direct exposure to the intraventricular BP and the anatomy of the coronary circulation.[77-79] As a result, longitudinal function is impaired first in CAD. Measurements of longitudinal motion and deformation are therefore, the most sensitive markers of CAD especially in patients with severe coronary stenosis, where intermittent ischemia may result in subtle forms of stunning that may be detectable with strain measurements. Severe CAD is known to lead to LV dysfunction specifically HF with reduced ejection fraction (HFrEF). However, the LV ejection fraction is usually normal at a relatively early stage.[80] Which can be explained by that impairment

in longitudinal systolic function is known to be compensated by augmentation of circumferential deformation.

Development of atherosclerosis is a slow process with a long silent phase before the clinical manifestations appear. cIMT particularly IC IMT is generally considered to be an early indicator of subclinical atherosclerosis. Many studies have shown that IC IMT is associated with incidence of acute coronary events and stroke even after adjustments for hypertension and other atherosclerosis risk factors.[81-83] A study from Multi-Ethnic Study of Atherosclerosis (MESA) reported that cIMT correlated with different measures of the regional myocardial function in asymptomatic individuals.[18] It is conceivable that cIMT and mainly IC IMT reflects the generalized atherosclerotic disease process of an individual that ultimately results in HF and specifically HFrEF. However, it is largely unknown whether cIMT is a risk factor for developing clinical HF.

Moreover, HFpEF has merged as an important public health concern. It is associated with high rates of clinical events similar to HFrEF and is linked to the growth of an aging population.[84] Currently, there are ongoing efforts to identify the specific mechanisms and useful clinical markers for early-stage myocardial dysfunction that are related to chronic hemodynamic load status, presumably a key pathological factor involved in the development of HFpEF.[85, 86] Several cardiovascular risk factors, primarily arterial hypertension (HTN) and aging, can modify the structure and function of myocardium as well as the central and peripheral arteries, a process known as cardiovascular remodeling[87, 88] in which arterial wall thickening and decreased arterial distensibility and may therefore be better associated with HFpEF.[89-94]

Most studies of cIMT have focused on its relationship with CAD. There may also be a role for cIMT in HF risk prediction. cIMT may be associated with risk of HFrEF due to shared atherosclerosis pathways as CAD underlies the majority of HFrEF cases.[11, 71] On the other hand, cIMT may be associated with HFpEF through mechanisms other than myocardial ischemia or

infarcts as increasing cIMT reflects a decrease in arterial distensibility,[95] which in turn leads to increased pressure afterload, pressure wave propagation, and eventually diastolic dysfunction.[96, 97]

To our Knowledge, there are no studies that have examined the association between cIMT and incident HF stratified by ejection fraction (EF). This is important since HFrEF and HFpEF are distinct phenotypes and may have different relationships with cIMT. Furthermore, the association between cIMT and HF may differ depending on the carotid artery segment being examined. For example, increased IMT of the proximal ICA may reflect coronary atherosclerosis and, therefore, could be more associated with HFrEF.[98] However, increased IMT of the CCA approximates diffuse arterial wall thickening and decreased arterial distensibility and may therefore be better associated with HFpEF.[89-94]

Hypothesis

In this sample of 6,814 participants from MESA, we hypothesize that cIMT is associated with atherosclerosis and HF in both men and women.

Primary Specific Aim

To evaluate the association between cIMT and incident HF after adjustment for potential confounders.

Secondary Specific Aims

1- To evaluate the association between IC IMT and incident HFrEF and HFpEF after adjustment for potential confounders.
2- To evaluate the association between CC IMT and incident HFrEF and HFpEF after adjustment for potential confounders.

Conclusion

In recent years, a wealth of evidence has demonstrated the relationship between cIMT and HF. However, to our knowledge, there are no studies that have examined the association between cIMT and HF incident stratified by ejection fraction. This is important since HFrEF and

HFpEF are distinct phenotypes and may have different relationships with cIMT. Furthermore, the association between cIMT and HF may differ depend on carotid artery segment been examined. The following study evaluates the association between cIMT and HF in a multi-ethnic cohort.

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CHAPTER TWO: MANUSCRIPT

Carotid Intima-Media Thickness and Its Relationship with Incident Heart Failure with Reduced and Preserved Ejection Fraction: The Multi-Ethnic Study of Atherosclerosis (MESA)

Short Title: Carotid intima-media thickness and heart failure

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Relationship of Carotid Intima-Media Thickness with Incident Heart Failure with Reduced Versus Preserved Ejection Fraction: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Key words**:** carotid intima-media thickness, heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, coronary artery disease.

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ABSTRACT

Background: Carotid intima-media thickness (cIMT) is associated with heart failure (HF) in previous studies, but it is unknown whether the association of cIMT differs between HF with reduced (HFrEF) versus preserved ejection fraction (HFpEF).

Methods: We studied 6726 participants (mean age 62 ± 10 yrs., 47% male, and 38% white) from the Multi-Ethnic Study of Atherosclerosis (MESA) with cIMT measurements at baseline. An adjudication committee ascertained HF events for a mean follow-up of 12.1 yrs. We classified HF events as HFrEF (EF <50%) or HFpEF (EF ≥ 50%) at the time of diagnosis. Cox proportional hazard regression was used to compute hazard ratios (HR), and 95% confidence intervals (CI) for the association between the IMT Z-score (measured maximum IMT of IC and CC sites as the mean of the maximum IMT of the near and far walls of right and left sides), and incident HFrEF or HFpEF. Models were adjusted for covariates and interim coronary artery disease (CAD) events.

Results: A total of 152 HFrEF and 132 HFpEF events occurred during follow-up. In multivariable analysis, each 1 standard deviation increase in the measured maximum IMT (Z-score); was associated with both HFrEF and HFpEF in the unadjusted and demographically adjusted models but not in the fully adjusted models [HRs, 95% CI 1.54 (1.37-1.73) and 1.57 (1.39-1.77); respectively].

Conclusion: During long-term follow-up in a large, ethnically diverse population-based cohort, cIMT is significantly associated with incident HF, but the association is partially attenuated with adjustment for demographic factors and becomes non-significant after adjustment for other traditional heart failure risk factors and interim CAD events. There was no difference in the association of IMT measures with HFrEF versus HFpEF.

Introduction

Heart failure (HF) related mortality, morbidity, health care costs, and poor quality of life are a major public health problem in the United States as its prevalence and incidence continue to rise. [1-4] Similar prevalence and outcomes are observed for HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). [5-7] Identifying individuals at high risk for HF may help increase prevention efforts to slow progression or prevent development of HF.

Development of atherosclerosis is a slow process with a long silent phase before the clinical manifestations appear. Carotid intima-media thickness (cIMT) is generally considered to be an early indicator of subclinical atherosclerosis and is a widely available, reproducible and safe measure. Most studies of cIMT have focused on its relationship with coronary artery disease (CAD).[8, 9] There may also be a role for cIMT in HF risk prediction. cIMT may be associated with risk of HFrEF due to shared atherosclerotic pathways as CAD underlies the majority of HFrEF cases.[10, 11] On the other hand, cIMT may be associated with HFpEF through mechanisms other than myocardial ischemia or infarct as increasing cIMT reflects a decrease in arterial distensibility,[12] which in turn leads to increased pressure afterload, pressure wave propagation, and eventually diastolic dysfunction.[13, 14]

Data on the relationship between cIMT and HF in population-based cohort studies is limited. In a cross-sectional study from the Atherosclerosis Risk in Communities (ARIC) study, a higher mean cIMT was observed among participants with HF than participants without HF.[15] These findings however, were not adjusted for cardiovascular risk factors. In prospective analysis from the same cohort, each one standard deviation (SD) increase in cIMT was associated with risk of incident HF, which was similar regardless of gender or race.[16] This analysis, however, did not distinguish HF phenotypes (HFrEF versus HFpEF) in relation to cIMT.

To date, there are no studies that have examined the association between cIMT and incident HF stratified by ejection fraction (EF). This is important since HFrEF and HFpEF are distinct phenotypes and may have different relationships with cIMT. Furthermore, the association between cIMT and HF may differ depending on the carotid artery segment being examined. Increased intima-media thickness (IMT) of the proximal internal carotid artery (ICA) may reflect coronary atherosclerosis and, therefore, may be more associated with HFrEF.[17] However, increased IMT of the common carotid artery (CCA) approximates diffuse arterial wall thickening and decreased arterial distensibility and therefore may be better associated with HFpEF.[18-22] Therefore, utilizing data from MESA we sought to study the association between cIMT and HF both overall and stratified by HFrEF versus HFpEF. We also study the relationship between ICA versus CCA IMT with HFrEF and HFpEF, respectively.

Methods

Study population

MESA is a multi-ethnic, multicenter, prospective observational cohort [23] of 6,814 men and women aged 45 to 84 years without clinical CVD at baseline (participants rate was 60% among those eligible) who were recruited between July 2000 and August 2002 from 6 US communities (Forsyth county, NC, Baltimore, MD, Chicago, IL, Los Angeles County, CA, northern Manhattan, NY; and St. Paul, MN). All participants provided written informed consent and the study was approved by the institutional review boards at all field centers. For this analysis, participants were excluded if they were missing baseline cIMT data, baseline characteristics, or HF follow-up data.

Baseline Characteristics

Participant's characteristics were collected during the initial MESA visit. Age, sex, race/ ethnicity, and education were self-reported. Education was categorized as high school or less or some college or more. Smoking was defined as ever (current or former) versus never smoker.

Blood samples were obtained after a 12-hour fast, and measurements of total cholesterol, high-density lipoprotein cholesterol, and plasma glucose were used. Diabetes mellitus was defined as fasting glucose values $\geq$ 126 mg/dl or a history of diabetes medication use. Blood pressure was measured for each participant after 5 minutes in the seated position, and systolic measurements were recorded 3 separate times, and the mean of the last 2 values was used. The use of aspirin, statins, and antihypertensive medications was self-reported. Body mass index was computed as the weight in kilograms divided by the square of height in meters. Resting heart rate was obtained from baseline ECGs.

Measurement of Carotid IMT

The participants were imaged supine with their head rotated 45 degrees away from the side being imaged, and the images were recorded on superVHS videotape. The CCA was imaged at 45 degrees from the vertical with the beginning of the bulb shown to the left of the image. The ICA was imaged in 3 projections centered on the ICA flow divider: anterior, lateral (at 45 degrees), and posterior. Sonographers were instructed to make slight adjustments to the imaging plane in order to capture the largest wall thickness, whether it was located on the near or far wall of the carotid bulb or proximal ICA. A matrix array probe (M12L, General Electric, Waukesha, WI) was used with the frequency set at 13 MHz for the CCA and 9 MHz for the ICA, and with 2 focal zones at a frame rate of 32 frames-per-second.

Carotid artery measurements were blinded and made at the Ultrasound Reading Center in Boston, MA. Videotaped images were reviewed and image frames that showed clear wall interfaces on an image near the smallest diameter (end-diastolic) of the artery were digitized into a workstation. cIMT was measured on near and far walls of the common carotid (1 projection) and the ICA (3 projections) using hand-drawn continuous tracings of the intima-lumen and media-adventitia interfaces that were then processed using a previously described algorithm.[24]

The average of the mean far wall CC IMT and the maximum of the near and far wall IC IMT values seen on either side or projection were used for these analyses.[25]

We calibrated the IMT measurements for inter-reader differences by adding previously determined bias terms to a given reader's measurements.[26] Blinded replicate scans were performed on 150 participants read by the same reader; interclass correlation coefficients were 0.92 for CCA IMT and 0.88 for ICA IMT. Inter-reader reproducibility was assessed on the image sets of 74 participants (interclass correlation coefficients of 0.81 for CCA IMT and 0.88 for ICA IMT). All paired differences between sets of readings did not show significant divergence from zero. In addition, in MESA they created a composite Z score for overall maximal IMT by summing the two carotid IMT sites after standardization (subtraction of the mean and division by standard deviation of each measure), and then dividing by the standard deviation of the sum. If only one of the two measures were available, it was used. The resulting variable, hereafter referred to as Z score maximum IMT.

Ascertainment of Heart Failure

The ascertainment of incident HF events in MESA has been described previously.[27] Participants were followed for incident cardiovascular events from baseline through December 31, 2013. Clinical outcomes were assessed at MESA study examinations and by telephone interview every 9 to 12 months. Records were obtained for approximately 99% of hospitalizations and 97% of outpatient cardiovascular diagnostic encounters through the end of calendar year 2012. Incident HF required symptoms of HF, a physician diagnosis of HF, and another objective feature of HF (dilated or poor LV function, pulmonary edema by chest radiograph, treatment, or evidence of diastolic dysfunction). HF events were stratified by type as HFrEF or HFpEF per events committee. HFpEF events were defined as cases with ejection fraction $\geq$50% per ACC/AHA guidelines classify patients with a LVEF of >50% as having a preserved EF.[28] Two physicians from MESA events committee blinded to other study data independently

reviewed all medical records for classification and dating of events. If reviewers disagreed, they adjudicated differences depends on the misclassification rates and central assessors, the assessor with smallest misclassification rate was chosen. If disagreement persisted, the full events committee made the final classification.

Statistical Data Analysis

Comprehensive statistics were performed to characterize the data, and baseline characteristics were compared by HF status. Categorical variables were reported as frequency and percentage, whereas continuous variables were recorded as mean $\pm$SD. Statistical significance for categorical variables was tested using χ^2 method and the ANOVA procedure for continuous variables.

Follow-up time was defined as the time between the baseline cIMT measurement until a diagnosis of HF, death, loss to follow-up, or end of follow-up (December31, 2013). Cox regression was used to compute hazard ratios (HRs) and 95% confidence intervals (CI) for the association between each CC IMT and IC IMT measurement with HF. *P* values for the HRs were computed using the likelihood ratio method. Separate analyses were conducted for HFrEF and HFpEF. In another set of analyses, Cox regression was used to compute HRs and 95% CI for the association between Z-score for maximal IMT with HF total, HFrEF and HFpEF subsequently. Z-score for maximal IMT; measured maximum IMT of the IC and CC sites as the mean of the maximum IMT of the near and far walls of the right and left sides. Multivariable models were conducted as follows: model 1 adjusted for age, sex and race/ethnicity; model 2 adjusted for model 1 covariates plus body mass index (BMI), diabetes mellitus (DM), systolic blood pressure, left ventricular hypertrophy and heart rate; model 3 adjusted for model 1 and model 2 covariates in addition to interim CAD events. Statistical significance was defined as $p<0.05$ SAS version 9.4 (Cary, NC, United States) was used for all analyses.

Results

Baseline Characteristics of Participants

A total of 6726 participants (mean age 62 ± 10 years, 53% women, 42% whites, 20% blacks, 24% Hispanics, 14% Chinese American) were included in the final analysis. Baseline characteristics stratified by the development of HF are shown in Table 1. As shown, participants who did not develop HF were more likely to be young, to be female, to have higher educational attainment, and to have fewer cardiovascular risk factors compared with those who developed HFrEF or HFpEF. Compared with HFrEF, participants with HFpEF were more likely to be older, to be female, to report smoking, and to have higher systolic blood pressure and resting heart rate. Over a median follow-up of 12.1 years, a total of 284 HF cases (incidence rate per 1000 person-years: 4.16) were identified. Of these, 152 (53%) were HFrEF and 132 (46%) were HFpEF.

Association of IC IMT with Incident HF, HFrEF and HFpEF

In the multivariable analysis, we computed hazard ratios (HR), and 95% confidence intervals (CI) for the association between the IC IMT and incident HF, HFrEF and HFpEF (Table 2). Models were adjusted for covariates and interim CAD. In the unadjusted model, IC IMT was significantly associated with incident HF, HFrEF and HFpEF (HR for HF 1.84, 95% CI: 1.61 to 2.10; HR for HFrEF 1.78, 95% CI: 1.48 to 2.16; and HR for HFpEF 1.85, 95% CI: 1.52 to 2.25 respectively) $p<0.001$. The strength of this association is partially attenuated with adjustment for demographic factors (HR for HF 1.34, 95% CI: 1.15 to 1.56; HR for HFrEF 1.33, 95% CI: 1.07-1.64; and HR for HFpEF 1.32, 95% CI: 1.06 to 1.65 respectively). Furthermore, the association between IC IMT and incident HF, HFrEF and HFpEF becomes non-significant after adjustment for other traditional HF risk factors and interim CAD events (HR for HF 1.15, 95% CI: 0.97 to 1.35; HR for HFrEF 1.13, 95% CI: 0.90 to 1.43; and HR for HFpEF 1.12, 95% CI: 0.89 to 1.42 respectively.

Association of CC IMT with Incident HF, HFrEF and HFpEF

In a separate multivariable analysis, we computed HR, and 95% CI for the association between the CC IMT and incident HF, HFrEF and HFpEF (Table 2). Models again were adjusted for covariates and interim CAD. In the unadjusted model, CC IMT was significantly and strongly associated with incident HF, HFrEF and HFpEF (HR for HF 6.92, 95% CI: 4.56 to 10.50; HR for HFrEF 6.84, 95% CI: 3.84 to 12.20; and HR for HFpEF 6.93, 95% CI: 3.73 to 12.85 respectively) $p<0.001$. The strength of association between CC IMT with incident HF and HFrEF is partially attenuated with adjustment for demographic factors (HR for HF 2.00, 95% CI: 1.18 to 3.40; and HR for HFrEF 2.17, 95% CI: 2.17, 95% CI: 1.04 to 4.53 respectively). Furthermore, the association between CC IMT and incident HF, HFrEF and HFpEF becomes non-significant after adjustment for other traditional HF risk factors and interim CAD events (HR for HF 1.16, 95% CI: 0.66 to 2.05; HR for HFrEF 1.21, 95% CI: 0.55 to 2.65; and HR for HFpEF 1.09, 95% CI: 0.46 to 2.56 respectively).

Association of Combined IC IMT and CC IMT Measurements with Incident HF, HFrEF and HFpEF

Cox proportional hazard regression was used to compute HR, and 95% CI for the association between the Z-score IMT (measured maximum IMT of IC and CC sites as the mean of the maximum IMT of the near and far walls of right and left sides), and incident HF, HFrEF and HFpEF, models were adjusted for covariates and interim CAD events (Table 3, Figures 1-3). In the unadjusted model, Z-score IMT (1 SD, 0.18 mm increase in IMT) was significantly associated with incident HF, HFrEF and HFpEF (HR for HF 1.56, 95% CI: 1.44 to 1.69; HR for HFrEF 1.54, 95% CI: 1.37 to 1.73; and HR for HFpEF 1.57, 95% CI: 1.39 to 1.77 respectively) $p<0.001$. The strength of association between Z-score IMT with incident HF and its phenotypes is partially attenuated with adjustment for demographic factors (HR for HF 1.20, 95% CI: 1.08 to 1.33; HR for HFrEF 1.22, 95% CI: 1.06 to 1.41; and HR for HFpEF 1.21, 95% CI:1.04 to 1.40

respectively). Finally, the association between Z-score IMT and incident HF, HFrEF and HFpEF becomes non-significant after adjustment for other traditional risk factors and interim CAD events (HR for HF 1.08, 95% CI: 0.97 to 1.20; HR for HFrEF 1.08, 95% CI: 0.92 to 1.26; and HR for HFpEF 1.07, 95% CI: 0.91 to 1.26 respectively).

Discussion

The objective of this study was to investigate the association of carotid IMT with incident HF and HF phenotypes (Figure 4). The association between carotid IMT combined measurement and incident HFrEF, HFpEF and HF total is partially attenuated with adjustment for demographic factors and becomes non-significant after adjustment for other traditional HF risk factors and interim CAD events. Similarly, IC and CC IMT are also not associated with HFrEF and HFpEF after adjustment for traditional HF risk factors.

Carotid IMT is a well validated measure of pre-clinical atherosclerosis lesions.[29, 30] In this population based study, we found mean carotid IMT to be 0.87±0.19 mm. Relatively similar mean far wall estimates have been reported in other populations of similar age groups; in the Carotid Atherosclerosis Progression Study[31] and Malmo Diet and Cancer Study,[8] mean far wall IMT was 0.73±0.16 mm and 0.77±0.15 mm, respectively. The present study has shown that carotid IMT is not associated with incident HF, with IMT modeled as combined measured (Z-score) variable and subtype (CC IMT, IC IMT) variables, after taking into account associations explained by age, gender, race, BMI, diabetes mellitus, systolic blood pressure, left ventricular hypertrophy, heart rate and interim CAD events. Our results are different than those described by Engstrom et al,[32] who reported a significant association of increased IMT and HF hospitalizations in a sample of 4691 subjects with 75 cases of HF. Our results show no association even after adjustment for prevalent and incident cases of CAD, which has been reported to be a major cause of HF.

Our study found no association of carotid IMT with HF after adjustment for prevalent and incident CAD and traditional cardiovascular disease risk factors. This suggests that carotid IMT may be associated with HF through a mechanism that is different from that causing discrete clinical episodes of myocardial ischemia or infarct. This concept is strengthened by demonstrating that results were only slightly attenuated after adjustment for demographic but not CAD or other traditional cardiovascular risk factors.

A recent study from the Atherosclerosis Risk in Communities Study (ARIC),[33] their findings support our study results that cIMT as a less reliable predictor of HF. In that study, they examined 13,590 participants from ARIC has shown that cIMT may be a less reliable predictor of HF among persons with diabetes due to a high absolute risk of HF among adults with DM (HR per SD increase in cIMT for DM 1.12, 95% CI: 1.05 to 1.21; compared to HR for non DM 1.27, 95% CI: 1.20 to 1.34) p=0.015.[33] Our study findings clearly more broad and meaningful; since we looked at incident HF and HF phenotypes after adjustment for all major CV comorbidities including DM status.

Finally, a Sweden cohort consists of 28,449 subjects, they examined the association between cIMT, systemic inflammation marker such as N-terminal pro-brain natriuretic peptide (NT-proBNB) and high sensitivity C-reactive protein with incidence of heart failure hospitalization.[32] The end point of their study were cases that had been hospitalized with a primary diagnosis of acute decompensated HF with already altered inflammatory biomarkers. Thus, the results of their study could not explain or prove any relationship between cIMT and acute decompensated HF through alteration of inflammatory biomarker. Our study results different from their findings since we examined the association between cIMT and incident HF total including HF phenotypes and not just with acute decompensated HF cases.

The potential mechanism relates to the findings from prior studies that increasing common carotid IMT was associated with reduced myocardial flow reserve in adults with[34] and without[35-37] CAD, but they were unable to prove that CAD can mediate the association between carotid IMT and HF. Some prospective and cross-sectional studies have established an association between increasing carotid IMT and regional LV myocardial systolic and diastolic dysfunction,[38, 39] as a predictor of HF,[40] but none of these studies were able to establish a direct causal relationship between carotid IMT and HF. Furthermore, aging and hypertension can play a major role in carotid artery thickness, dilatation and remodeling.[41] Enlargement and thickening of carotid arteries with aging is generally attributed to fracture of the load-bearing elastin fibers in response to the fatiguing effect of tensile stress. It is worth emphasizing that such observed large artery remodeling in terms of either wall thickening through proteoglycan/collage matrix deposition or increased internal diameter per se may share a similar pathophysiology with ventricular remodeling and worsened myocardial deformation, a putative precursor in the development of heart failure.[38, 42, 43] Indeed no study addressed direct causal relationship through aforementioned pathophysiology.

By 2030, the prevalence of HF is projected to increase by 23%, with medical costs increasing to nearly $53 billion.[44] Accordingly, the identification of at-risk individuals by low-cost, noninvasive, reproducible and safe measure is of paramount important, but our study does not support measuring carotid IMT to predict any form of heart failure.

Strengths and limitations

To the best of our knowledge, our study is the first to investigate the association of carotid IMT and its subtypes with all form of HF in a large diverse cohort with more than a decade of follow-up. There are nonetheless a number of limitations to this study that should be mentioned. First, although rigorous methods were used to account for all HF cases, some events may have been missed. It is unlikely, however, that the resulting bias would have been

differential in nature rather than merely reducing effect estimates toward the null. Second, although numerous covariates were included in our multivariate models, we acknowledge that residual confounding remains a possibility. Finally, we did not adjust our analyses for novel biomarkers that could potentially influence the relationship between carotid IMT and HF, such as N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity C-reactive protein. However, in a prior published study, the association of carotid IMT with HF remained unaffected by the presence of these markers.[32]

Conclusion

The results of this study demonstrated that increasing thickness of the carotid intima and media is not associated with the any form of HF and beyond the risks accounted for by traditional cardiovascular risk factors and CAD. Further research is needed to determine whether different tests or images are able to identify individuals in whom targeted preventive therapies are warranted to reduce the current and future burden of HF.

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Disclosures

None.

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CHAPTER THREE: ADDITIONAL ANALYSES AND DISCUSSION

Heart failure (HF) remains a rising global epidemic with an estimated prevalence of >37.7 million individuals globally.[1, 2] Within the USA alone, an estimated 5.7 million individuals live with HF and 870,000 new cases are diagnosed every year.[3] Over the last decades HF epidemiology has been informed by advances in cardiac imaging, identification of novel biomarkers and refinements in pathophysiology and classification. Risk assessment is refined by the integration of imaging, biomarkers, and novel assessments. Risk scores are fundamental and essential for advancing risk prediction and serve multiple functions to enhance epidemiological and clinical assessment. First, risk scores provide an avenue to integrate established exposures with novel, contemporary assessments in risk quantification. Second, risk scores may target at-risk populations such as 'stage A' and 'stage B' HF, for example with the goal of disease prevention. Third, individualized risk scores can provide personal assessments of risk, be a tool for patient education or focus efforts to optimize prevention. Ultimately, the utility of a risk score is determined by its clinical relevance: can it be employed to target preventive strategies in HF, and 'turn back the clock' for a disease where the median survival upon diagnosis is a dismal as 5 years.[4] Can the addition of novel imaging or biomarkers be implemented in cost-effective manner?.

The results or our current study demonstrated that increasing thickness of the carotid intima and media (as cost-effective manner) is not associated with any form of HF and beyond the risks accounted for by traditional cardiovascular risk factors and CAD. As a part of our current study we conducted some additional analyses (outlined in subsequent sections) and demonstrated the important of HF risk prediction tools[5, 6] including biomarkers, HF risk models[7], HF tool calibration and reclassification analyses such as categorical and category-less Net reclassification index (NRI).

Heart Failure Risk Assessment Tools

Framingham Heart Failure Diagnostic Criteria

The Framingham HF diagnostic criteria algorithm are 100% sensitive and 78% specific for identifying persons with definite congestive HF. Diagnosis of congestive HF requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria. Minor criteria are acceptable only if they can't be attributed to another medical condition (such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome).

The Major criteria include the following:

- Paroxysmal nocturnal dyspnea.
- Neck vein distention.
- Rales.
- Radiographic cardiomegaly (increasing heart size on chest radiography).
- Acute pulmonary edema.
- Increased central venous pressure (>16 cm H2O at right atrium).
- S3 gallop.
- Hepatojugular reflux.
- Weight loss >4.5 kg in 5 days in response to treatment.

The Minor criteria include the following:

- Bilateral ankle edema.
- Nocturnal cough.
- Dyspnea on ordinary exertion.
- Hepatomegaly.
- Pleural effusion.
- Decrease in vital capacity by one third from maximum recorded.
- Tachycardia (heart rate >120 beats/min).

The Atherosclerosis Risk in Communities Study (ARIC) Heart Failure Risk Assessment

The ARIC HF risk assessment tool uses information from the ARIC study and is designed for African American and white adults, 55-75 years old. It predicts a person's chance of having new onset hospitalized HF in the next 10 years using the following clinical factors:

- Age, gender and race.
- Cigarette smoking (current, former).
- Heart rate bpm.
- Systolic blood pressure mmHg.
- Body mass index kg/m^2.
- Personal history of coronary heart disease.
- Taking any medication to treat high blood pressure.
- Personal history of diabetes mellitus.

Optimal levels of risk factors are being a non-smoker, total cholesterol less than 200 mg/dl, HDL cholesterol greater than 60 mg/dl, having systolic blood pressure less than 200 mmHg and not needing treatment for high blood pressure.

MESA Heart Failure Risk Assessment

MESA HF risk score present a novel score developed from the MESA study in over 6600 MESA participants. The score includes readily accessible covariates that have survived application in the other HF risk scores. MESA's ethnic and racial diversity enhances this HF risk score.[8]

Clinical factors:

- Age and gender.
- Current smoking.
- Body mass index kg/m^2.
- Systolic blood pressure mmHg.
- Heart rate bpm.
- Diabetes mellitus.

- N-terminal pro-B-type natriuretic peptide (NT proBNP).
- Left ventricular mass index (LVMI) per 10 gm/m^2.

The addition of BNP improved the C-statistics from 0.80 from baseline to 0.87 with its inclusion. Net reclassification improvement (NRI) was similarly enhance (0.37)[9]. Interestingly, while the model was strengthened with the addition of LVMI, adding LVMI on top of BNP yielded only modest improvement. However, adding BNP to a model with LVMI yielded a 15% NRI. From MESA risk predictor model, BNP emerged a critical and salient contributor towards HF risk prediction.[9]

Net Reclassification Analyses

There are two versions of the net reclassification index (NRI) statistics: the original (categorical) NRI, introduced by Pencina and colleagues in 2008[10] and the non-categorical (continuous) version, introduced by Pencina and colleagues in 2011.[11]

Categorical Net Reclassification Index

Hypothetically, the risk model for HF could be categorized as: high risk, medium risk, and low risk. These may be the ranges for which clinical decisions can be made; e.g., if high, take some additional action, if low, do not, and if medium have a discussion to consider taking some action. Thus, it would be advantageous if the risk model correctly predicted more patients at higher risks of HF into the highest category and those with low risk to lowest category. Unlike the C statistic, which can be computed for a single model, NRI needs 2 models, it is a comparison statistic. Here is how it works: suppose the risk prediction from an existing standard model (M) is being compared to that of a proposed model with an additional risk factor (M+). One way to compare the clinical value of the 2 risk models is to compare how the patients that were distributed into those 3 HF risk category by the 2 models actually fared, HF risk-wise. The categorical NRI does just that, it measures the net improvement, of M+ over M, in placing

patients into the appropriate category; more HF risk in to a higher category, low HF risk in to low category.

Category-Free (Continuous) NRI

A limitation of the NRI described above is the dependence on the definition of categories. That is, it is not an absolute value, but will vary depending on the number of categories (3 in the above discussion) and the cut points used to define the categories (low, medium, and high in the above discussion).

The way around this limitation is to eliminate the categories entirely, by treating each individual prediction as own "category" as precisely as it is defined. Thus, for every patient who has HF, the M+ model is considered superior if it assigned that patient a higher risk (HFH) than the original M model and is considered inferior if it assigned that patient a lower risk (HFL). And for patients who are in low HF category, the M+ model is better if it assigns a lower risk (LoHFL) than did the original M model, and worse if it assigns a higher risk (LoHFH).

Then, HFH – HFL is the net improvement in predictions for those who have HF, and LoHFL – LoHFH is the net improvement in predictions for those who have no HF or low risk HF. The category-free NRI is the sum of these 2 components, taken as percentages of the HF and LoHF, respectively: (HFH-HFL)/HF is the net proportion of HF patients who assigned a higher risk by M+ model, and (LoHFL-LoHFH)/LoHF is the net proportion of no HF or low risk HF who are assigned a lower risk. The M+ model will show improved prediction if both of these components are positive as it then assigns higher probability of HF to the higher risk category, and lower probabilities of HF to the lower risk category.

Additional Analyses

Categorical Net Reclassification Index, C-statistic and Area Under the Curve (AUC)

We conducted the analysis to look at NRI, C-statistic and AUC by adding Z-score cIMT to Framingham Risk Score (FRS) and race sequentially. The result was significant p=0.045 (Table 4) after adding Z-score cIMT to FRS and race with incident total HF.

Category-Free NRI

When we compared categorical NRI with category-free NRI after adding Z-score cIMT to FRS and race with incident HF, no difference was identified after calibration of FRS (categories or cut-points) or not (Table 5), since it's all related to relative risk change.

Alternative NRIs

We utilized alternative NRI approaches with incident HF by; I) adding maximum cIMT to FRS and race, II) adding interquartile cIMT (difference between upper and lower cIMT quartiles) to FRS and race, III) adding 75% cIMT (cIMT >75 percentile vs. cIMT$\leq$75 percentile) to FRS and race. Only NRI by interquartile of cIMT was significant p=0.046 (Table 6).

Sensitivity analysis

To evaluate the most influential hazard ratio, point estimates for the association between Z-score cIMT and HF phenotypes and HF total. Diabetes mellitus, BMI and hypertension were having the greatest effect on hazard ratio, but hypertension status was the most influential in this relationship and specifically with incident of HFpEF (Table 7).

Conclusion

Ultrasonographic measurements of IMT can be limited to the common carotid artery,[12, 13] averaged across multiple carotid-artery segments,[14, 15] or combined as a score.[16] A review of eight epidemiological studies showed that the IMT of the common carotid artery by itself (in all eight studies) or combined with the IMT of internal carotid artery and presented as a score (in one of the eight studies) had independent predictive power with respect to cardiovascular events.[17] Three studies with separate measurements for the common and internal carotid arteries showed significant associations of cardiovascular events with IMT.[14, 18, 19] Our study confirms that

common carotid artery IMT, internal carotid artery IMT and their combined score are not independent predictors of HF and its phenotypes.

It is not clear whether the IMT incrementally adds value to the Framingham risk factors for cardiovascular prediction. The addition of IMT measurements slightly increased the predictive power with respect to cardiovascular risk assessment in one study[20] and with respect to stroke in another study.[21] The presence of plaque (defined as an internal carotid artery IMT >1.9 mm) has been shown to be associated with increased event rates.[22] Our data clearly show that addition of the combined common carotid artery and internal carotid artery IMT increases the net reclassification index of risk categories based on race and Framingham risk factors, but it's not clear if its due to adding cIMT as a risk factor, or its simply due to Framingham HF diagnostic criteria algorithm.

Reclassification is a practical approach to gauging the effects of adding new risk factors to the traditional Framingham risk factors when differences in the C statistics are marginal.[10] A recent meta-analysis reviewed studies suggesting that a new risk factor added predictive value to the Framingham risk score.[23] We performed our study according to the criteria proposed in the meta-analysis: verification of regression calibration, predictive value of the new risk factor in a multivariable model with Framingham risk factors, positive change in the C statistic, and an increased net reclassification index. The IMT of common carotid artery and internal carotid artery satisfied all these metrics.

To the best of our knowledge, our study is the first to investigate the association of carotid IMT and its subtypes with all form of HF, also we conducted rigorous analyses by adding HF risk models in a large diverse cohort with more than a decade of follow-up. There are some limitations to this study that should be mentioned. 1) although rigorous methods were used to account for all HF cases, some events may have been missed. It is unlikely, however, that the

resulting bias would have been differential in nature rather than merely reducing effect estimates toward null. 2) Although numerous covariates were included in our multivariate models, we acknowledge that residual confounding remains a possibility.

We conclude that maximum common carotid IMT, Internal carotid IMT and their combined measurement may have contributed significantly but modestly to the predictive power of HF risk factors used in calculating HF risk scores.

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Table 1. Baseline characteristics by heart failure phenotypes

	No Heart Failure (N=6418)	**HFrEF (N=152)**	**HFpEF (N=132)**	***P* Value**
Age, years	61.8 +/- 10.2	67.4 +/- 9.0	69.5 +/- 8.7	**<0.001**
Males, %	2991, 46.6%	106, 69.7%	64, 48.5%	**<0.001**
Race/Ethnicity, %				**<0.001**
White	2473, 38.5%	57, 37.5%	56, 42.2%	**0.005**
Chinese	776, 12.1%	4, 2.6%	14, 10.6%	
African American	1755, 27.3%	58, 38.2%	35, 26.5%	
Hispanic	1414, 22.0%	33, 21.7%	27, 20.5%	
Education, high school or less, %	5267, 82.3%	121, 8.1%	98, 74.2%	0.046
Body mass index, kg/m^2	28 +/- 5.4	29.4 +/- 5.4	30.1 +/- 6.3	**<0.001**
Diabetes mellitus, %	760, 11.9%	43, 28.3%	37, 28.0%	**<0.001**
Total cholesterol, mg/dL	194.4 +/- 35.8	188.8 +/- 35.9	188.1 +/- 34.5	**0.03**
high-density lipoprotein cholesterol, mg/dL	51.1 +/- 14.8	47.1 +/- 12.9	50.0 +/- 14.3	**0.004**
Lipid-lowering medication use, %	117.4, 31.5%	114.5, 32.8%	111.7, 31.7%	0.07
Healthy diet*, %	2893, 47.0%	66, 46.8%	69, 54.3%	0.26
Systolic blood pressure	126.0 +/- 21.2	137.6 +/- 22.6	139.2 +/- 23.4	**<0.001**
Heart rate, beat-per-minute	63 +/- 9.6	64 +/- 10.9	66 +/- 10.1	**0.001**
LVH, mm	0.0085 +/- 0.092	0.0461+/- 0.210	0.0385 +/- 0.193	**<0.001**
Anti-hypertensive medication use, %	2310, 36.0%	89, 58.6%	76, 57.6%	**<0.001**
Family history of coronary heart disease, %	2552, 42.3%	75, 54.7%	52, 42.6%	**0.02**
Cigarette smoking, %				**0.02**
Never	3252, 50.8%	63, 41.7%	55, 41.7%	
Former	2320, 36.3%	61, 40.4%	61, 46.2%	
Current	827, 12.9%	27, 17.9%	16, 12.1%	
Alcohol use, %				**<0.001**
Never	1315, 20.6%	22, 14.6%	27, 20.5%	
Former	1494, 23.4%	53, 35.1%	46, 34.9%	
Current	3564, 55.9%	76, 50.3%	59, 44.7%	
Internal Carotid IMT, mm	1.1 +/- 0.59	1.3 +/- 0.71	1.4 +/- 0.69	**<0.001**
Common Carotid IMT, mm	0.87 +/- 0.19	0.96 +/- 0.21	0.95 +/- 0.17	**<0.001**

Continuous variables presented as mean (standard deviation) and categorical variables as count (percentage).

* Healthy diet consisted of adequate quantities of 5 items identified by American heart Association (fruits and vegetables, fish, wholegrains, sodium <1500 mg/day, and sugar-sweetened beverages ≤450 kcal (36 oz) per week).

Table 2. Hazard ratios (95% confidence interval) for the association between internal carotid (IC), common carotid (CC) intimal-media thickness (IMT) and incident heart failure with reduced and preserved ejection fractions

Internal carotid IMT									
Outcome	Events (n)	**Unadjusted**		**Model 1**		**Model 2**		**Model 3**	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
HFrEF	152	**1.78 (1.48-2.16)**	**<0.001**	**1.33 (1.07-1.64)**	**0.009**	1.19 (0.95-1.49)	0.121	1.13 (0.90-1.43)	0.283
HFpEF	132	**1.85 (1.52-2.25)**	**<0.001**	**1.32 (1.06-1.65)**	**0.012**	1.14 (0.90-1.44)	0.264	1.12 (0.89-1.42)	0.317
HF, total	284	**1.84 (1.61-2.10)**	**<0.001**	**1.34 (1.15-1.56)**	**<0.001**	**1.18 (1.01-1.38)**	**0.034**	1.15 (0.97-1.35)	0.087
Common carotid IMT									
Outcome	Events (n)	**Unadjusted**		**Model 1**		**Model 2**		**Model 3**	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
HFrEF	152	**6.84 (3.83-12.20)**	**<0.001**	**2.17 (1.04-4.53)**	**0.038**	1.39 (0.62-3.09)	0.419	1.21 (0.55-2.65)	0.620
HFpEF	132	**6.93 (3.73-12.85)**	**<0.001**	1.81 (0.82-4.00)	0.140	1.09 (0.46-2.61)	0.831	1.09 (0.46-2.56)	0.842
HF, total	284	**6.92 (4.56-10.50)**	**<0.001**	**2.00 (1.18-3.40)**	**0.010**	1.24 (0.70-2.22)	0.452	1.16 (0.66-2.05)	0.595

- Model 1 adjusted for age, sex, race/ethnicity
- Model 2 adjusted for Model 1 covariates in addition to body mass index, diabetes mellitus, systolic blood pressure, left ventricular hypertrophy, heart rate
- Model 3: adjusted for model 1 & 2 covariates in addition to interim CAD events
- Bolded items are significant

Table 3. Unadjusted and Adjusted HRs (95% CI) for Incident HFrEF, HFpEF and HF total per 1 SD (0.18 mm) increase in Carotid intima-media thickness (IMT)*

Outcome	**Unadjusted**		**Model 1**		**Model 2**		**Model 3**	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
HFrEF	**1.54 (1.37-1.73)**	**<0.001**	**1.22 (1.06-1.41)**	**0.004**	1.11 (0.96-1.29)	0.145	1.08 (0.92-1.26)	0.317
HFpEF	**1.57 (1.39-1.77)**	**<0.001**	**1.21 (1.04-1.40)**	**0.012**	1.07 (0.91-1.26)	0.353	1.07 (0.91-1.26)	0.389
HF, total	**1.56 (1.44-1.69)**	**<0.001**	**1.20 (1.08-1.33)**	**<0.001**	1.09 (0.98-1.22)	0.102	1.08 (0.97-1.20)	0.147

***** Z-score for maximal IMT (measured maximum IMT of the IC and CC sites as the mean of the maximum IMT of the near and far walls of the right and left sides)

Model 1 adjusted for age, sex, race/ethnicity

Model 2 adjusted for Model 1 covariates in addition to body mass index, diabetes mellitus, systolic blood pressure, left ventricular hypertrophy, heart rate

Model 3: adjusted for model 1 & 2 covariates in addition to interim CAD events

Bolded items are significant

Figure 1. Kaplan-Meier Curves showing Proportion Free from HFrEF by cIMT Percentile

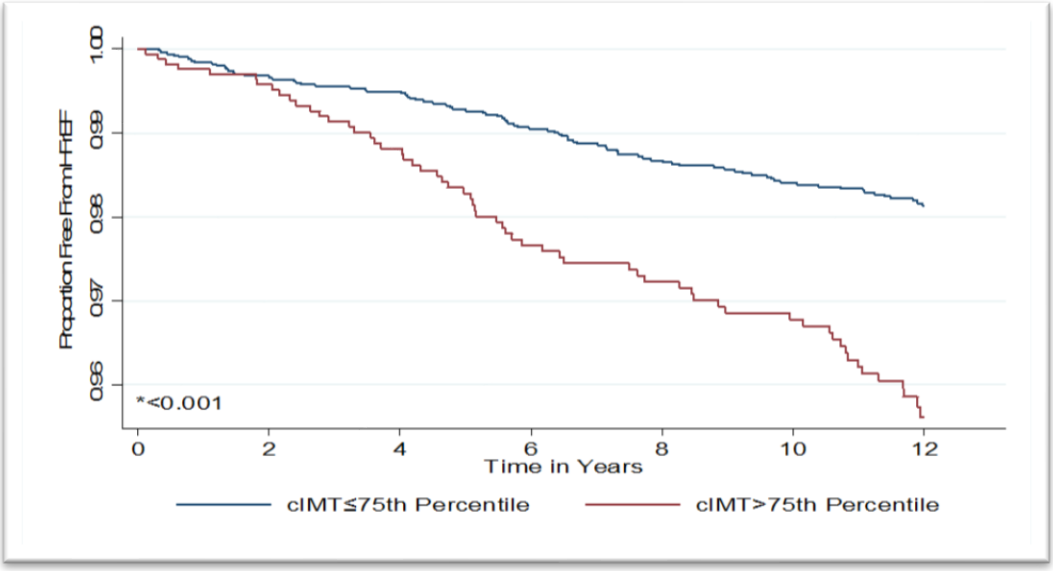

Figure 2. Kaplan-Meier curves showing proportion free from HFpEF by cIMT Percentile

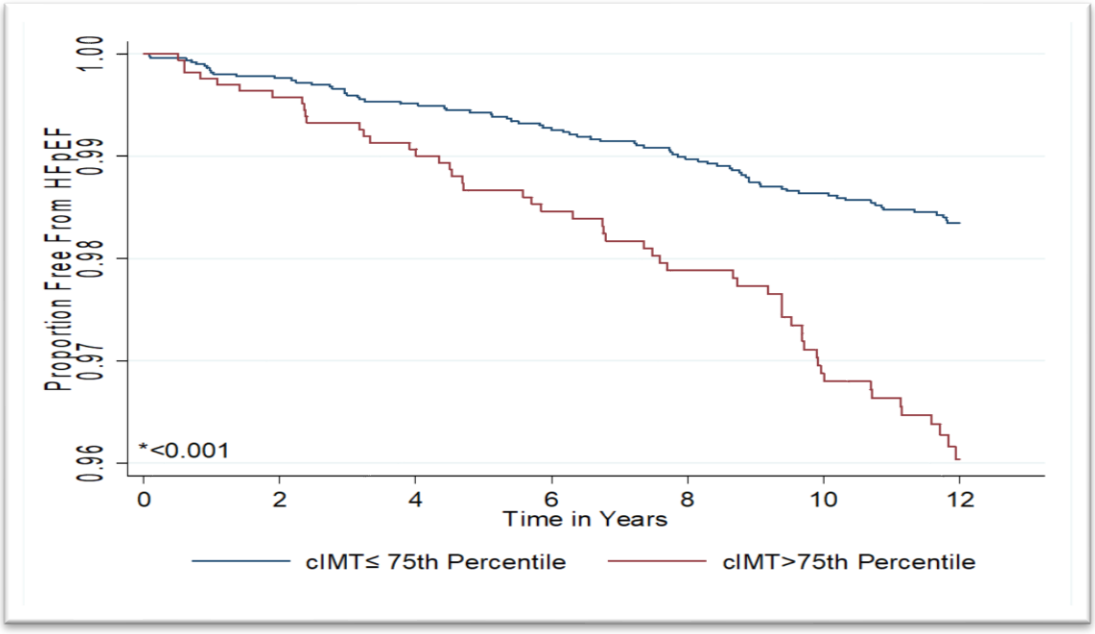

Figure 3. Kaplan-Meier curves showing proportion free from HF by cIMT Percentile

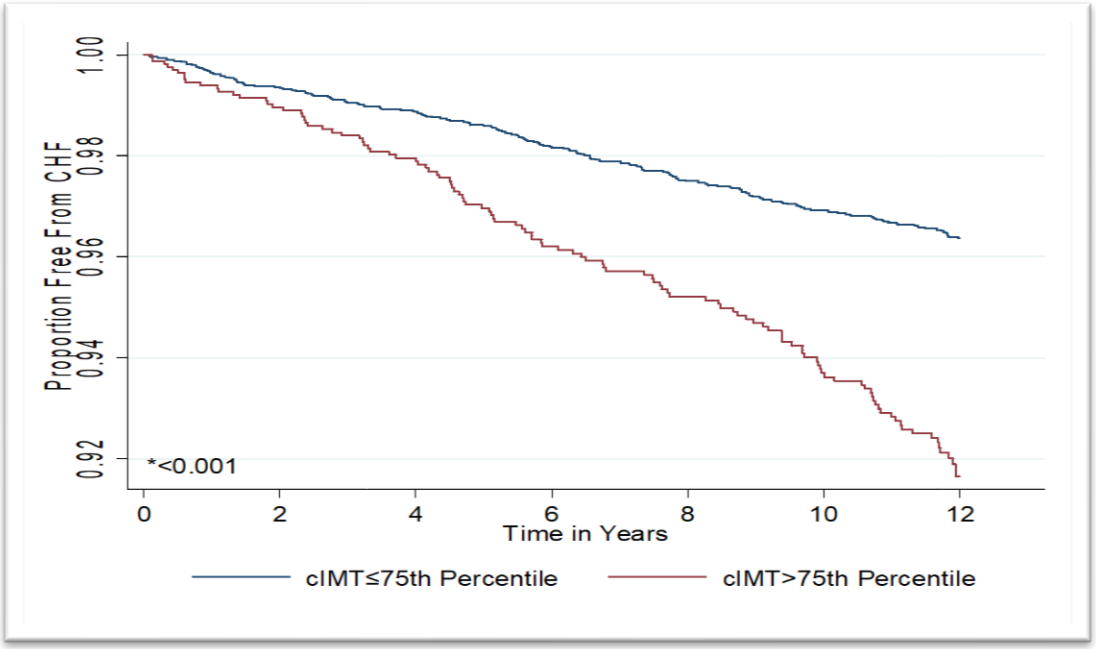

Figure 4.

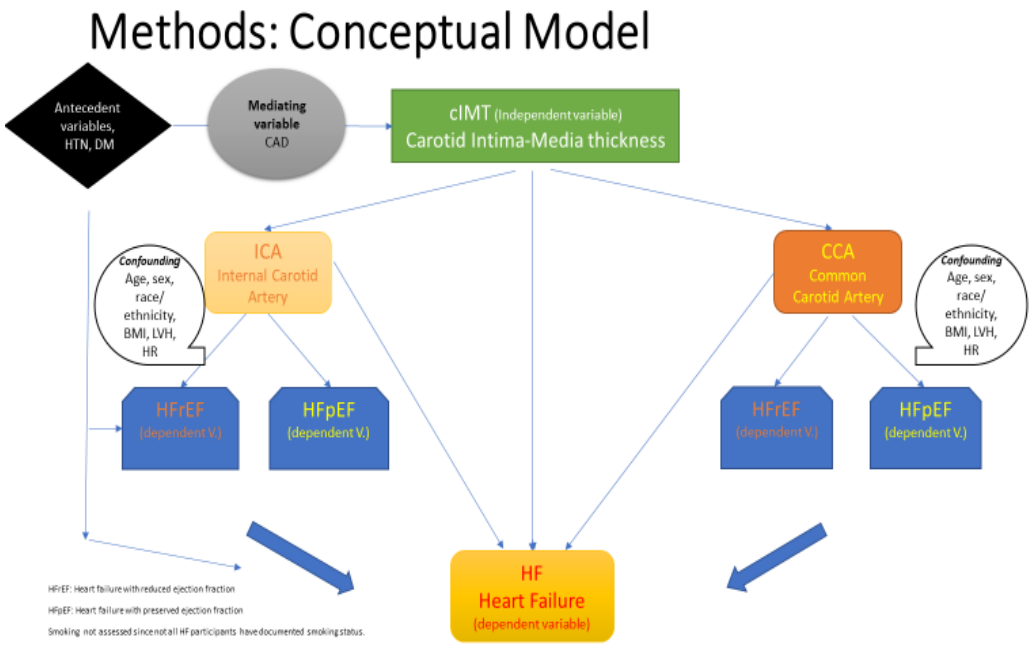
Methods: Conceptual Model
Antecedent variables, HTN, DM
Mediating variable CAD
cIMT (Independent variable)
Carotid Intima-Media thickness
ICA
Internal Carotid Artery
CCA
Common Carotid Artery
Confounding
Age, sex, race/ ethnicity, BMI, LVH, HR
Confounding
Age, sex, race/ ethnicity, BMI, LVH, HR
HFrEF
(dependent V.)
HFpEF
(dependent V.)
HFrEF
(dependent V.)
HFpEF
(dependent V.)
HF
Heart Failure
(dependent variable)
HFrEF: Heart failure with reduced ejection fraction
HFpEF: Heart failure with preserved ejection fraction
Smoking not assessed since not all HF participants have documented smoking status.

Table 4. NRI, C-statistics and AUC by adding Z-score cIMT to Framingham risk score with incidence heart failure

Outcome: CHF All	C-statistic	AUC*	NRI for the Addition of Z-Score cIMT	p-value
Framingham Risk Score	0.69	0.68	----	----
Framingham Risk Score+ Race	0.69	0.68	----	----
Z-Score cIMT + Framingham	0.71	0.70	0.028	0.18
Z-Score cIMT + Framingham+ Race	0.71	0.70	0.042	**0.045**

*P 0.005 this is the p-value testing the addition of Z-score cIMT to the model including Framingham risk score and race (AUC).

Table 5. Comparing category-less NRI and categorical NRI by adding Z-score cIMT to Framingham risk score and race with incident heart failure

Outcome: CHF All	Category-less NRI	Category NRI	p-value
Z-Score cIMT + Framingham	0.34	0.34	<0.0001
Z-Score cIMT + Framingham+ Race	0.3360	0.33	<0.0001

Table 6. Alternative NRIs by adding (cIMT, Interquartile cIMT, 75% cIMT) to Framingham risk score and race with incident heart failure

Outcome: CHF All	NRI by cIMT	p-value	NRI by Interquartile cIMT	p-value	NRI by 75% cIMT	p-value
cIMT + Framingham+ Race	0.0073	0.575	**0.0300**	**0.046**	0.0232	0.095

Table 7. Hazard ratios (95% confidence interval) for the association between Z score IMT and incident HFpEF by Hypertension status (sensitivity analysis)

Z score IMT	**No-Hypertension (n=39)**		**Hypertension (n=91)**	
	HR* (95% CI)	***p*-value**	**HR* (95% CI)**	**p-value**
HFpEF	**1.50 (1.08-2.05)**	**<0.014**	0.96 (0.80-1.14)	0.643

Model adjusted for age, sex, race/ethnicity, body mass index, diabetes mellitus, systolic blood pressure, left ventricular hypertrophy, heart rate, HTN medications and interim CAD events.

*The hazard ratio for Z-score is highly significant in those with-out hypertension, but not in those with hypertension. This means that the relationship of Z-score and outcome differs according to hypertension status.

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PROFESSIONAL LICENSURE:

North Carolina, Full, Exp. Date 09/2019
Maryland, Full, Exp. Date 9/2018

California, Full-voluntary, Exp. Date: 9/2019

BOARD CERTIFICATIONS:

American Board of Internal Medicine
American Board of Family Medicine
ABIM/ABFM, Geriatric Medicine

RESEARCH EXPERIENCE:

Research Associate, University of California San Diego, 2001-2005, Dr. Alexandra Schwartz, Supervisor.

EMPLOYMENT:

Attending Physician, Division of Immediate Care, Cigna Health, Baltimore, MD, 2013-2017, Shahzad Usmani, MD, Supervisor

Faculty Physician, Greater Baltimore Medical Center, Baltimore, MD, Internal Medicine and Geriatric Medicine, 2011-2013, Anthony Riley, MD, Supervisor

HONORS AND AWARDS:

-Certificate of Recognition: American Heart Association, 43rd Ten-Day Seminar, Tahoe City, California, 2017.
-Leaders team, Cigna Safety Committee, 2016-2017
-Award of appreciation and gratitude, Manor Care Ruxton Nursing Home, Baltimore, MD, 3/2012
-Elected Member/GMEC, Geriatric fellowship program, LSU, 2008-2009
-Member, Safety Committee, LSU, 2008-2009
-Member, Safety & Pharmacy-Therapeutic Committee, LSU, 2006-2008
-Member, Ethics Committee, LSU, 2005-2008
-Elected Member/GMEC, Residency Program, LSU, 2005-2008

MEMBERSHIPS:

-Fellow in Training, American College of Cardiology (FIT-ACC)
-Fellow, American College of Physicians (FACP)
-Fellow, American Academy of Family Physicians (FAAFP)
-Fellow, American College of Physicians, North Carolina chapter
-Fellow, American College of Physicians, Maryland Chapter, June/2017
-Fellow, North Carolina Academy of Family Physicians
-Fellow, Maryland Academy of Family Physicians, June/2017
-Member, American Heart Association

SCHOLARSHIPS:

Fellow in training scholarship, North Carolina/ South Carolina ACC chapter meeting, September 2018

Kiawah Island, SC

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Peer-Reviewed Manuscripts:

Aladin AI, Whellan, D, Mentz R, Reeves G, Duncan P, Malaver D, Rosenberg P, Fitzgerald K, Kitzman DW. Relationship of Physical Function and Quality of Life in Elderly Patients with Acute Decompensated Heart Failure: The Rehabilitation Therapy in Older Acute Heart Failure Patients (The REHAB-HF Trial). Under-Submission.

Aladin AI, Soliman EZ, Kitzman DW, Dardari Z, Rasool SH, Yeboah J, Al Rifai M, Budoff MJ, Psaty BM, Ouyang P, Polak JF, Blumenthal RS, McEvoy JW, Gandhi SK, Herrington DM. Relationship of Carotid Intima-Media Thickness with Incident Heart Failure with reduced versus preserved Ejection Fraction. Under-submission.

Chevli, PA, Ahmad, MI, Jogu, HR, Dutta, A, Anees, MA, Sunkara, PR, **Aladin, AI**. Electrocardiographic Subclinical Myocardial Injury and Alcohol Consumption: A cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey. Am J Cardiovasc Dis. 2018 Dec 15;8(5):58-65. PMID: 30697451

Wang S, Fashanu O, Zhao D, Guallar E, Gottesman R, Schneider A, McEvoy J, Norby F, Alonso A, **Aladin AI**, Michos E. Elevated Resting is Associated with Cognitive Change Over 20-years: The Atherosclerosis Risk in communities (ARIC) Study. *Am J Cardiol* 2019 Jan; 123(2):334-340. PMID: 30424869

Aladin AI, Al Rifai M, Rasool SH, Dardari Z, Yeboah J, Nasir K, Budoff MJ, Psaty BM, Blumenthal RS, Blaha MJ, McEvoy JW. Relationship of Coronary Artery Calcium and Extra-Coronary Aortic Calcium to Incident Hypertension (From t*he Multi-Ethnic Study of Atherosclerosis (MESA). Am J Cardiol* 2018 Jan; 121(2):210-216. PMID 29174140.

Aladin AI, Al Rifai M, Rasool SH, Keteyian SJ, Brewer CA, Blumenthal RS, Al-Mallah MH, Blaha MJ, McEvoy JW. Relation of Resting Heart Rate to Incident Atrial Fibrillation. The Henry Ford Hospital Exercise Testing (FIT) project. *Am J Cardiol* 2016 Dec;119(2):262-267. PMID 28126149.

Aladin AI, Al Rifai M, Rasool SH, Keteyian SJ, Brewer CA, Michos ED, Blaha MJ, Al-Mallah MH, McEvoy JW. The Association of Resting Heart Rate and Incident Hypertension. The Henry Ford Hospital Exercise Testing (FIT) Project. *Am J of Hypertens* 2016 Feb; 29(2): 251-257. PMID 26112864.

Aladin AI, Whelton SP, Al-Mallah MH, Blaha MJ, Keteyan SJ, Juraschek SP, Kuzniecky JR, Brewer CA, Michos ED. Relation of resting heart rate to risk for all-cause mortality by gender

after considering exercise capacity (the Henry Ford exercise testing project). *Am J Cardiol*. 2014 Dec 1;114(11):1701-6. PMID: 25439450.

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Aladin, AI, Chevli, PA, Ahmad, MI, Rasool, SH, David M. Herrington, DM. Alcohol Consumption and Risk of Hypertension. Journal of the American College of Cardiology, 2019 March; 73(9):1041-03.

Parag Chevli**, Aladin AI**, Diego M, Kanaya A, Herrington D. Association of Alcohol Consumption and Subclinical Atherosclerosis among Asymptomatic South Asians: The Mediators of Atherosclerosis in South Asians Living in America (MASALA) study. Circulation. 2018 November; 138: A13224.

Aladin AI, Whellan, D, Mentz R, Reeves G, Duncan P, Malaver D, Rosenberg P, Fitzgerald K, Kitzman D. Relationship of Physical Function and Quality of Life in Elderly Patients with Acute Decompensated Heart Failure: The Rehabilitation Therapy in Older Acute Heart Failure Patients (The REHAB-HF Trial). Circulation. 2018 March;137: AP160.

Wang S, Fashanu O, Zhao D, Guallar E, Gottesman R, Schneider A, McEvoy J, Norby F, Alonso A, **Aladin AI**, Michos E. Elevated Resting is Associated with Cognitive Change Over 20-years: The Atherosclerosis Risk in communities (ARIC) Study. Circulation. 2018 March;137: AP013.

Aladin AI, Soliman EZ, Kitzman DW, Dardari Z, Rasool SH, Yeboah J, Al Rifai M, Budoff MJ, Psaty BM, Ouyang P, Polak JF, Blumenthal RS, McEvoy JW, Gandhi SK, Herrington DM. Relationship of Carotid Intima-Media Thickness with Incident Heart Failure with reduced versus preserved Ejection Fraction: The Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2017, Nov; 136: A14797.

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Aladin AI, Al Rifai M, Rasool SH, Keteyian SJ, Brewer CA, Blumenthal RS, Al-Mallah MH, Blaha MJ, McEvoy JW. Prospective Association of Resting Heart Rate and Incident Atrial Fibrillation. FIT Project. Circulation 2015, Nov; 132(3): A12256.

Aladin AI, Al Rifai M, Rasool SH, Keteyian SJ, Brewer CA, Michos ED, Blaha MJ, Al-Mallah MH, McEvoy JW. The Association of Resting Heart Rate and Incident Hypertension. The Henry Ford Hospital Exercise Testing (FIT) Project. Circulation 2014, Nov; 130(2): A12933.

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Lectures/ Oral Presentations:

Aladin, AI, Chevli, PA, Ahmad, MI, Rasool, SH, David M. Herrington, DM. Alcohol Consumption and Risk of Hypertension. American College of Cardiology; Annual Scientific Sessions. New-Orleans/LA, March 2019.

Amer AI, Elsayed SZ, Kitzman DW, Dardari Z, Rasool SH, Yeboah J, Al Rifai M, Budoff MJ, Psaty BM, Blumenthal RS, McEvoy JW, Gandhi SK, Herrington DM. Relationship of Carotid Intima-Media Thickness with Incident Heart Failure with reduced versus preserved Ejection Fraction. CME earning event presentation at Wake Forest University School of Medicine, Research Conference. January/2018.

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Aladin AI, James Porterfield. Heart Failure with Reduced Ejection fraction (HFrEF) and risk of falls in Elderly. Presentation at GBMC, 03/2012.

Aladin AI, James Porterfield. Aortic Stenosis progression in elderly with Dementia and on Cholinesterase Inhibitors. Presentation at GBMC, 06/2011.

Aladin AI. Stroke and Rehab. Presentation at GBMC, 04/2011, (Part I & II).

Aladin AI. Vision and Hearing problems in Elderly. Presentation at GBMC 12/2010 (Part I), 04/2011 (part II).

Aladin AI. Prevention & Treatment of Alzheimer. Presentation at University Medical Center /LSU, 08/2009, and at GBMC 12/2010.

Aladin AI. Evaluation & Management of Dementia. Presentation at University Medical Center / LSU, 08/2009, and at GBMC 12/2010.

Aladin AI. Physical Activity, Diet and Risk of Alzheimer. Presentation at University Medical Center/LSU, 08/2009.

Aladin AI. Pulmonary-Vein Isolation for Atrial Fibrillation in Patients with Heart Failure. Presentation at University Medical Center / LSU, 05/2009.

Aladin AI. 10-year Probability of Recurrent Fractures Following Wrist and Other Osteoporotic Fractures. Presentation at University Medical Center / LSU, 03/2009.

Posters:

Parag Chevli**, Aladin AI**, Diego M, Kanaya A, Herrington D. Association of Alcohol Consumption and Subclinical Atherosclerosis among Asymptomatic South Asians: The Mediators of Atherosclerosis in South Asians Living in America (MASALA) study. Presentation at American Heart Scientific Sessions, Chicago/IL, November 2018.

Aladin AI, Whellan, D, Mentz R, Reeves G, Duncan P, Malaver D, Rosenberg P, Fitzgerald K, Kitzman D. Relationship of Physical Function and Quality of Life in Elderly Patients with Acute Decompensated Heart Failure: The Rehabilitation Therapy in Older Acute Heart Failure Patients (The REHAB-HF Trial). Poster presentation at: Internal Medicine Research Day, Wake Forest Baptist Health Medical Center. Winston-Salem/NC, May 2018.

Aladin AI, Whelton SP, Al-Mallah MH, Blaha MJ, Keteyan SJ, Juraschek SP, Kuzniecky JR, Brewer CA, Michos ED. Relation of resting heart rate to risk for all-cause mortality by gender after considering exercise capacity (the Henry Ford exercise testing project). Poster presentation at: Women Health Research Day, Wake Forest Baptist Medical Center. Winston-Salem/NC, April/2018.

Aladin AI, Whellan, D, Mentz R, Reeves G, Duncan P, Malaver D, Rosenberg P, Fitzgerald K, Kitzman D. Relationship of Physical Function and Quality of Life in Elderly Patients with Acute Decompensated Heart Failure: The Rehabilitation Therapy in Older Acute Heart Failure Patients (The REHAB-HF Trial). Presentation at American Heart Association EPI/Life Style Scientific Conference. New Orleans/LA. March/ 2018.

Wang S, Fashanu O, Zhao D, Guallar E, Gottesman R, Schneider A, McEvoy J, Norby F, Alonso A, **Aladin AI**, Michos E. Elevated Resting is Associated with Cognitive Change Over 20-years: The Atherosclerosis Risk in communities (ARIC) Study. Presentation at American Heart Association EPI/Life Style Scientific Conference. New Orleans/LA. March/ 2018.

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Aladin AI, Soliman EZ, Kitzman DW, Dardari Z, Rasool SH, Yeboah J, Al Rifai M, Budoff MJ, Psaty BM, Ouyang P, Polak JF, Blumenthal RS, McEvoy JW, Gandhi SK, Herrington DM. Relationship of Carotid Intima-Media Thickness with Incident Heart Failure with reduced versus preserved Ejection Fraction: The Multi-Ethnic Study of Atherosclerosis (MESA). Poster presentation at American Heart Association Scientific Sessions, Anaheim/CA, November/2017.

Aladin AI, Al Rifai M, Rasool SH, Dardari Z, Yeboah J, Nasir K, Budoff MJ, Psaty BM, Blumenthal RS, Blaha MJ, McEvoy JW. Coronary Artery Calcium and Incident Hypertension in a Population-Based Cohort: *The Multi-Ethnic Study of Atherosclerosis (MESA).* Poster presentation at *American College of Cardiology; Annual Scientific Sessions*, Washington DC, March/2017.

Aladin AI, Al Rifai M, Rasool SH, Keteyian SJ, Brewer CA, Michos ED, Blaha MJ, Al-Mallah MH, McEvoy JW. The Association of Resting Heart Rate and Incident Hypertension. The Henry Ford Hospital Exercise Testing (FIT) Project. Poster presentation at American Heart Association Scientific Sessions, Chicago/IL, November/2014.

Aladin AI, Whelton SP, Al-Mallah MH, Blaha MJ, Keteyan SJ, Juraschek SP, Kuzniecky JR, Brewer CA, Michos ED. Relation of resting heart rate to risk for all-cause mortality by gender

after considering exercise capacity (the Henry Ford exercise testing project). Poster presentation at American Heart Association Scientific Sessions, Dallas/TX, November/2013.

Aladin AI. Gallstone pancreatitis in pregnancy, poster presentation at University Medical Center/ LSUHSC-New Orleans, March/2009.

Aladin AI. Severe Pustular Psoriasis, Poster presented at regional meeting in Louisiana (Annual Family Medicine Conference, regional meeting), (October/2007); Many, Cypress Bend Resort, LA.

Journal invited reviewer:

Aladin, AI, Herrington D. "Contemporary assessment of diabetes-related all-cause and cardiovascular mortality in national cohort of adults" *JAMA Cardiology*, June 2018

Aladin, AI, Herrington D. **"**Risk Factors Control for Primary Prevention of Cardiovascular Disease: Evidence from the Aragon Workers Health Study (AWHS). PlosOne, December 2017

Aladin AI, "The role of cardiac magnetic resonance in diagnosis of cardiomyopathy: a systematic review" *Malawi Medical Journal*, September 2017

Aladin AI, Herrington D. "Lipoprotein (a) does not predict recurrent ischemic events following acute coronary syndrome" *JAMA-Cardiology*, July 2017

Aladin AI, "The association of Resting Heart Rate and risk of cardiovascular versus Non-cardiovascular death" *American Journal of Cardiology*, October 2016

Clinical Trials:

Aladin AI (Sub-investigator) **TACT2 Trial,** A randomized, double blind controlled factorial clinical trial of edetate disodium-based chelation and high-dose oral vitamins and minerals to prevent recurrent cardiac events in diabetic patients with a prior myocardial infarction. January 2018-present

Aladin AI (Sub-investigator) **CLEAR Trial,** A randomized, double-blind. Placebo-controlled Study to Assess the Effects of Bempedoic Acid (ETC-1002) on the Occurrence of Major Cardiovascular Events in Patients with, or at high risk for, Cardiovascular Disease who are Statin Intolerance. November 2017-present

Aladin AI (Sub-investigator), **GOULD Trial** (A registry of High Cardiovascular Risk Subjects in the United States) Getting to an imprOved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia management. September 2017-present

Aladin AI (Sub-investigator), The **dal-GenE Trial**, a phase III, double-blind, randomized placebo-controlled study to evaluate the effects of dalcetrapib on cardiovascular risk in a genetically defined population with a recent Acute Coronary Syndrome (ACS). July 2017-present

Aladin AI (Sub-investigator), **REDUCE-IT Trial** (Reduction of Cardiovascular Events with EPA- Intervention trial) a multi-center, Prospective, Randomized, Double-blind, Placebo-Controlled, Parallel-Group study to evaluate the effect of AMR101 on cardiovascular health and mortality in hypertriglyceridemic patients with cardiovascular disease or at high risk for cardiovascular disease. July 2017-November 2018

Aladin AI (Sub-investigator), **STRENGTH Trial**, a long-term outcomes study to assess statin residual risk reduction with EpaNova in high cardiovascular risk patients with hypertriglyceridemia. July 2017-present