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ORIGINAL RESEARCH

Microvascular Disease and Incident Heart Failure Among Individuals With Type 2 Diabetes Mellitus

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BACKGROUND: Microvascular disease (MVD) is a potential contributor to the pathogenesis of diabetes mellitus–related cardiac dysfunction. However, there is a paucity of data on the link between MVD and incident heart failure (HF) in type 2 diabetes mellitus. We examined the association of MVD with incident HF in adults with type 2 diabetes mellitus.

METHODS AND RESULTS: A total of 4095 participants with type 2 diabetes mellitus and free of HF were assessed for diabetes mellitus–related MVD including nephropathy, retinopathy, or neuropathy at baseline in the Look AHEAD (Action for Health in Diabetes) study. Incident HF events were prospectively assessed and adjudicated using hospital and death records. Cox models were used to generate hazard ratios and 95% CIs for HF. Of 4095 participants, 34.8% (n=1424) had MVD, defined as the presence of ≥1 of nephropathy, retinopathy, or neuropathy at baseline. Over a median of 9.7 years, there were 117 HF events. After adjusting for relevant confounders, participants with MVD had a 2.5-fold higher risk of incident HF than those without MVD (hazard ratio, 2.54; 95% CI, 1.73–3.75). This association remained significant after additional adjustment for interval development of coronary artery disease (hazard ratio, 2.42; 95% CI, 1.64–3.57). The hazard ratios for HF by type of MVD were 2.22 (95% CI, 1.51–3.27), 1.30 (95% CI, 0.72–2.36), and 1.33 (95% CI, 0.86–2.07) for nephropathy, retinopathy, and neuropathy, respectively.

CONCLUSIONS: MVD is associated with an excess HF risk in individuals with type 2 diabetes mellitus after adjusting for other known risk factors. Our findings underscore the contribution of MVD to the development of diabetes mellitus–related HF.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00017953.

Key Words: heart failure ■ microvascular disease ■ type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) and heart failure (HF) are highly prevalent, and each is associated with a significant burden of morbidity, mortality, and costs.[1,2] T2DM and HF often occur together, and extant evidence suggests a 2- to 4-fold higher risk of HF in adults with T2DM compared with those without T2DM, independently of other cardiovascular risk factors including high blood pressure (BP), hypercholesterolemia, and coronary artery disease (CAD).[3,4] Animal studies have helped to define diabetes mellitus–related cardiac dysfunction,[5,6] and suggested several pathways linking diabetes mellitus to HF, which include microvascular dysfunction. Microvascular disease (MVD) is the hallmark of diabetes mellitus, with retinopathy serving as the basis of its definition.[7] MVD's contribution to HF may be independent of CAD, especially as functional studies have shown an alteration of the myocardial microvasculature among individuals with diabetes mellitus in the absence of CAD.[8–11] Although a few population-based studies have explored the link between individual microvascular complications of diabetes mellitus and HF risk in T2DM,[11,12] there is overall

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CLINICAL PERSPECTIVE

What Is New?

- Data on the relation of microvascular disease with incident heart failure in diverse cohorts of adults with type 2 diabetes mellitus are scant.
- Microvascular disease was highly prevalent (34.8%) among individuals with type 2 diabetes mellitus.
- Microvascular disease was associated with increased risk of heart failure, independently of traditional heart failure risk factors including coronary artery disease.

What Are the Clinical Implications?

- Our findings highlight the contribution of microvascular disease to the development of heart failure among people with type 2 diabetes mellitus.

Nonstandard Abbreviations and Acronyms

AHEAD	Action for Health in Diabetes
MNSI	Michigan Neuropathy Screening Instrument
MVD	microvascular disease
T2DM	type 2 diabetes mellitus

a paucity of epidemiological data on the relationship between MVD and incident HF in T2DM.

We conducted an analysis of the prospective data from the Look AHEAD (Action of Health in Diabetes) study to evaluate the associations of MVD), assessed in multiple vascular beds, and incident HF in a large sample of individuals with T2DM.

METHODS

Study Design

The data used for the analyses are available through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository. The Look AHEAD study was a randomized double-blind clinical trial that enrolled 5145 participants from August 2001 to April 2004 across 16 clinical centers in the United States.[13,14] Participants were randomly assigned to participate in an intensive lifestyle intervention (intervention group) or to receive diabetes mellitus support and education (control group). Eligible participants met the following criteria at baseline: age 45 to 76 years; self-reported diagnosis of T2DM verified through measured glucose levels, use of antidiabetic medication, or a physician's report; body mass index of ≥25 kg/m^2 (or ≥27 kg/m^2 if patients were on insulin); glycosylated hemoglobin ≤11%; systolic BP <160 mm Hg; diastolic BP <100 mm Hg; triglyceride levels <600 mg/dL; the ability to complete a valid maximal exercise test, indicating that it was safe to exercise; as well as an established relationship with a primary care provider.[13,14]

For the current analysis, we excluded participants with consent restrictions (n=244), history of HF or atherosclerotic cardiovascular disease, defined as history of prior myocardial infarction or stroke at baseline (n=691), and those with missing data on nephropathy, retinopathy, and/or neuropathy (n=115). After these exclusions, 4095 participants were included in our analyses.

The research protocol was approved by the institutional review board at each participating center, and each participant gave an informed consent.

Assessment of Microvascular Disease

Urine albumin and creatinine were measured on spot urine. Serum and urine creatinine were assayed by the Jaffa rate method on the Hitachi 917 autoanalyzer.[14] The estimated glomerular filtration rate calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.[15] Nephropathy was defined as urine albumin–creatinine ratio ≥0.03 and/or estimated glomerular filtration rate <60 mL/min per 1.73 m^2.

The presence of neuropathy was assessed using the Michigan Neuropathy Screening Instrument (MNSI) questionnaire administered at baseline.[16] The MNSI questionnaire consists of 15 questions, 13 of which have an affirmative response scored as 1 point, and 2 of which have a negative response scored as 1 point, giving a possible maximal score of 15 points. Neuropathy was defined on the basis of a MNSI score ≥4, because this cutoff has been shown to have a good performance at diagnosing peripheral neuropathy.[16]

The presence of retinopathy was based on a self-report of a doctor diagnosis, using the question: "Have you ever been told that diabetes mellitus has affected the back of your eye, that is, the retina? (Do not include treatment for cataracts or glaucoma)."

We defined MVD as the presence of at least one of the following: nephropathy, retinopathy, neuropathy.

Ascertainment of Incident Heart Failure Events

Participants were followed from baseline through annual visits and semiannual telephone calls. HF events were classified by an Events Adjudication Committee that reviewed all relevant medical records and death certificates to confirm HF events.[13,14,17] Each case was classified into one of the following groups: definite or

possible acute decompensated HF, chronic stable HF, HF unlikely, or unclassifiable. Incident HF events were defined as the first hospitalization for definite or possible acute decompensated HF.[18]

Assessment of Covariates

Data on covariates including age, sex, race/ethnicity, duration of diabetes mellitus, history of cardiovascular disease, medication use, current smoking, and alcohol use were obtained from each participant at baseline using standardized questionnaires.[13,14,17] BP and anthropometric measures were obtained by trained staff using standardized methods.[13,14,17] Fasting plasma glucose was assayed using the glucokinase method. Glycosylated hemoglobin was measured by a dedicated ion exchange high-performance liquid chromatography instrument (Variant II; Bio-Rad Laboratories).[13,14,17] Total cholesterol and triglyceride were measured enzymatically using methods standardized to the Centers for Disease Control and Prevention reference methods.[14,19] High-density lipoprotein cholesterol was measured by the treatment of whole plasma with dextran sulfate-Mg^{2+} to precipitate all of the apolipoprotein B–containing lipoproteins.[20] Low-density lipoprotein cholesterol concentrations were calculated using the Friedewald equation.[21]

Statistical Analysis

We compared the baseline characteristics of participants by incident HF status using the *t* test, Kruskal-Wallis test, or the χ^2 test, as appropriate. The time-to-event distributions for incident HF by MVD status were assessed using the Kaplan-Meier curve and compared using the log-rank test. Incidence rates per 1000 person-years were calculated by dividing the cumulative number of events by all at-risk person-years during follow-up. The person-years were estimated from the baseline evaluation to the date of incident HF event, date of death, or September 14, 2012 (the trial's termination date), whichever occurred first. We used Cox proportional hazards models to generate hazard ratios (HRs) and 95% CIs relating MVD to the outcome. We evaluated the proportional hazards assumption using formal testing based on Schoenfeld residuals.[22] Similar analyses were performed relating the outcome to each individual type of MVD (nephropathy, retinopathy, and neuropathy). We also performed stratified analyses by race/ethnicity. We further explored the effect of neuropathy by evaluating the association of the MNSI score modeled as a continuous variable with incident HF.

We constructed regression models in a hierarchical fashion. Model 1 adjusted for age, sex, race/ethnicity, randomization arm. Model 2 included variables in Model 1 plus current smoking, alcohol drinking, body mass index, systolic BP, use of antihypertensive medications, ratio of total to high-density lipoprotein cholesterol, glycosylated hemoglobin, and duration of diabetes mellitus. Model 3 included variables in Model 2 plus interval development of CAD during follow-up.

A 2-sided *P* value of <0.05 was considered statistically significant for all analyses. All analyses were performed using Stata 14.2 (StataCorp, College Station, TX).

RESULTS

Baseline Characteristics

Table 1 and Table S1 display the baseline characteristics of participants. The study sample consisted of 4095 participants (mean age, 58.3 years [SD, 6.6 years]; 61.9% women). Of the entire sample, 34.8% of participants had MVD (n=1424), 18.2% had nephropathy (n=745), 6.9% had retinopathy (n=284), and 16.6% had neuropathy (n=681). The participants with MVD were older, more frequently Hispanic, and they had higher body mass index, waist circumference, triglycerides, systolic BP, glycosylated hemoglobin, duration of diabetes mellitus, albumin–creatinine ratio, and MSNI score. They also had a lower estimated glomerular filtration rate, and were more likely to use antihypertensive medications and insulin (Table 1).

Incident Heart Failure by Microvascular Disease Status

During a median follow-up of 9.7 years (interquartile range, 8.9–10.3 years), 117 participants experienced a HF event (incidence rate, 3.1; 95% CI, 2.6–3.7; over person-years). In unadjusted comparisons, participants with MVD had higher cumulative risks of developing HF compared with those without MVD (Table 2 and Figure, *P* value log rank <0.001).

After controlling for age, sex, race/ethnicity, treatment arm, body mass index, current smoking, alcohol consumption, use of antihypertensive medication, systolic BP, ratio of total to high-density lipoprotein cholesterol, glycosylated hemoglobin, and duration of diabetes mellitus, MVD was associated with increased risk of incident HF (HR, 2.54; 95% CI, 1.73–3.75; *P*<0.001). Additional adjustment for interval development of CAD did not affect the magnitude and significance of the association significant (HR, 2.42; 95% CI, 1.64–3.57; *P*<0.001).

Incident Heart Failure by Individual Type of Microvascular Disease

We assessed the risks of HF by type of MVD. For each type of MVD assessed individually, the cumulative risk of developing HF was higher among those with the specific MVD compared with those without it (Figure).

Table 1. Characteristics of Participants by Microvascular Disease Status at Baseline in the Look AHEAD Study

	Entire Sample	No Microvascular Disease	Microvascular Disease	*P* Value
No.	4095	2671	1424	…
Age, y	58.3 (6.6)	57.9 (6.5)	59.0 (6.8)	<0.001
Women, %	62.0	62.4	61.2	0.446
Race/ethnicity, %				0.021
White	64.7	64.7	64.5	
Non-Hispanic Black	17.1	18.1	15.2	
Hispanic	14.8	13.8	16.5	
Other race/ethnicity	3.5	3.3	3.8	
Treatment assignment, %				0.386
Diabetes mellitus support and education	50.2	49.7	51.1	
Intensive lifestyle intervention	49.8	50.3	48.9	
Body mass index, kg/m^2	36.0 (5.9)	35.8 (5.9)	36.5 (6.0)	<0.001
Waist circumference, cm	113.6 (14.1)	112.8 (13.9)	115.6 (14.2)	<0.001
Current smoking, %	4.0	3.6	4.8	0.065
Alcohol drinking, %	32.7	33.1	32.0	0.472
Systolic blood pressure, mm Hg	129.0 (16.9)	127.8 (16.2)	131.3 (17.8)	<0.001
Diastolic blood pressure, mm Hg	70.4 (9.5)	70.5 (9.4)	70.3 (9.6)	0.554
Hypertension, %	85.6	82.8	90.8	<0.001
Use of antihypertensive medication, %	70.9	66.3	79.6	<0.001
Glycosylated hemoglobin, %	7.2 (1.2)	7.2 (1.1)	7.4 (1.2)	<0.001
Duration of diabetes mellitus, y	5.0 (2.0–9.0)	4.0 (2.0–8.0)	6.0 (3.0–11.0)	<0.001
Use of insulin, %	13.8	10.4	20.4	<0.001
Total cholesterol, mg/dL	193.1 (36.8)	192.8 (35.9)	193.7 (38.3)	0.480
HDL-cholesterol, mg/dL	43.9 (11.9)	44.2 (11.9)	43.3 (12.0)	0.028
LDL-cholesterol, mg/dL	114.4 (31.9)	115.2 (31.4)	112.9 (32.9)	0.030
Total/HDL-cholesterol ratio	4.7 (1.5)	4.6 (1.5)	4.8 (1.6)	0.005
Triglycerides, mg/dL	152 (107–218)	146 (103–207)	164 (113–237)	<0.001
Albumin–creatinine ratio	0.008 (0.005–0.017)	0.007 (0.005–0.011)	0.018 (0.007–0.057)	<0.001
eGFR, mL/min per 1.73 m^2	91.1 (15.8)	92.7 (13.9)	88.1 (18.5)	<0.001
MNSI score	1 (0–3)	1 (0–2)	3 (1–5)	<0.001

Data are presented as mean (standard deviation), median (interquartile range), or proportion (%) as appropriate.

AHEAD indicates Action for Health in Diabetes; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and MNSI, Michigan Neuropathy Screening Instrument.

After adjusting for the relevant confounders (Table 3), nephropathy was associated with increased risk of incident HF (HR, 2.21; 95% CI, 1.50–3.26). This association remained significant after adjusting for interval CAD at follow-up (HR, 2.22; 95% CI, 1.51–3.27).

The adjusted HR for incident HF associated with the presence of retinopathy was 1.34 (95% CI, 0.74–2.44); the HR was 1.30 (95% CI, 0.72–2.36) after additionally accounting for interval CAD (Table 3).

The adjusted HR for incident HF related to neuropathy was 1.57 (95% CI, 1.02–2.41) in the minimally adjusted model. When evaluated on a continuous scale using the MNSI score (Table 4), the HR for incident HF per 1–standard deviation increment in the MNSI score was 1.23 (95% CI, 1.04–1.44). Upon accounting for interval CAD during follow-up, the HR for HF was 1.13 (95% CI, 0.96–1.34; Table 4).

In the analyses stratified by race/ethnicity, among White participants, the presence of MVD, nephropathy, and neuropathy were each associated with higher risks of incident HF; whereas among non-White participants, only MVD and nephropathy were associated with incident HF in the maximally adjusted model (Table S2).

Table 2. Rates and Hazard Ratios for Incident Heart Failure by Microvascular Disease Status at Baseline in the Look AHEAD Study

	Microvascular Disease		*P* Value
	Absent	Present	
No events/no at risk	44/2671	73/1424	…
Person-years	24 765.1	12 795.6	…
IR (95% CI) per 1000 person-years	1.8 (1.3–2.4)	5.7 (4.5–7.2)	…
Model, hazard ratio (95% CI)			
Model 1	Reference	3.02 (2.08–4.40)	<0.001
Model 2	Reference	2.54 (1.73–3.75)	<0.001
Model 3	Reference	2.42 (1.64–3.57)	<0.001

Model 1 is adjusted for age, sex, race/ethnicity, and randomization arm. Model 2 includes variables in Model 1 with further adjustment for body mass index, current smoking (yes/no), alcohol drinking (ounces per week), systolic blood pressure, use of antihypertensive medications (yes/no), ratio of total to high-density lipoprotein cholesterol, glycosylated hemoglobin, and duration of diabetes mellitus. Model 3 includes variables in Model 2 with additional adjustment for interval development of coronary artery disease (as a time-dependent covariate). AHEAD indicates Action for Health in Diabetes; and IR, incidence rate.

Sensitivity Analysis

We tested the robustness of our results by performing additional adjustment for use of insulin. This did not affect the magnitude or significance of our results (Table 5).

DISCUSSION

This study comprehensively evaluated the association of MVD, assessed in multiple vascular beds, with incident HF in a large sample of individuals with T2DM. We found that overall MVD in each microvascular territory was associated with an increased risk of incident HF, after accounting for the degree of glycemic control, duration of diabetes mellitus, BP, and CAD. The association of MVD and HF was mainly driven by nephropathy, although neuropathy was associated with incident HF among White participants. Our findings point to the importance of accounting for MVD in the assessment of HF risk within the framework of T2DM.

Our study is one of a few to comprehensively assess the effect of MVD in several territories on HF incidence in individuals with T2DM. Previous studies that assessed the influence of MVD on HF occurrence were limited in several ways, because these included the assessment of only one microvascular bed,[23–27] were not focused on people with T2DM,[24,28] or included samples of mainly White individuals.[29–31] Our results are consistent with prior reports from the general population

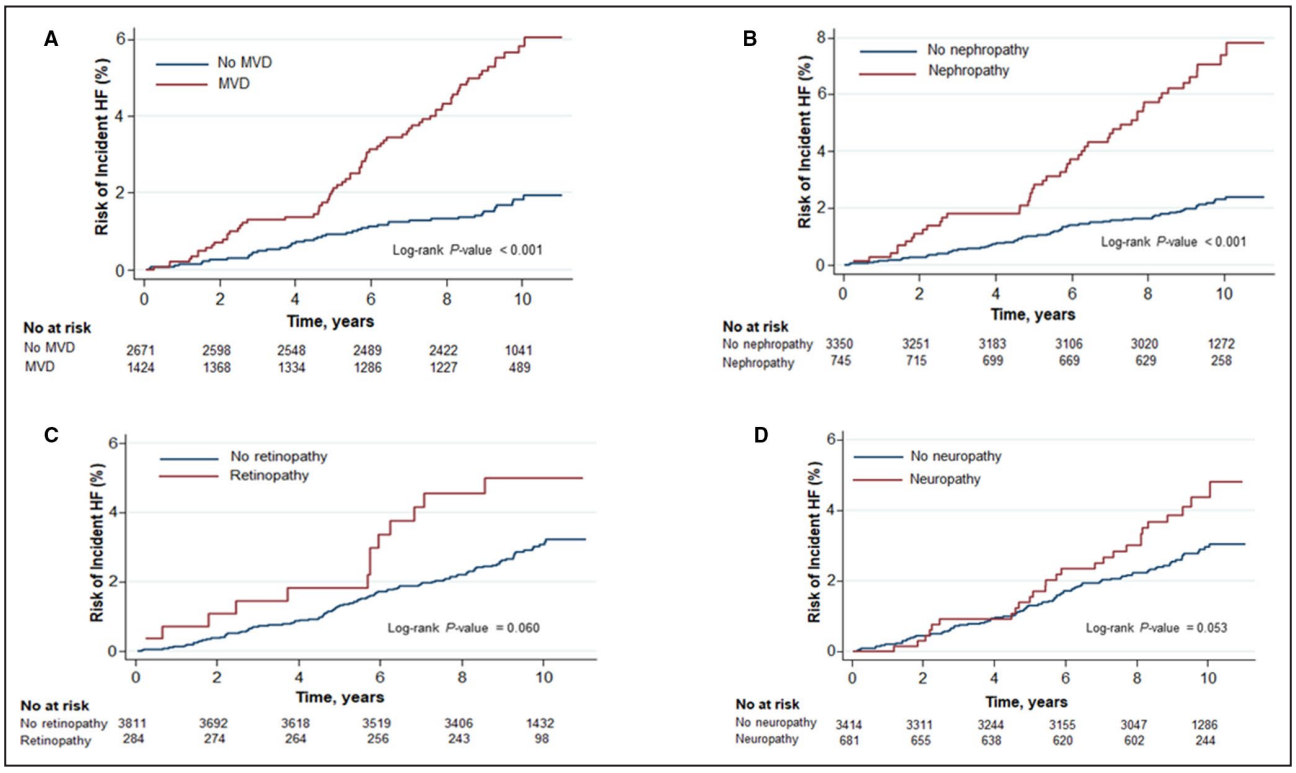

Figure. Cumulative hazards of incident heart failure (HF) by evidence of microvascular disease (MVD) (A), nephropathy (B), retinopathy (C), and neuropathy (D) in the Look AHEAD (Action of Health in Diabetes) study.

Table 3. Rates and Hazard Ratios for Incident Heart Failure by Individual Type of Microvascular Disease at Baseline in the Look AHEAD Study

	Nephropathy		Retinopathy		Neuropathy	
	Absent	Present	Absent	Present	Absent	Present
No events/no at risk	69/3350	48/745	104/3811	13/284	90/3414	27/681
Person-years	30905.9	6654.9	35012.8	2547.9	31 376.0	6184.7
IR (95% CI) per 1000 person-years	2.2 (1.8–2.8)	7.2 (5.4–9.6)	3.0 (2.5–3.6)	5.1 (3.0–8.8)	2.9 (2.3–3.5)	4.4 (3.0–6.4)
Model, hazard ratio (95% CI)						
Model 1	Reference	2.88 (1.99–4.19)†	Reference	1.59 (0.89–2.83)	Reference	1.57 (1.02–2.41)*
Model 2	Reference	2.21 (1.50–3.26)†	Reference	1.34 (0.74–2.44)	Reference	1.46 (0.94–2.25)
Model 3	Reference	2.22 (1.51–3.27)†	Reference	1.30 (0.72–2.36)	Reference	1.33 (0.86–2.07)

Model 1 adjusted for age, sex, race/ethnicity, and randomization arm. Model 2 includes variables in Model 1 with further adjustment for body mass index, current smoking (yes/no), alcohol drinking (ounces per week), systolic blood pressure, use of antihypertensive medications (yes/no), ratio of total to high-density lipoprotein cholesterol, glycosylated hemoglobin, and duration of diabetes mellitus. Model 3 includes variables in Model 2 with additional adjustment for interval development of coronary artery disease (as a time-dependent covariate). AHEAD indicates Action for Health in Diabetes; and IR, incidence rate.

*$P<0.05$.

†$P<0.001$.

describing an increased HF risk among individuals with nephropathy[24–27] or retinopathy.[28] Likewise, our findings corroborate prior studies of people with T2DM, although limited in number, which showed an increased risk of HF associated with retinopathy in a 1021 sample of US adults.[23] Similarly, our results are in agreement with prior reports that found that MVD increased the risk for HF hospitalizations in people with T2DM, although these studies were limited by their inclusion of a majority of White[29–32] or Asian individuals.[33]

Several mechanisms could explain the positive association between MVD and incident HF in people with T2DM. A possible mechanism is related to structural myocardial microvascular changes among individuals with diabetes mellitus.[11,34] High glucose exposure leads to the formation of advanced glycation end-product from cross-linked collagen molecules that may deposit in arteriolar walls and endothelial cells.[34,35] Deposition of these products in arterioles have been linked to microvascular remodeling, capillary basement membrane thickening, and microaneurysms formation with ensuing alterations in nitric oxide production.[34] Endothelial damage and reduced nitric oxide availability results in endothelial dysfunction, which leads to a lower coronary blood flow reserve and cardiac hypertrophy–diastolic failure.[34,36] Other mechanisms include the activation of protein kinase C (a family of serine/threonine-related protein kinases) pathways in various tissues, which has been specifically shown to be a driving factor in diabetes mellitus nephropathy or retinopathy, for example.[37] Additional mechanisms, include the production of toxic metabolites, such as the advanced glycation end products and redox products, as well as the alteration of osmols and redox potential through activation of the polyol pathway.[37] Another potential mechanism might be linked to cardiac autonomic neuropathy. In healthy individuals, sympathetic stimulation results in vasodilation of coronary vessels, which improves left ventricle systole and diastole.[34,35] Cardiac autonomic neuropathy in diabetes mellitus leads to sympathetic denervation, exhaustion of myocardial catecholamine, and impairment in cardiac sympathetic nerve fibers. These processes have been shown to increase the rates of both systolic and diastolic HF.[34,35,38] Peripheral neuropathy served as a proxy of cardiac autonomic neuropathy in our study, as it tends to track with peripheral neuropathy among individuals with T2DM.[39]

Our findings of the predominance of the effect of nephropathy in the occurrence of HF could have many explanations. On one hand, chronic kidney disease may be the sign of significantly advanced disease with a higher prevalence of traditional risk factors than subjects with diabetes mellitus with chronic kidney disease (and thus associated with a higher burden of cardiovascular

Table 4. Hazard Ratios for Incident Heart Failure According to the Michigan Neuropathy Screening Instrument Score in the Look AHEAD Study

	Hazard Ratio (95% CI)	*P* Value
Model 1	1.23 (1.04–1.44)	0.014
Model 2	1.17 (1.00–1.39)	0.058
Model 3	1.13 (0.96–1.34)	0.154

Hazard ratios are reported per 1–standard deviation increment in the Michigan Neuropathy Screening Instrument Score.

Model 1 adjusted for age, sex, race/ethnicity, and randomization arm. Model 2 includes variables in Model 1 with further adjustment for body mass index, current smoking (yes/no), alcohol drinking (ounces per week), systolic blood pressure, use of antihypertensive medications (yes/no), ratio of total to high-density lipoprotein cholesterol, glycosylated hemoglobin, and duration of diabetes mellitus. Model 3 includes variables in Model 2 with additional adjustment for interval development of coronary artery disease (as a time-dependent covariate).

AHEAD indicates Action for Health in Diabetes.

Table 5. Hazard Ratios for Incident Heart Failure by Individual Type of Microvascular Disease at Baseline in the Look AHEAD Study

	Nephropathy		Retinopathy		Neuropathy		Microvascular disease	
	Absent	Present	Absent	Present	Absent	Present	Absent	Present
Hazard ratio (95% CI)	Reference	2.21 (1.50–3.26)*	Reference	1.21 (0.67–2.21)	Reference	1.30 (0.84–2.01)	Reference	2.36 (1.59–3.48)*

Hazard ratio was obtained from multivariable Cox model adjusted for age, sex, race/ethnicity, randomization arm, body mass index, current smoking, alcohol drinking (ounces per week), systolic blood pressure, use of antihypertensive medications (yes/no), ratio of total to high-density lipoprotein cholesterol, glycosylated hemoglobin, duration of diabetes mellitus, interval development of coronary artery disease (as a time-dependent covariate), and use of insulin.

AHEAD indicates Action of Health in Diabetes.

*$P<0.001$.

disease) compared with those with other microvascular complications. Chronic kidney disease may reflect generalized endothelial dysfunction and increased vascular permeability or abnormalities in the coagulation and fibrinolytic systems, or may denote the greater severity of end-organ damage.[40] On the other hand, our assessment of other types of MVD was probably less precise than that of chronic kidney disease.

The implications of our findings are manifold for people with T2DM. Our observations suggest the potential relevance of diabetes mellitus–related microvascular complications in the pathogenesis of diabetes mellitus–related cardiac dysfunction. Our findings point to the need to further examine the additive predictive value of MVD in HF risk stratification among individuals with diabetes mellitus. Prior data on cardiovascular disease risk estimation in diabetes mellitus indicate that the inclusion of retinopathy and/or neuropathy improves outcome discrimination.[41,42] Such an exploration of the incremental predictive value of MVD remains to be conducted specifically for the risk of HF.

The limitations of our study should be acknowledged. First, diabetic retinopathy was assessed by self-report of doctor diagnosis; thus, we might have underestimated the extent of the frequency of retinopathy in our sample, which may have led to an underestimation of the true association between retinopathy and HF.[43] Second, we did not assess the microvasculature in the coronary bed using cardiac positron emission tomography, for example, as was done by Taqueti et al in a small and short study (including only 201 participants observed over 4.1 years) that did not specifically focus on individuals with diabetes mellitus.[44] Such an approach would provide a more direct form of evidence on the impact of myocardial microvascular dysfunction on cardiac remodeling. Third, we did not assess the subtypes of HF, which may be differentially associated with MVD.[33] Our study has several strengths. First, we used a prospective design and a large multiethnic/racial sample of participants. Second, we assessed MVD in multiple vascular territories in contrast to previous studies.[23–28] Third, the presence of neuropathy was assessed using the MNSI, a standardized instrument that has been previously shown to have good performance at detecting peripheral neuropathy in diabetes mellitus.[16] Finally, the adjudication of HF events was standardized, and we conducted robust adjustments for relevant cofounders.

In conclusion, in a large sample of adults with T2DM, we observed that MVD, assessed in multiple vascular beds, is associated with higher risk of incident HF after adjusting of traditional risk factors such as BP or coronary heart disease. Our findings support the notion that microangiopathy is involved in the pathogenesis of HF in T2DM.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics of Participants by Evidence of Incident Heart Failure Over Time in the Look AHEAD Study.

	Entire Sample	No Incident Heart Failure	Incident Heart Failure	*P* Value
N	4095	3978	117	…
Age, years	58.3 (6.6)	58.2 (6.6)	61.2 (6.4)	<0.001
Women, %	61.9	62.3	49.6	0.005
Race/ethnicity, %				0.318
White	64.6	64.7	64.1	
Non-Hispanic Black	17.1	16.9	22.2	
Hispanic	14.8	14.9	10.3	
Other/mixed	3.5	3.5	3.4	
Treatment assignment, %				0.238
Diabetes Support and Education	50.2	50.0	55.6	
Intensive Lifestyle Intervention	49.8	50.0	44.4	
Body mass index, kg/m^2	36.0 (5.9)	36.0 (5.9)	37.6 (6.5)	0.003
Waist circumference, cm	113.6 (14.1)	113.5 (14.0)	119.7 (15.3)	<0.001
Current smoking, %	4.0	4.0	6.0	0.268
Alcohol drinking, %	32.7	32.8	29.9	0.518
Systolic blood pressure, mm Hg	129.0 (16.9)	128.9 (16.8)	134.1 (18.1)	0.001
Diastolic blood pressure, mm Hg	70.4 (9.5)	70.4 (9.5)	71.2 (9.7)	0.387
Hypertension, %	85.6	85.3	93.2	0.018
Use of antihypertensive drug, %	70.9	70.4	86.3	<0.001
Use of ACEI/ARB, %	56.9	56.6	67.8	0.017
Use of beta blocker, %	17.0	16.5	35.0	<0.001
Hemoglobin A_{1C}, %	7.3 (1.2)	7.2 (1.2)	7.6 (1.2)	0.004
Duration of diabetes, years	5.0 (2.0-9.0)	5.0 (2.0-9.0)	6.0 (3.0-11.0)	0.012
Use of insulin, %	13.9	13.5	25.6	0.001
Use of antidiabetic medication, %				
Total cholesterol, mg/dL	193.1 (36.8)	193.3 (36.7)	187.9 (38.6)	0.123
HDL-cholesterol, mg/dL	43.9 (11.9)	44.0 (12.0)	41.7 (10.4)	0.038
LDL-cholesterol, mg/dL	114.4 (31.9)	114.5 (31.9)	109.3 (32.7)	0.081
Total/HDL-cholesterol Ratio	4.7 (1.5)	4.7 (1.5)	4.8 (1.5)	0.443
eGFR, $mL/min/1.73m^2$	91.1 (15.8)	91.2 (15.7)	87.5 (18.2)	0.012
Albumin-Creatinine Ratio	0.008 (0.005-0.017)	0.007 (0.005-0.011)	0.018 (0.007-0.057)	<0.001
MNSI Score	1 (0-3)	1 (0-3)	2 (1-3)	0.009
Nephropathy, %	18.2	17.5	41.0	<0.001
Retinopathy, %	6.9	6.8	11.1	0.071
Neuropathy, %	16.6	16.4	23.1	0.057
Microvascular disease, %	34.8	34.0	62.4	<0.001

Data are mean (standard deviation), median (interquartile range), or proportion (%) as appropriate.

AHEAD indicates Action for Health in Diabetes; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MNSI, Michigan Neuropathy Screening Instrument

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Table S2. Hazard Ratios for Incident Heart Failure by Microvascular Disease Status Stratified by Race/Ethnicity in the Look AHEAD Study.

Hazard ratio (95% CI)	Nephropathy		Retinopathy		Neuropathy		Microvascular disease	
	Absent	Present	Absent	Present	Absent	Present	Absent	Present
White (n = 2647)								
Model 1	Reference	2.57 (1.60-4.12)‡	Reference	1.95 (0.97-3.92)	Reference	1.94 (1.17-3.21)*	Reference	3.26 (2.03-5.23)‡
Model 2	Reference	1.94 (1.19-3.18)†	Reference	1.70 (0.82-3.55)	Reference	1.85 (1.11-3.09)*	Reference	2.82 (1.72-4.61)‡
Model 3	Reference	1.90 (1.16-3.12)*	Reference	1.69 (0.81-3.53)	Reference	1.76 (1.05-2.95)*	Reference	2.71 (1.65-4.46)‡
Nonwhite (n = 1448)								
Model 1	Reference	3.35 (1.81-6.18)‡	Reference	1.01 (0.36-2.85)	Reference	1.05 (0.44-2.49)	Reference	2.60 (1.40-4.83)†
Model 2	Reference	2.64 (1.38-5.05)†	Reference	0.80 (0.28-2.32)	Reference	0.98 (0.41-2.34)	Reference	2.16 (1.14-4.09)*
Model 3	Reference	3.37 (1.76-6.44)‡	Reference	0.69 (0.24-2.01)	Reference	0.85 (0.35-2.09)	Reference	2.31 (1.21-4.41)*

Model 1 adjusted for age, sex and randomization arm. Model 2 includes variables in model 1 with further adjustment for body mass index, current smoking (yes/no), alcohol drinking (oz/week), systolic blood pressure, use of antihypertensive medications (yes/no), ratio of total to high-density lipoprotein cholesterol, hemoglobin A_{1C}, duration of diabetes. Model 3 includes variables in model 2 with additional adjustment for interval development of coronary artery disease (as a time-dependent covariate).
AHEAD indicates Action for Health in Diabetes; CI, confidence interval.
* $P<0.05$, † $P<0.01$, ‡ $P<0.001$