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ORIGINAL RESEARCH ARTICLE

Microvascular disease and heart failure with reduced and preserved ejection fraction in type 2 diabetes

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Abstract

Aims Identification of patients with type 2 diabetes (T2D) at increased risk of incident heart failure (HF) beyond traditional risk factors such as prior myocardial infarction (MI) might allow selection of patients who would benefit from preventative treatment. Microvascular disease (MiVD) is thought to play a pathophysiological role in the development of HF in T2D; however, its association with new-onset HF with reduced or preserved ejection fraction has not been specifically defined.

Methods and results Patients in the Genetics of Diabetes Audit and Research Tayside Scotland study were linked to echocardiography, prescriptions, and clinical outcomes. In total, 9141 patients with T2D were identified for analysis. Clinical variables and the presence of retinopathy, nephropathy, and neuropathy were assessed. Cumulative incidence was calculated for the association of both individual and the total number of MiVD states and incident HF. Median follow-up was 9.3 years. In total, there were 900 HF events. The presence of any MiVD was independently associated with both HF with reduced ejection fraction (hazard ratio 1.40; 95% confidence interval 1.11–1.76, $P = 0.004$) and HF with preserved ejection fraction (hazard ratio 1.38; 95% confidence interval 1.10–1.72, $P = 0.005$), with a stepwise association between the number of MiVD states and risk of incident HF (P for trend <0.001). Similar associations were found in sensitivity analyses limited to patients without a prior MI, and using competing risks analysis.

Conclusions Individuals with T2D and with MiVD are at risk of incident HF independent of a history of prior HF or MI. Patients with MiVD could benefit from screening for HF and individualized therapy with treatments that lower HF risk.

Keywords Type 2 diabetes; Heart failure; Microvascular disease

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Introduction

Individuals with type 2 diabetes mellitus (T2D) are at high risk of developing heart failure (HF). Several studies have shown an HF prevalence of at least 20% in patients with T2D, with the development of HF being associated with significantly worse prognosis.[1] Commonly, the development of HF in patients with T2D is attributed to macrovascular disease, with myocardial ischaemia and infarction leading to HF with reduced ejection fraction (HFrEF). T2D itself increases the risk of HF however that may be independent of coronary artery disease, myocardial infarction (MI), and other concomitant conditions such as hypertension.[2,3] There is increasing recognition of the high prevalence of HF with preserved ejection fraction (HFpEF), which is not always associated with risk factors such as coronary artery disease but rather may be caused by the presence of diabetes itself.[4,5] The prevalence of HFpEF in patients with T2D is increasing and now accounts for almost half of all HF,[6] constituting a huge unmet need as HFpEF currently has no evidence-based therapies.

Sodium-glucose co-transporter 2 inhibitors reduce HF hospitalization in patients with T2D both with and without a history of HF—indeed, the majority of patients in the cardiovascular (CV) outcome trials did not have a history of HF.[7–9] Consequently, current guidelines recommend sodium-glucose co-transporter 2 inhibitors use to lower risk

of HF hospitalization in patients with T2D.[10,11] Given that patients with T2D are often at high risk of HF even in the absence of atherosclerotic disease, identification of other risk factors for incident HF in T2D could allow patients to start these preventative treatments in a more targeted way before overt HF develops.

One of the main pathophysiological processes thought to be implicated in the development of HF in patients with T2D is microvascular disease (MiVD) which is prevalent in T2D and may contribute to the development of both HFpEF and HFrEF.[12] Although coronary MiVD is not routinely measured in clinical practice, T2D screening programmes do assess for the presence of three types of MiVD—retinopathy, nephropathy, and neuropathy. Both retinopathy[13] and nephropathy[14] have been independently associated with HF mortality or hospitalization in observational cohort studies. There are less data on peripheral neuropathy and HF outcomes; however, the presence of neuropathy is associated with worse CV outcome.[15] Additionally, the 'burden' of MiVD, that is, the sum of MiVD states, has also been shown to be associated with CV outcomes.[16,17] What is not known is whether the presence of MiVD is similarly associated with both HFrEF and HFpEF.

The aim of this study was to determine the independent association of MiVD with incident HF events in a large cohort of patients with T2D with available echocardiographic data.

Methods

Cohort derivation

Patients with T2D were identified from the Genetics of Diabetes Audit and Research Tayside Scotland (GoDARTS) registry; the full details have been published previously.[18] In brief, GoDARTS is an epidemiological cohort study comprising 18 306 participants including 10 149 with T2D and 8157 controls without T2D. Only patients with T2D were included in this study. Baseline data are collected on all patients as well as blood samples for genotyping, and all patients consent to prospective electronic record linkage for drug prescriptions, blood samples, retinal screening, and clinical outcomes. For this specific analysis, study entry and baseline data were taken from the time of recruitment to GoDARTS. We excluded patients with an HF hospitalization prior to recruitment. Clinical outcomes are obtained from the Scottish Mortality and Morbidity Record while deaths are obtained from the General Records Office Scotland. Patient data are linked back as far as 1987 through a unique patient number (Community Health Index number), and the data were available until December 2016. Collection and analysis of data in GoDARTS were approved by the East of Scotland Research and Ethics Committee, in compliance with the declaration of Helsinki.

Assessment of microvascular disease

The current Scottish Intercollegiate Guidelines Network (SIGN) guideline for management of T2D recommends that all patients with T2D in Scotland have annual retinal and foot screening as well as annual measurement of albumin/creatinine ratio.[19] Patients are invited to take part, and this is typically performed either at the patient's primary care physician, a hospital clinic, or optometrist. We were able to capture this through the patients' electronic health records.

The presence of MiVD (retinopathy, nephropathy, and neuropathy) at the time of recruitment was determined. The presence of retinopathy was assessed by retinal photography and based on the Scottish Diabetic Retinopathy Grading System,[20] which itself is similar to the American Academy of Ophthalmology International Clinical Disease System for Diabetic Retinopathy.[21] The Scottish system reports diabetic retinopathy in seven categories: R0, no retinopathy; R1, mild background retinopathy; R2, moderate background; R3, severe background; R4, proliferative; R5, enucleated; and R6, unable to assess. The highest grade of the two eyes at the time of photograph was used for this study. The presence of retinopathy was classified as $\geq$R1 at any point prior to recruitment as previously described.[22,23]

The presence of nephropathy was classified according to urine albumin/creatinine ratio taken within 24 months of recruitment. If patients had more than one sample taken, the median value within that time period was taken. Nephropathy was diagnosed if the urine albumin/creatinine ratio was $>$30 mg/mmol, that is, severely increased as per the Kidney Disease Improving Global Outcomes guidelines.[24]

Neuropathy was assessed using monofilament screening data, with any abnormal monofilament test classed as the presence of neuropathy. During each test, a monofilament is applied to 10 sites on each foot, and a positive result suggestive of neuropathy is recorded if sensation is absent $\geq$2/5 sites in either foot.[25]

The total MiVD burden was assessed by summing together the presence of the three individual MiVD states. As not all patients had available data on all three MiVD states, we only analysed MiVD burden in patients who had available data in all three MiVD beds prior to recruitment.

Other baseline variables

Diagnosis of prior MI and HF hospitalization before study entry was made based on ICD-10 coding (I21 and I22 and I50, respectively). Continuous variables for which there may have been more than one measurement were taken as the median value over the 2 years prior to the start date for this study [body mass index (BMI), total and HDL cholesterol, blood pressure, haemoglobin A1c (HbA1c), and serum creatinine],

taking advantage of the longitudinal nature of our electronic health records to ensure we obtained a more accurate reflection of clinical status for these variables. Baseline data were also obtained on use of insulin, duration of diabetes, and history of smoking at the time of recruitment.

Identification of incident heart failure

Patients included from GoDARTS were linked to the Tayside echocardiography database which has been described previously.[26] In brief, this database contains data on over 110 000 clinically requested echocardiograms from 1994 onwards. Echocardiograms are reported by fully accredited sonographers (either British Society of Echocardiography or European Society of Cardiovascular Imaging). This database has been used previously to determine the presence of left ventricular systolic dysfunction.[26,27]

HF outcomes were linked using ICD-10 coding as mentioned earlier. Incident HF hospitalization or death was recorded if HF was either the primary cause of death or hospitalization or within the first two secondary causes. Where echocardiography had been performed, for the purposes of this study, HFrEF was classified as an HF event in a patient with prior LVEF $<50\%$ at any point before the event (encompassing both HFrEF and HF with mid-range ejection fraction), while HFpEF was an HF event with LVEF $\geq 50\%$ and no previous echocardiography showing LVEF $<50\%$.[5,28]

Statistical analysis

Continuous variables are reported as mean ± SD or median (interquartile range) as appropriate while categorical variables are reported as number (percentage). Kaplan–Meier and multivariable Cox regression were performed to ascertain the association of MiVD with incident HF overall and HFpEF and HFrEF following recruitment into GoDARTS. Given that MI is associated with HF development sensitivity analysis was performed with the competing risk of MI using the Fine-Gray model to account for the possibility of individuals dying or having an MI prior to potential HF development. Both Cox and competing risk regression models were fully adjusted for age; gender; smoking; prior MI; duration of T2D; BMI; systolic blood pressure; glycosylated haemoglobin (HbA1c); total and HDL cholesterol; and insulin, statin, and aspirin use. We also performed a sub-analysis excluding patients with a prior MI to determine the association of MiVD and HF in patients without prior MI. All *P* values reported are two sided, and a *P* value <0.05 was considered significant. All statistical analysis was performed using R version 3.5.1.

Results

Baseline characteristics

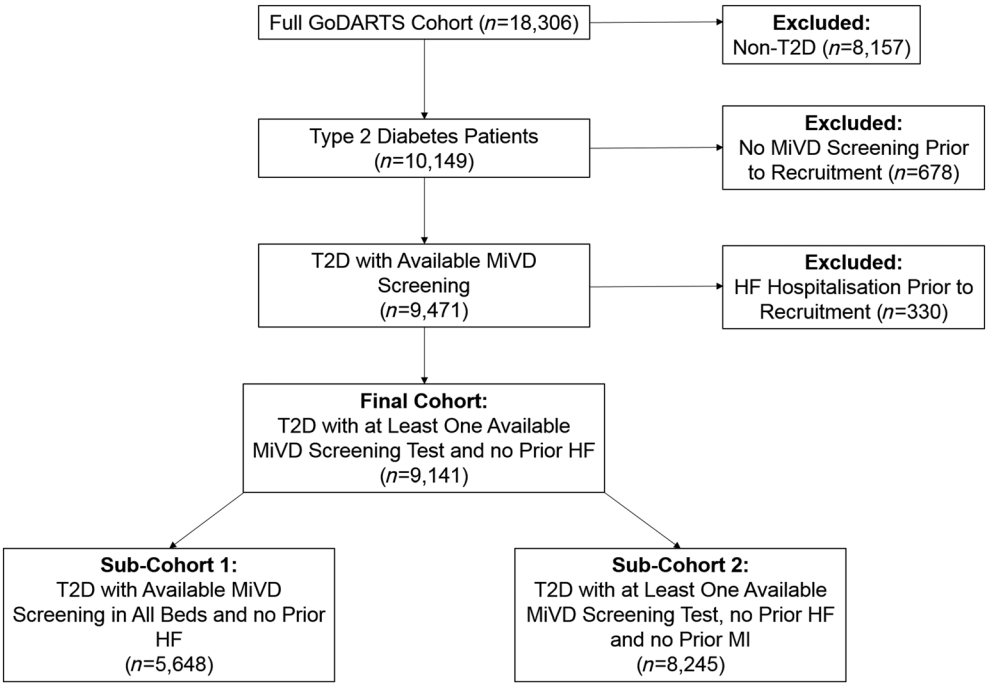
In total, 9141 patients with T2D were included in the study. Of these, 5648 (61.8%) had available data on all three MiVD states at recruitment. Baseline characteristics of the cohort are summarized in *Table 1*, while derivation of the dataset used for analysis is summarized in *Figure 1*. The mean age of the cohort was 65 ± 12 years, and 5063 (55.4%) patients were male. In total, 4182 patients had no MiVD (45.7%). At baseline, 4239 patients (46.4%) had any retinopathy, 550 (6.0%) had nephropathy, and 1173 (12.8%) had neuropathy.

Table 1 Baseline characteristics

	No microvascular disease (n = 4182)	Any microvascular disease (n = 4959)	*P* value
Age (years)	63 ± 12	66 ± 12	<0.001
Male	2219 (55.8)	2844 (57.1)	<0.001
Median duration of diabetes (years)	3.2 (2.2–4.4)	7.7 (3.2–12.2)	<0.001
Smoker	788 (17.6)	736 (15.9)	0.031
Prior myocardial infarction	372 (8.9)	524 (10.6)	0.008
Body mass index (kg/m^2)	30.5 ± 6.1	31.2 ± 5.6	<0.001
History of hypertension	1870 (44.7)	2534 (51.1)	<0.001
COPD	44 (10.5)	47 (9.5)	0.69
Atrial fibrillation	128 (3.1)	218 (4.4)	0.001
Systolic blood pressure (mmHg)	143 ± 6	144 ± 6	0.67
Insulin use	965 (23.1)	1506 (30.4)	<0.001
Metformin use	1586 (37.9)	2290 (46.2)	<0.001
Sulfonylurea use	882 (21.1)	1614 (32.5)	<0.001
HbA1c (%)	7.5 ± 1.1	7.7 ± 1.1	<0.001
Total cholesterol (mmol/L)	4.57 ± 0.73	4.59 ± 0.8	0.18
HDL cholesterol (mmol/L)	1.26 ± 0.32	1.28 ± 0.34	0.016
Serum creatinine (mmol/L)	89 ± 24	96 ± 33	<0.001
Aspirin	1190 (28.5)	1931 (39.0)	<0.001
Statin	1991 (47.6)	2667 (53.8)	<0.001
ACEI/ARB	1639 (39.2)	2618 (52.8)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; HbA1c, haemoglobin A1c.

Figure 1 Cohort derivation. Derivation of the study cohort from the Genetics of Diabetes Audit and Research Tayside Scotland (GoDARTS) dataset.



Of the 5648 patients with available data on all three MiVD states, 2509 had no MiVD (44.4%), 2450 (43.4%) had one MiVD, 623 (11.0%) had two MiVD, and 66 (1.2%) had three MiVD.

Patients with MiVD were older and more likely to be male than those without MiVD. The presence of MiVD was associated with significantly longer duration of T2D, reduced likelihood of smoking, higher BMI, lower HDL cholesterol, and higher HbA1c. MiVD was also associated with increased likelihood of prior MI and increased use of cardioprotective medications, insulin, metformin, and sulfonylureas.

Association between microvascular disease and incident heart failure

Median follow-up was 9.3 years (interquartile range 4.8–14.1 years). In total, there were 900 individuals who had an incident HF event (including 51 HF deaths and 858 HF hospitalizations; 11.1% of the total cohort). Of these, 366 were classified as HFrEF events and 382 as HFpEF events, with the remaining 109 unclassified as no echocardiogram was available.

After adjusting for relevant baseline variables (age, gender, duration of diabetes, insulin, metformin, sulfonylurea and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, prior MI, HbA1c, HDL and total cholesterol, systolic blood pressure, serum creatinine, smoking status, and body mass index) the presence of any MiVD was independently associated with incident HF (hazard ratio, HR 1.39; 95% CI, confidence interval 1.20–1.61, $P < 0.001$). In the same fully adjusted model, all individual MiVD states were also independently associated with incident HF (retinopathy: HR 1.33; 95% CI 1.16–1.53, $P < 0.001$; neuropathy: HR 1.23; 95% CI 1.03–1.47, $P = 0.022$; nephropathy: HR 1.60; 95% CI 1.26–2.03; $P < 0.001$) (*Table 2* and *Figure 2*). These results were similar when analysed taking into account competing risk of MI, with significant associations between the presence of any MiVD, retinopathy and nephropathy, and incident HF. In the 5648 patients who had available data on all three MiVD states at baseline, there was also a stepwise trend seen with increased number of MiVD states present being associated with increasing risk of incident HF (one MiVD: HR 1.42; 95% CI 1.16–1.74, $P < 0.001$; two or three MiVD: HR 1.98; 95% CI 1.53–2.56, $P < 0.001$, P for trend <0.001).

In the whole cohort, after adjustment for all baseline variables, the presence of MiVD was independently associated with both HFrEF (HR 1.40; 95% CI 1.11–1.76, $P = 0.004$) and HFpEF (HR 1.38; 95% CI 1.10–1.72, $P = 0.005$) (*Table 3*). There remained a stepwise association between the number of MiVD states at baseline and incident HFrEF (one MiVD: HR 1.65; 95% CI 1.19–2.27, $P = 0.003$; two or three MiVD: HR 2.41; 95% CI 1.62–3.60, $P < 0.001$, P for trend <0.001). Patients with two or three MiVD states were more likely to develop incident HFpEF than those with no or one MiVD (one MiVD: HR 1.25; 95% CI 0.91–1.71, $P = 0.16$; two or three MiVD: HR 1.85; 95% CI 1.24–2.75, $P = 0.002$, P for trend = 0.003) (*Figure 3*).

Table 2 Association between microvascular disease and incident heart failure

Microvascular disease	Number of events/number at risk (%)	Multivariable cox regression		Adjustment for competing risk of MI	
		Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Any microvascular disease	899/9141 (9.8)	1.39 (1.20–1.61)	<**0.001**	1.27 (1.08–1.50)	**0.005**
Retinopathy	892/9043 (9.9)	1.33 (1.16–1.53)	<**0.001**	1.19 (1.01–1.40)	**0.034**
Neuropathy	835/7882 (10.6)	1.23 (1.03–1.47)	**0.022**	1.17 (0.96–1.44)	0.12
Nephropathy	588/6804 (8.6)	1.60 (1.26–2.03)	<**0.001**	1.82 (1.39–2.38)	<**0.001**
Number of microvascular disease states					
0	153/2509 (6.1)	Baseline		Baseline	
1	258/2450 (10.5)	1.42 (1.16–1.74)	<**0.001**	1.26 (0.99–1.59)	0.061
2/3	116/689 (16.8)	1.98 (1.53–2.56)	<**0.001**	1.77 (1.31–2.39)	<**0.001**

Adjusted for age, sex, duration of diabetes, insulin use, sulfonylurea use, metformin use, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, prior myocardial infarction, haemoglobin A1c, HDL and total cholesterol, systolic blood pressure, serum creatinine, smoking status, and body mass index. CI, confidence interval.

Figure 2 Microvascular disease burden incident heart failure. Kaplan–Meier curves demonstrating the association between microvascular disease and incident heart failure.

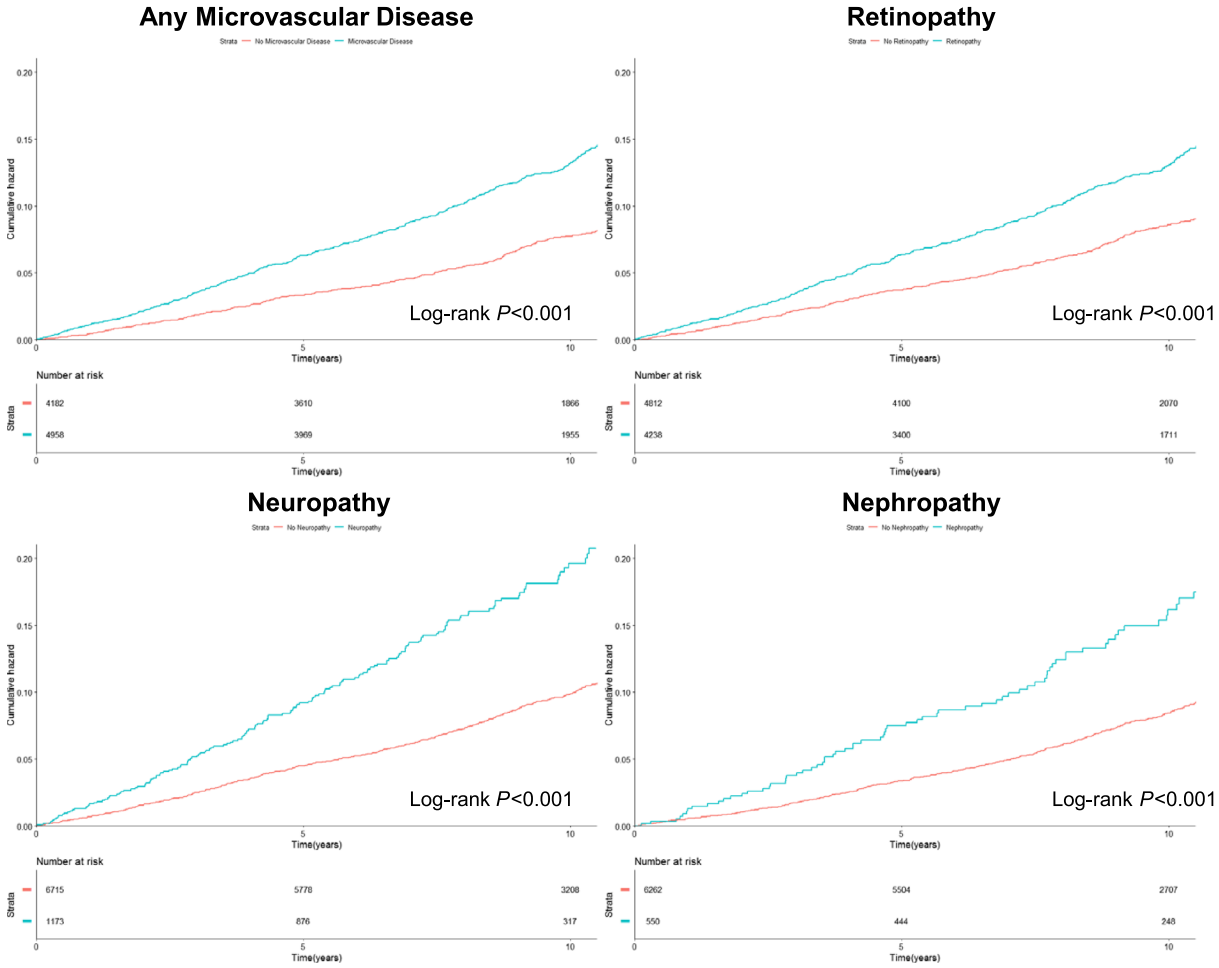


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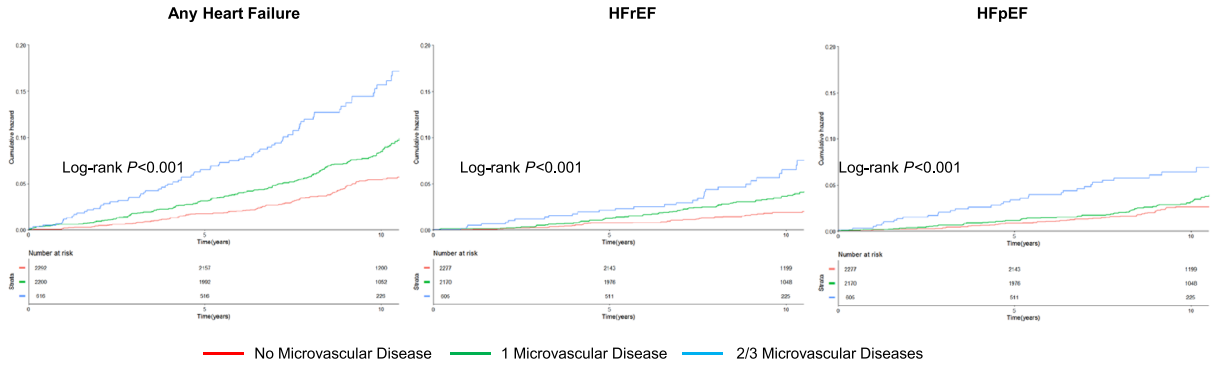
Table 3 Association between microvascular disease and heart failure with reduced and preserved ejection fraction

	HFrEF			HFpEF		
	Number of events/available patients	Hazard ratio (95% CI)	*P* value	Number of events/available patients	Hazard ratio (95% CI)	*P* value
No microvascular disease	121/4182 (2.9)	Baseline		130/4182 (3.1)	Baseline	
Any microvascular disease	245/4959 (4.9)	1.40 (1.11–1.76)	**0.004**	252/4959 (5.1)	1.38 (1.10–1.72)	**0.005**
Number of microvascular disease states						
0	59/2493 (2.4)	Baseline		71/2493 (2.8)	Baseline	
1	114/2417 (4.7)	1.65 (1.19–2.27)	**0.003**	100/2417 (4.1)	1.25 (0.91–1.71)	0.16
2/3	50/674 (7.4)	2.41 (1.62–3.60)	**<0.001**	47/674 (7.0)	1.85 (1.24–2.75)	**0.002**

Adjusted for age, sex, duration of diabetes, insulin use, sulfonylurea use, metformin use, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, prior myocardial infarction, haemoglobin A1c, HDL and total cholesterol, systolic blood pressure, smoking history, and body mass index. CI, confidence interval; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction.

Figure 3 Number of microvascular disease states and risk of heart failure. Kaplan–Meier curves demonstrating the association between the number of microvascular disease states present and risk of incident heart failure (HF), HF with reduced ejection fraction (HFrEF), and HF with preserved ejection fraction (HFpEF).



Association between microvascular disease and heart failure in patients without a history of myocardial infarction

After excluding the 896 patients with a prior MI, 8245 individuals remained for analysis. In this sub-cohort, the presence of any MiVD remained significantly associated with incident HF (HR 1.36; 95% CI 1.16–1.60, $P < 0.001$). The presence of MiVD was significantly associated with both HFrEF (HR 1.34; 95% CI 1.04–1.74, $P = 0.026$) and HFpEF (HR 1.38; 95% CI 1.08–1.75, P = 0.010) (*Supporting Information*, *Table S1*). Both retinopathy (HR 1.31; 95% CI 1.12–1.52, $P < 0.001$) and nephropathy (HR 1.67; 95% CI 1.28–2.17, $P < 0.001$) were significantly associated with incident HF, while there was also a non-significant association between neuropathy and increased risk of incident HF (HR 1.22; 95% CI 1.00–1.49, $P = 0.054$). There was a stepwise association between the number of MiVD states present and increased risk of incident HF (one MiVD: HR 1.38; 95% CI 1.10–1.74, $P = 0.005$; two or three MiVD: HR 1.71; 95% CI 1.10–1.74, $P < 0.001$; *P* for trend <0.001). A similar trend was found for the association between number of MiVD states and incident HFrEF (one MiVD: HR 1.54; 95% CI 1.06–2.24, $P = 0.022$; two or three MiVD: HR 2.02; 95% CI 1.26–3.23, $P = 0.004$; *P* for trend <0.001). Patients with two or three MiVD were at particularly increased risk of HFpEF (HR 1.75; 95% CI 1.12–2.73, $P = 0.0173$).

Discussion

In this large observational cohort study of individuals with T2D without a prior history of HF, we have shown that the presence of any MiVD is independently associated with incident HF, including HFrEF and HFpEF, after adjustment for multiple clinical variables, including prior MI, duration of diabetes, and glycaemic control and independent of the competing risk of incident MI. We have also shown that the burden of MiVD (measured by the number of MiVD states present) is significantly associated with increased risk of HF in a stepwise manner. Finally, we have shown that the association between MiVD and HF is present even in patients without a history of MI, and in particular, the presence of MiVD is

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associated with increased risk of HF. These results would suggest that the presence of MiVD may also be considered an independent risk factor for HF and may be used by clinicians in individualized selection of diabetes therapy.

Several previous cohort studies have shown that individual features of MiVD are associated with development of HF in patients with T2D. A cohort study of 1021 patients by Cheung *et al*.[13] reported the independent association of retinopathy with incident HF. Nephropathy has also been independently associated with development of HF.[29] There are limited data on neuropathy; however, it has been associated with composite CV outcomes.[15] A large study of patients >65 years also identified that retinopathy, nephropathy, and neuropathy were all independently associated with development of HF; however, the study did not adjust for many factors which could modify HF risk including HbA1c, duration of T2D, blood pressure, and medication use.[17] Importantly, our study extends these findings by using echocardiographic data, allowing us to show for the first time that the association between MiVD and HF is present in HFrEF and HFpEF. Additionally, we have used a competing risk regression model to increase the robustness of our findings. One possible explanation for our findings is that the presence of MiVD may simply be a surrogate for macrovascular disease risk, leading to MI and subsequent HF. Our analysis suggests however that MiVD is itself a risk factor for HF independent of a prior history of MI.

To the best of our knowledge, our study is the first to show that MiVD is also associated with incident HFpEF as well as HFrEF. T2D is itself associated with a number of structural abnormalities such as left ventricular hypertrophy, a common finding in HFpEF which is thought to be of pathophysiological importance.[30,31] Recent studies have shown that MiVD in patients with T2D and diagnosed HFpEF is highly prevalent and associated with HF severity and worse outcome[32]; however, ours is the first to show the independent prognostic association between MiVD and development of HFpEF. Echocardiographic studies have shown that T2D is associated with abnormalities of diastolic function independent of the presence of coronary artery disease.[33,34] In addition, the presence of MiVD in patients with T2D also seems to be associated with the presence of diastolic dysfunction.[35–37] It is possible that MiVD plays a role in the pathophysiology of incident HFpEF but, perhaps more importantly, that MiVD is a risk factor for development of HFpEF. This is of particular importance as HFpEF accounts for almost half of all HF in individuals with T2D and, at present, does not have any evidence-based treatment.[38]

Our finding that the increased burden of MiVD is associated with a stepwise increase in risk of HF also mirrors the findings from a large cohort study published recently.[16] In this study of almost 50 000 individuals with over 2000 events, the authors reported an increased relative risk of 32% for those with one MiVD, 62% for those with two MiVD, and 99% for those with three MiVD for the combined primary outcome of CV death and non-fatal MI or stroke. Our study confirms this similar pattern for both HFrEF and HFpEF.

Although our results only show association, they do raise the possibility that MiVD may be a risk factor that could be used to identify individuals with T2D in whom overt HF could be prevented. Coronary MiVD measured invasively using coronary flow reserve has also been shown to be associated with risk of HFpEF independent of coronary artery disease[39] and is associated with increased severity of HF in patients with a diagnosis of HFpEF.[40] This MiVD may lead to inflammation and fibrosis, thus predisposing to HFpEF.[41,42] A recent imaging study found that the presence of coronary MiVD in patients with T2D defined as reduced myocardial perfusion in the absence of significant epicardial coronary stenosis was associated with structural and functional abnormalities that could lead to HF.[43] The hyperinsulinaemic state associated with T2D and MiVD also plays a role in increasing HF risk.[43,44] Traditionally, prevention of MiVD has been through strict glycaemic control; however, previous trials of pure glucose-lowering therapies such as sulfonylureas and insulin have not shown any CV benefit over the duration of the studies.[45,46] It may be however that other mechanisms, for example, insulin resistance, oxidative stress, and metabolic changes, which are associated with MiVD are also important in development of HF.[3,47]

The major clinical implication of our work might be the use of the presence of MiVD as a screening tool to identify patients at risk of HF in the absence of other traditional risk factors such as MI, hypertension, and hyperlipidaemia. This would be of particular interest given the recent positioning of SGLT2 inhibitors as preferred treatments in patients with T2D at high-risk of HF rather than other therapies that have demonstrated CV risk reduction such as glucagon-like peptide-1 receptor agonists.[10,11] While features such as the presence of left ventricular dysfunction or history of prior MI would certainly place patients at high-risk of HF, many patients with T2D without these features remain at high-risk of incident HF. Of the major SGLT2 outcome trials, only CANVAS had mention of MiVD (albuminuria) as one of the inclusion criteria in patients without established atherosclerotic cardiovascular disease.[9] Our work also shows that patients with neuropathy and retinopathy are also at high risk of incident HF and may be used to help identify patients who might benefit from these therapies.

The major SGLT2 outcome trials in patients with T2D only included ~10% of patients with a history of HF, and the CV risk reduction was similar regardless of the presence of HF at baseline. A recent post hoc analysis of the EMPA-REG trial also reported that the presence of MiVD was associated with increased risk of HF hospitalization and that empagliflozin caused a significant HF risk reduction compared to placebo.[48] More recently, the results of the DAPA-HF trial in HFrEF patients demonstrated a reduction in mortality and HF hospitalization regardless of T2D status.[49] Clinicians might consider watching

for signs of HF or undertaking echocardiography in patients with MiVD who might benefit from targeted treatment with SGLT2 inhibitors to prevent HF hospitalization.[38] This is important as it has been identified that less than half of all patients with T2D and HF meet the current US Food and Drug Administration criteria for prescribing of SGLT2 inhibitors.[50]

Our study does have some limitations. First, due to its observational nature, we are not able to definitively prove causality of MiVD with HF. Nevertheless, a strength of our study is its large cohort size and the adjustment for several confounders using longitudinal data, as well as using a competing risk regression model. Second, our definition of HFpEF was pragmatic, based on the nature of routine clinical reports, which often omit other diagnostic features of HFpEF such as left atrial size and mitral inflow velocities. Additionally, as measurement of natriuretic peptides is not routinely available in Scotland, this provided a further limitation.

Conclusions

Microvascular disease (MiVD) is independently associated with both incident HFrEF and HFpEF in patients with T2D, even in patients without prior MI. Patients with MiVD may be considered at high-risk of incident HF and may benefit from screening for HF and individualized therapy decisions with treatment aimed at prevention of HF.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Association between burden of microvascular disease and heart failure events in patients without prior myocardial infarction.

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