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Diabetes Status Modifies the Association between Carotid Intima-Media Thickness and Incident Heart Failure: The Atherosclerosis Risk in Communities Study

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Abstract

Aims—Increasing carotid intima-media thickness (CIMT) is associated with incident heart failure (HF). We investigated whether this association differs by diabetes status.

Methods—We characterized 13,590 Atherosclerosis Risk in Communities Study participants free of baseline HF into normal fasting glucose (NFG, glucose < 100 mg/dl), impaired fasting glucose (IFG, glucose 100–125 mg/dl), and type 2 diabetes (T2D, glucose ≥ 126 mg/dl, self-report, or use of diabetes drugs). CIMT was assessed by B-mode ultrasound. Incident HF was defined using

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CONFLICTS OF INTEREST

None

DISCLOSURES

All authors have read and approved this final version of the manuscript.

CONTRIBUTORS

VSE was involved with conception and design of the research, statistical analysis and interpretation of the data, and drafting the manuscript; EEM was involved with data interpretation, critical review and drafting the manuscript; CJR was involved with conception and design of the research, interpretation of the data, and critical review of the manuscript; LEW was involved with obtaining funding and supervising the work, acquisition of the data, interpretation of the data, and critical review of the manuscript; GWE was involved with conception and study design, statistical analysis and interpretation of the data, acquisition of the data, and critical review of the manuscript; PPC was involved with study design, data interpretation and critical review of the manuscript; AGB was involved with obtaining funding and supervising the work, study conception and design, data analysis and interpretation, and critical review of the manuscript.

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ICD-9 or 10 codes from hospitalizations and death certificates. Cox regression was used to estimate hazard ratios (HR) for incident HF, adjusting for age, sex, race, education, hypertension medication, blood pressure, BMI, waist circumference, HDL, LDL, triglycerides, lipid-lowering medication, smoking, alcohol, serum creatinine, and interim CHD.

Results—T2D participants had higher mean CIMT (0.79 ± 0.20 mm), compared to IFG (0.75 ± 0.19 mm) and NFG (0.70 ± 0.17 mm) ($p < 0.0001$). Over 20.6 years of median follow-up, 15% developed HF. Rates of HF (per 1,000 person-years) were substantially higher for those with T2D (24.7), compared to IFG (7.7) and NFG (5.8). In adjusted analyses, the CIMT-HF association was significantly modified by diabetes status ($P_{\text{interaction}} = 0.015$): for NFG (HR per SD increase in CIMT: 1.27; 95% CI: 1.20–1.34), IFG (HR 1.18; 95% CI: 1.11–1.25) and T2D (HR 1.12; 95% CI: 1.05–1.21).

Conclusions—CIMT is associated with increased risk of HF, particularly among persons without diabetes. Due to a high absolute risk of HF among adults with T2D, CIMT may be a less reliable predictor.

Keywords

Heart failure; carotid intima-media thickness; subclinical atherosclerosis; diabetes mellitus

1. INTRODUCTION

Heart failure (HF) is a major public health problem, with over 23 million cases worldwide. [1] Each year about 500,000 people are newly diagnosed with HF in the USA with a substantial economic cost and human impact.[2] Despite advances in therapy and management, a diagnosis of HF carries a substantial risk of morbidity and mortality. Based on data from the Framingham Heart Study, the 30-day mortality after diagnosis is approximately 10%, 20%–30% at 1 year, and 45%–60% at 5 years.[3] The risk of HF is remarkably higher in persons with abnormal glucose metabolism, particularly those with type 2 diabetes (T2D).[4, 5, 6] Similarly, impaired fasting glucose (IFG) and T2D states are strongly associated with increased left ventricular (LV) mass and LV wall thickness, and lower end-diastolic volume, all markers of HF.[7] The prevalence of T2D is on the rise, which suggests that the incidence of HF may continue to increase. Therefore, predicting HF risk, especially in persons with abnormal glucose metabolism (IFG and T2D), could be beneficial in mitigating its burden.

Carotid intima-media thickness (CIMT), a reliable marker of early atherosclerosis, is associated with subclinical cardiovascular disease. Fernandes and colleagues, using data from asymptomatic participants in the Multi-Ethnic Study of Atherosclerosis, showed that increased CIMT is associated with alterations of various regional myocardial parameters, [8] which predict future risk of HF. Some studies have also shown a direct relationship between CIMT and incident HF, independent of coronary heart disease.[9, 10] A review of 21 studies including 24,111 people with T2D and impaired glucose tolerance found that CIMT was greater in persons with T2D by 0.13 mm (95% CI: 0.12–0.14).[11] Given the strong association between CIMT and incident HF described in previous studies, and an increased CIMT in T2D, it is conceivable that CIMT would be more strongly associated with incident

HF in persons with T2D, compared to those without the condition. Our study sought to address this.

We analysed data from the Atherosclerosis Risk in Communities (ARIC) study cohort to assess the differences in the association between CIMT and incident HF in subjects with normal fasting glucose (NFG), IFG and T2D.

2. SUBJECTS, MATERIALS AND METHODS

2.1. Subjects

The ARIC study recruited 15,792 participants aged 45–64 years from four communities: Washington County, Maryland; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Forsyth County, North Carolina.[12] The baseline exam was conducted between 1987 and 1989. Response rates at baseline were 46% in Jackson and 65–67% for the other communities. The institutional review boards from each site approved the ARIC study and all participants provided a written informed consent.

From those present at baseline, we excluded participants with missing values of CIMT ($n = 607$) and those with missing criteria to define diabetes status ($n = 148$). In addition, we also excluded participants with prevalent HF defined as stage 3 or by the use of HF medications (e.g. digoxin and diuretics) or by the Gothenburg criteria, or those who were missing criteria to define HF ($n = 1039$). Some participants reported a race other than Caucasian or African American. Because of their limited number ($n = 48$), they were also excluded. After exclusions, a final sample of 13,590 participants was retained for analysis.

2.2. Ascertainment of Heart Failure Cases

Incident HF cases were identified through annual phone calls, hospitalization codes (ICD-9 428.0 – 428.9) and death registers (code 428 or ICD-10 I50).[13] From 2005 onward, hospitalized HF cases were abstracted and reviewed by two ARIC Heart Failure Mortality and Morbidity Classification Committee (HF MMCC) members.[14] Differences between these reviewers were adjudicated by the Chair of the HF MMCC. The adjudicated classification becomes the event's final classification. HF cases occurring prior to 2005 were not adjudicated. The percent 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%)[14]. Only ARIC community surveillance systematically subtyped HF (as HFrEF vs HFpEF). Thus ARIC cohort HF cases that were not seen in surveillance were not subtyped.

Follow up time for those with incident HF events was defined as the time from the baseline exam to the incident event. For participants who did not develop HF, the end of follow up was either the date of last contact for those lost to follow up, the date of death, or December 31, 2009, whichever came first.

2.3. Measurement of Carotid IMT

This was achieved by high resolution B-mode ultrasound via a Biosound 2000 (Biosound, Indianapolis, Indiana) IISA system and images were recorded on a VHS tape. The

ultrasound examinations were performed according to a detailed standardized protocol by trained, certified sonographers subject to semi-annual evaluation.[15] Technicians scanned three specified segments of the extra-cranial carotid arteries on both sides: the common, the internal, and the bifurcation. 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. [16] The common carotid intima and media was assessed in a 1-cm segment proximal to the dilatation of the carotid bulb. All far wall measurements from these 6 segments were averaged and used in our analysis as an estimate of CIMT. 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). [15, 17]

2.4. Definition of Diabetes Status

Fasting serum glucose was measured by the optimized direct analysis in real time (DART) GLUCOSE reagent method. T2D was defined as a fasting glucose level of ≥ 7.0 mmol/l (≥ 126 mg/dl), a random glucose of ≥ 11 mmol/l (≥ 200 mg/dl), use of diabetes medication (oral hypoglycaemic agents and/or insulin), or a self-reported physician diagnosis. IFG was defined as 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. NFG was defined as any participant who did not meet the criteria for T2D and IFG.

2.5. Other Covariates

Participants provided information on demographic and behavioural variables, and on race, sex, current alcohol use, educational level, medication use (for dyslipidaemia and hypertension), and smoking status. 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 used in our analysis. 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. Triglycerides and HDL cholesterol were determined using enzymatic methods. LDL cholesterol was calculated using the Friedewald equation. [18] Serum creatinine concentration was measured using a modified kinetic Jaffe method. Prevalent CHD was defined as a history of myocardial infarction (MI), MI from adjudicated baseline ECG data, a self-reported history of physician-diagnosed MI, or a prior coronary reperfusion procedure. Incident CHD was defined as any case of adjudicated hospitalized MI, fatal CHD or ECG-diagnosed MI by the end of the study period.

2.6. Statistical Analysis

All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Baseline characteristics were compared by diabetes status using one-way analysis of variance (continuous variables) and Chi-square test (categorical variables). Our results are presented as mean $\pm$ SD for continuous variables and number (percentage) for categorical variables. For variables with a non-normal distribution, the SD was computed as the antilog of the logarithmic SD. Cox proportional hazard regression was used to estimate the hazard ratios (and 95% confidence intervals, CI) for incident HF per unit SD increase in CIMT, stratified by diabetes status. Multivariable models were sequentially adjusted for covariates: model 1

(demographic model) was adjusted for age, sex, race, and level of education. Model 2 (clinical and biological model) was adjusted for covariates in model 1, plus 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 3 (CHD model) was adjusted for covariates in model 2, plus CHD modelled as a time-dependent covariate that incorporated both prevalent and incident events. A similar adjustment approach was used with CIMT modelled in quartiles. The cumulative incidence of HF by diabetes status was also estimated. The proportional hazard assumption was assessed by visually examining the log (-log survival) plots and time-covariate interaction terms. Covariates for analysis were selected based on their associations with diabetes and HF demonstrated in previous studies. Statistical significance was inferred at two-sided $p < 0.05$.

3. RESULTS

Overall, 10.5% of the sample at baseline had type 2 diabetes (T2D), 33.6% had impaired fasting glucose (IFG), and 55.9% had normal fasting glucose (NFG). There was a total of 248,846 person-years of follow up, and 14.8% ($n = 2008$) of the sample developed heart failure (HF). Table 1 displays characteristics of sample participants at baseline.

Mean CIMT was significantly higher among participants with T2D (0.79 ± 0.20 mm), compared to those with IFG (0.75 ± 0.19 mm) and NFG (0.70 ± 0.17 mm) ($p < 0.0001$). Slightly more than one-third of participants with T2D developed HF over the course of follow up compared to 11% of those with NFG. In addition, participants with T2D were more obese, had adverse lipid profiles and hypertension than those with IFG and NFG. The crude incidence rates, per 1000 person years, of HF were 5.8 (95% CI: 5.4 – 6.2) for participants with NFG, 7.7 (95% CI: 7.2 – 8.4) for those with IFG, and 24.7 (95% CI: 22.7 – 26.9) for those with T2D.

Figure 1 displays the rates of HF by quartiles of CIMT, and by diabetes status. The rates of incident HF increased across each quartile of CIMT, regardless of diabetes status. Participants with T2D displayed rates of incident HF 2.6 to 4.6 times higher than the rates for those with IFG and NFG, across all quartiles of CIMT. In fact the absolute risk of HF for participants with T2D in the lowest quartile of CIMT (rate 14.8, 95%CI: 11.2 – 19.7) was higher than that of participants with IFG (rate 13.1, 95%CI: 11.7 – 14.7) and NFG (rate 12.4, 95%CI: 11.1 – 13.8) in the highest quartiles of CIMT (Figure 1). The difference in risk of HF between the 1st and 4th quartiles of CIMT was greater among participants with T2D (rate 17.7/1000 person-years), compared to those with IFG (rate 9.8/1000 person-years) and NFG (8.2/1000 person-years). Figure 2 illustrates a plot of the cumulative hazard for HF by diabetes status. While the cumulative hazard for subjects with NFG and IFG were comparable from baseline to about 4 years of follow up, and increased for those with IFG thereafter, the cumulative hazard for those with T2D was disproportionately higher from the start of follow up relative to subjects with NFG and IFG.

3.1. Multivariable analysis

With CIMT modelled as a continuous variable, the HRs for incident HF per unit standard deviation (SD) increase in CIMT (0.18 mm) for the entire sample were compared across all 3 categories of diabetes status (Table 2).

After adjusting for demographic factors, the CIMT-HF association appeared stronger among participants with NFG (HR 1.44, 95%CI: 1.38 – 1.52) than those with IFG (HR 1.32, 95%CI: 1.25 – 1.40) and T2D (HR 1.22, 95%CI: 1.14 – 1.31) ($p_{\text{interaction}} = 0.015$ in the fully adjusted model). These associations were attenuated with further adjustment for clinical and biologic risk factors in the second model. After final adjustment for prevalent and incident CHD, the association remained stronger among participants with NFG (HR 1.27, 95%CI: 1.20 – 1.34), than those with IFG (HR 1.18, 95%CI: 1.11 – 1.25) and T2D (HR 1.12, 95%CI: 1.05 – 1.21).

Table 3 shows adjusted HRs for incident HF by CIMT quartile, and stratified by diabetes status. For each category of diabetes status, the HR for HF increased across quartiles of CIMT. When the models were completely adjusted for covariates, CIMT was significantly associated with HF in the 4th quartile among participants with NFG (HR 1.73, 95%CI: 1.13 – 2.63) and IFG (HR 1.90, 95%CI: 1.14 – 3.17), but not among those with T2D (HR 1.41, 95%CI: 0.71 – 2.79). The CIMT-HF association was weaker among participants with T2D.

4. DISCUSSION

In this study we investigated and compared the association between CIMT and incident HF in normal individuals (NFG), those with pre-diabetes (IFG) and with T2D. Our findings showed that individuals with T2D had a remarkably high absolute risk of incident HF compared to those with NFG and IFG, irrespective of CIMT quartile. However, the hazard ratios for incident HF appeared stronger among participants with NFG than among those with abnormal glucose metabolism (IFG and T2D).

Carotid IMT was significantly increased in participants with T2D than those with IFG and NFG. Our finding is consistent with results from previously published studies. Temelkova-Kurktschiev and colleagues reported that common carotid artery (CCA) IMT was increased in subjects with hyperglycaemia in the non-diabetic range.[19] Similarly, in the Insulin Resistance Atherosclerosis Study, CCA IMT was considerably greater among subjects with diagnosed T2D.[20] Carotid IMT may have been increased in persons with abnormal glucose metabolism, compared to those with a NFG, for a number of reasons including a direct effect of chronic hyperglycaemia on the carotid artery walls or an indirect effect of diabetes-related metabolic abnormalities. Chronic hyperglycaemia, advanced glycosylation end-products, [21, 22], and the acceleration of lipoprotein oxidation, [23] might increase the risk of carotid atherosclerosis in these individuals. In addition, T2D is also associated with CHD risk factors, including dyslipidaemia and hypertension, [20] both of which have been linked to greater CIMT.

A number of studies have examined the association between diabetes status and incident HF. Thrainsdottir and colleagues, [5] in a study involving 19,381 subjects aged 33–84 years,

showed a strong association between HF and diabetes status; HF was diagnosed in 3.2% of subjects with NGT, 6.0% with IFG and 11.8% with T2D. Similar findings have been reported in the Strong Heart Study, [6] and in an age- and sex-matched elderly sample of 9,591 individuals.[24] The increased risk of HF in persons with T2D may be due to a direct effect of chronic hyperglycaemia on myocardial mechanics, independent of coronary artery disease, as evidenced by subtle abnormalities of early LV relaxation.[25, 26] The degree of hyperglycaemia and long-term diabetes control (measured by HbA1c level) was directly related to the incidence of HF in the ARIC study[27] and Kaiser Permanente Diabetes Registry.[28] Another potential explanation for the increased risk of HF may be due to the strong association between T2D and CHD. In the EPICAL study, Zannad and colleagues reported T2D prevalence of 33% and 20% in HF patients with and without CHD, respectively.[29]

Given an increased incidence of HF in persons with T2D, a greater thickness of the carotid intima-media junction in this population, and a strong association between CIMT and HF in general, one would suspect that CIMT would be a strong predictor of HF in persons with T2D, compared to those without the condition. Interestingly in the present analysis, after accounting for demographic and CVD risk factors, the CIMT – HF association appeared stronger among participants with NFG, despite a substantially higher absolute risk of HF among participants with T2D. Each unit SD increase in CIMT was associated a 27% increase in the risk of HF for participants with NFG, 18% for those with IFG, and 12% for those with T2D ($p_{\text{interaction}} = 0.015$). This suggests that in persons with T2D, CIMT may not add considerable predictive value for HF beyond the risks already accounted for by diabetes. The weaker association between CIMT and HF among participants with diabetes may be explained in part by the structural and functional changes of the myocardium, not attributable to hypertension or CHD.[30] As many as 52%–60% of patients with optimal control of diabetes have asymptomatic diastolic dysfunction.[31, 32] The most likely cause of diastolic dysfunction is the formation of reactive oxygen species, induced by advanced glycaemic end-products. This leads to the deposition of collagen in the myocardium, fibrosis, insulin resistance and subsequent left ventricular hypertrophy.[33, 34] Chronic hyperglycemia also has a deleterious effect on the myocardium, favouring the development of myocellular hypertrophy and myocardial fibrosis.[35] Myocardial damage unexplained by CAD is also thought to be mediated by microvascular dysfunction, equally leading to myocardial injury, fibrosis and hypertrophy.[35, 36]

Another plausible explanation for weaker association between CIMT and HF among participants with diabetes could be a stronger association between the CVD risk factors and IMT in other vascular beds (such as femoral artery) compared to CIMT.[37, 38] In a study by Vaudo and colleagues, [38] larger associations between IMT and CVD risk factors (low HDL, hypertriglyceridemia, hyperglycemia, hyperinsulinemia) were observed for femoral IMT compared to CIMT. Of note, insulin level (a measure of insulin resistance, a core component of T2D) was associated with femoral IMT, but not CIMT. This selective effect of pro-atherogenic factors on the femoral artery may highlight the importance of this vascular bed in assessing CVD outcomes, including HF in persons with T2D. As such, it may be worth exploring additional vascular beds to better understand the predictive value of IMT in HF among persons with T2D.

Carotid atherosclerosis is an independent risk factor for HF[9, 10] and CHD.[39] In addition to the well-known associations between CHD and HF, our analysis showed that CIMT is a predictor of HF in participants with and without diabetes independent of the effects of prevalent and incident CHD and hypertension. One explanation for the independent effects of CIMT on HF could be carotid arterial stiffening, triggered by structural changes in the vessel wall, which can lead to increased pressure afterload and diastolic dysfunction.[40] Another potential explanation could be the presence of an association between increased CIMT, a reduction in myocardial flow reserve, [41] and regional LV myocardial dysfunction. [8] Likewise, the degree of long-term glycaemic control (measured by HbA1c level) is equally associated with a reduction in myocardial flow reserve, [42] suggesting that the mechanisms involved in the independent association of CIMT and HF, especially in persons with T2D, may be complex.

Our study has some limitations that should be discussed. First, HbA1c level and oral glucose tolerance testing (OGTT) were not used in defining cases of T2D as these parameters were not measured during the first ARIC visit, and as such we may have misclassified participants. A previous report in ARIC study participants without diabetes showed that the association between HbA1c (from the second visit) and HF was stronger than that of fasting glucose.[27] Therefore, we would expect a stronger association if HbA1c was used as a criterion to define T2D. Second, because we abstracted HF cases via hospital discharge codes and death registers, these may have been severe cases of the condition. This might raise the question of the association between CIMT and milder forms of HF, managed in an outpatient setting. However, reports of an association between CIMT and reduced systolic and diastolic myocardial strain suggest that there would be an association between CIMT and mild HF.[8] Third, we did not stratify our results by HF subtype (HFrEF versus HFpEF) to fully explore the mechanisms through which CIMT is associated with HF. Finally, because the ARIC study cohort was middle-aged at baseline and biracial, our findings may not apply to other age and race/ethnic groups. The sheer size of our cohort and incident HF cases (n = 2008), and the long duration of follow up (over 2 decades) give credence to the strengths of our study. Data on the predictive role of CIMT in HF among individuals of differing diabetes status is very limited. Our findings are significant and add to the literature in suggesting that, in terms of HF risk prediction, among individuals with T2D, vascular beds other than the carotid artery should be explored.

In conclusion, among individuals with T2D, despite the substantially high absolute risk of HF across all levels of CIMT, the independent association between CIMT and incident HF appeared weaker compared to individuals without T2D. This suggests that CIMT may be a better predictor of HF risk among those without T2D than those with the condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Association between carotid IMT and heart failure stronger in persons without diabetes.
- Rates of heart failure disproportionately higher in persons with diabetes.
- No black-white differences in association between carotid IMT and heart failure across diabetes status.

Figure 1.

Crude Heart Failure Incidence Rates per 1,000 person-years by Quartiles of Carotid Intima-Media Thickness and by Diabetes Status. IFG indicates impaired fasting glucose; NFG, normal fasting glucose; T2D, type 2 diabetes.

Figure 2. Cumulative Incidence of Heart Failure by Diabetes Status. Log rank $p < 0.0001$ indicates a significant difference in cumulative hazard between the 3 groups. IFG indicates impaired fasting glucose; NFG, normal fasting glucose; T2D, type 2 diabetes.

Table 1

Demographic and Clinical Characteristics of Study Participants by Diabetes Status

Characteristic	Diabetes Status		
	Normal Fasting Glucose (N = 7,591)	Impaired Fasting Glucose (N = 4,569)	Type 2 Diabetes (N = 1,430)
Age, years	53.5 ± 5.7	54.6 ± 5.7	55.7 ± 5.7
Women, n (%)	4,631 (61.0)	2,053 (44.9)	749 (52.3)
White, n (%)	5,869 (77.3)	3,520 (77.0)	838 (58.6)
Hypertension, n (%)	1,815 (23.9)	1,697 (37.2)	808 (56.5)
Systolic blood pressure, mmHg	118 ± 18	123 ± 18	129 ± 20
Diastolic blood pressure, mmHg	72 ± 11	75 ± 11	75 ± 12
Blood pressure medication, n (%)	1,508 (19.9)	1,399 (30.6)	712 (49.8)
Body mass index, kgm ⁻²	26.2 ± 4.6	28.1 ± 4.9	30.5 ± 5.6
Waist circumference, cm	92.8 ± 12.6	98.7 ± 12.6	105.0 ± 13.7
Completed at least college	2,920 (38.5)	1,593 (34.9)	381 (26.6)
Current smoker, n (%)	2,075 (27.3)	1,140 (24.9)	327 (22.9)
Current drinker, n (%)	4,383 (57.9)	2,828 (62.0)	550 (38.7)
Total Cholesterol, mmol/l	5.5 ± 1.1	5.6 ± 1.1	5.7 ± 1.2
LDL Cholesterol, mmol/l	3.5 ± 1.0	3.7 ± 1.0	3.7 ± 1.1
HDL Cholesterol, mmol/l	1.4 ± 0.5	1.3 ± 0.4	1.2 ± 0.4
Triglycerides, mmol/l [†]	1.14 ± 0.21	1.37 ± 0.21	1.70 ± 0.25
Fasting plasma glucose, mg/dL	92.7 ± 5.3	108.0 ± 5.9	184.5 ± 80.8
Lipid-lowering medication, n (%)	1,228 (16.3)	1,143 (25.1)	566 (40.0)
Carotid IMT, mm	0.70 ± 0.17	0.75 ± 0.19	0.79 ± 0.20
Incident HF, n (%)	834 (11.0)	646 (14.1)	528 (36.9)
Prevalent CHD, n (%)	224 (3.0)	216 (4.8)	115 (8.1)
Incident CHD, n (%)	710 (9.4)	584 (12.8)	433 (30.3)

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

[†]Results for triglycerides are presented as geometric mean ± SD. CHD indicates coronary heart disease; HDL, high-density lipoprotein; HF, heart failure; IMT, intima-media thickness; LDL, low-density lipoprotein.

Table 2

Adjusted Hazard Ratios (95% CI) for Incident Heart Failure per unit SD (0.18 mm) increase in Carotid Intima-Media Thickness and by Diabetes Status.

Models		HR (95% CI) by Diabetes Status		
		Normal Fasting Glucose	Impaired Fasting Glucose	Type 2 Diabetes
Number of events		834	646	528
Model 1	HR (95% CI)	1.44 (1.38, 1.52)	1.32 (1.25, 1.40)	1.22 (1.14, 1.31)
Model 2	HR (95% CI)	1.27 (1.20, 1.35)	1.19 (1.12, 1.26)	1.11 (1.04, 1.19) *
Model 3	HR (95% CI)	1.27 (1.20, 1.35)	1.18 (1.11, 1.25)	1.12 (1.05, 1.21) *

* P < 0.01, all other P < 0.001.

Model 1: adjusted for age, gender, race, level of education. Model 2: adjusted for covariates in model 1 and hypertension medication, systolic and diastolic blood pressure, waist circumference, HDL-cholesterol, LDL-cholesterol, triglycerides, lipid-lowering medication, smoking status and amount in pack-years, alcohol consumption, and serum creatinine. Model 3: adjusted for covariates in model 2, plus prevalent and incident CHD.

Table 3

Adjusted Hazard Ratios (95% CI) for Incident Heart Failure by Quartiles of Carotid Intima-Media Thickness and by Diabetes Status.

Diabetes Status	Quartiles of CIMT			
	CIMT < 0.62	CIMT 0.62 – 0.69	CIMT 0.70 – 0.79	CIMT > 0.79
Normal Fasting Glucose (N=7,591)				
N	2,373	2,001	1,678	1,539
Model 1: CIMT + demographic variables	Ref.	1.13 (0.90–1.40)	1.39 (1.12–1.73) [§]	2.76 (1.86–4.10) [‡]
Model 2: Model 1 + clinical and biologic variables	Ref.	0.96 (0.77–1.18)	1.02 (0.81–1.25)	1.82 (1.19–2.75) [§]
Model 3: Model 2 + interim CHD	Ref.	0.97 (0.76–1.21)	1.00 (0.80–1.26)	1.73 (1.13–2.61) [*]
Impaired Fasting Glucose (N=4,569)				
N	949	1,124	1,148	1,348
Model 1: CIMT + demographic variables	Ref.	1.48 (1.10–1.98) [§]	1.63 (1.23–2.17) [‡]	2.82 (1.73–4.60) [‡]
Model 2: Model 1 + clinical and biologic variables	Ref.	1.39 (1.03–1.88) [*]	1.30 (0.97–1.73)	2.0 (1.20–3.34) [§]
Model 3: Model 2 + interim CHD	Ref.	1.35 (1.0–1.81)	1.28 (0.95–1.73)	1.89 (1.13–3.16) [*]
Type 2 Diabetes (N=1,430)				
N	185	295	393	557
Model 1: CIMT + demographic variables	Ref.	1.23 (0.87–1.74)	1.33 (0.96–1.85)	1.90 (0.99–3.66)
Model 2: Model 1 + clinical and biologic variables	Ref.	1.04 (0.73–1.51)	1.09 (0.78–1.56)	1.57 (0.78–3.11)
Model 3: Model 2 + interim CHD	Ref.	1.01 (0.71–1.46)	1.06 (0.75–1.52)	1.40 (0.70–2.78)

^{*} P < 0.05;

[§] P < 0.01;

[‡] P < 0.001.

Demographic variables: age, gender, race, level of education; clinical and biologic variables: hypertension medication, systolic and diastolic blood pressures, waist circumference, HDL cholesterol, LDL cholesterol, triglycerides, lipid lowering medication, smoking status and amount in pack-years, alcohol consumption, and serum creatinine. CHD indicates coronary heart disease; CIMT, carotid intima-media thickness; Q, quartile.