Microvascular Disease in Patients With Diabetes With Heart Failure and Reduced Ejection Versus Preserved Ejection Fraction

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OBJECTIVE

Microvascular complications are common among patients with diabetes mellitus (DM). The presence of heart failure (HF) is presumed to be due to macrovascular disease (typically HF with reduced ejection fraction [HFrEF] following myocardial infarction). We hypothesized that HF with preserved ejection fraction (HFpEF) in patients with DM may be a manifestation of microvascular disease compared with HFrEF. The objective of this study was to examine the prevalence and association with clinical outcome of microvascular complications in patients with HF and DM.

RESEARCH DESIGN AND METHODS

We investigated the prevalence, association with clinical outcome, and cardiac structure and function of microvascular (neuropathy, nephropathy, and retinopathy) complications of DM in 2,800 prospectively enrolled participants with HF and DM (561 with HFpEF) from the ASIAN-HF registry.

RESULTS

A total of 601 (21.5%) participants with DM had microvascular complications. Participants with DM and any (one or more) microvascular complications were more likely to have HFpEF (odds ratio 1.70 [95% CI 1.15–2.50]; $P = 0.008$). Furthermore, the likelihood of having HFpEF increased with an increasing number of microvascular complications ($P_{trend} < 0.001$). Microvascular complications were associated with more left ventricular (LV) hypertrophy and a greater reduction in quality of life in HFpEF than HFrEF ($P_{interaction} < 0.001$ for all). Compared with participants with DM and without microvascular complications, the adjusted hazard ratio for the composite outcome of all-cause death or HF hospitalization was 1.35 (95% CI 1.04–1.76) for participants with DM and microvascular complications regardless of HF type ($P_{interaction} = 0.112$).

CONCLUSIONS

Diabetic microvascular disease is more common, and related to greater LV remodeling, more impairment of quality in life, and similar adverse outcomes, in participants with HFpEF compared with HFrEF. HFpEF may be a clinical manifestation of microvascular disease in DM.

In patients with diabetes mellitus (DM), microvascular disease is traditionally recognized as the presence of neuropathy, retinopathy, or nephropathy (1). In contrast, cardiac involvement in DM is usually categorized as macrovascular disease; namely, epicardial coronary artery disease with myocardial infarction leading to heart failure (HF) with reduced ejection fraction (HFrEF). However, patients with DM are increasingly

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recognized to be at risk for HF with preserved ejection fraction (HFpEF), where microvascular disease is postulated to play a dominant role compared with HFrEF (2,3).

Prior clinical studies of diabetic microvascular disease in HF were limited to only one of the HF types (HFrEF or HFpEF) and therefore could not distinguish the relative association of diabetic microvascular disease with HFpEF from that with HFrEF. Among participants with DM and HFrEF in the Beta-blocker Evaluation of Survival Trial (BEST), 32% had microvascular complications (neuropathy, retinopathy, or nephropathy), which were associated with worse outcomes (4). A recent report from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial showed that 32% of participants with DM and HFpEF had microvascular complications—a group that similarly had more adverse outcomes compared with those without microvascular disease (5). Neither studies examined the association of diabetic microvascular disease with cardiac structure and function.

We hypothesized that diabetic microvascular disease in noncardiac organ systems (neuropathy, retinopathy, or nephropathy) may be more prevalent in participants with HFpEF compared with HFrEF and associated with greater left ventricular (LV) hypertrophy and higher rates of all-cause mortality and HF hospitalization, thus implying that HFpEF in patients with DM may be a manifestation of predominant microvascular disease. To test these hypotheses, we compared the prevalence and association of DM microvascular complications with cardiac structure and function as well as outcomes in participants with HFrEF and HFpEF enrolled in the same prospective HF study.

RESEARCH DESIGN AND METHODS

Study Population

We studied 6,438 HF participants enrolled in the Asian Sudden Cardiac Death In Heart Failure (ASIAN-HF) Registry (6–9), which included participants from 46 centers across 11 Asian regions (Taiwan, Hong Kong, China, India, Malaysia, Thailand, Singapore, Indonesia, Philippines, Japan, and Korea). Inclusion criteria were age >18 years and symptomatic HF (at least one previous episode of decompensated HF in the previous 6 months resulting in a hospital admission or treatment in outpatient clinic). Participants were excluded if their HF was caused by valvular disease, presence of a comorbidity leading to a life expectancy <1 year, and if they were unable or unwilling to give consent. ASIAN-HF was originally designed to only include participants with HFrEF (LV ejection fraction [LVEF] <40%) (6,7), but a protocol amendment was undertaken in 2013 to also include participants with HFpEF (LVEF ≥50% and excluding any patient with a prior LVEF <50%) (9). Data on demographics, previous medical history, clinical symptoms, and functional status were collected. Health status was measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ), a 23-item self-administered HF-specific questionnaire validated in multiple HF-related disease states (10–13). Calculated KCCQ domain scores ranged from 0 to 100; higher scores represent better health status. Participants underwent standardized 12-lead electrocardiography and transthoracic echocardiography at inclusion. Participants were followed up for 3 years, and outcomes were adjudicated by an independent committee. All data were captured prospectively in an electronic database, with registry operations and data management handled by Quintiles Outcomes as the contract research organization appointed by the academic Executive Committee. Ethics approvals were obtained from the relevant human ethics committees at all sites. All participants provided informed consent, and this study adheres to the principles of medical research as laid down in the Declaration of Helsinki.

Study Definitions

DM microvascular complications were ascertained by self-reported history and medical record review. DM was defined as a clinical history of DM and/or receiving antidiabetes therapy. If a clinical history of DM was present, the investigators were asked if the patient had a history of microvascular disease and, if yes, the type(s) of microvascular disease (neuropathy, nephropathy, or retinopathy) was specified. The definitions of other comorbidities in ASIAN-HF have been reported (6,7,9). Obesity was defined, in accordance with the World Health Organization, as BMI ≥30 kg/m^2. Coronary artery disease (CAD) was defined as documented angiographic presence of significant coronary obstruction (>50% diameter loss in at least one major epicardial coronary artery), history of myocardial infarction, or prior coronary revascularization. Hypertension was defined as the clinical diagnosis (blood pressure ≥140/90 mmHg) and/or receiving antihypertensive therapy. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD Study equation, and chronic kidney disease was defined as eGFR <60 mL/min/1.73 m^2.

Echocardiography

The collection and processing of echocardiographic data have previously been described (8,14). Echocardiography was performed at each center according to internationally accepted guidelines (15). In addition to LVEF, LV, and left atrial dimensions, stroke volume, cardiac output, and echo Doppler estimates of LV diastolic dysfunction were collected. The Cardiovascular Imaging Core laboratory of the National University Health System, Singapore, provided oversight and imaging protocol guidelines as well as quality assurance of echocardiograms. Accuracy and reproducibility of interpreted results were ensured through consistent training and systematic analytical processes provided by the Core Laboratory according to international guidelines (15). For further calculations, LV mass was calculated from linear dimensions and indexed to body surface area (BSA) (15). Relative wall thickness (RWT) was calculated by the formula [(2 × diastolic posterior wall thickness)/diastolic LV internal diameter]. LV hypertrophy was determined as LV mass index >115 g/m^2 in men and >95 g/m^2 in women (15). Normal LV geometry was defined as having no LV hypertrophy and an RWT ≤0.42. Abnormal LV geometry was classified as concentric remodeling (no LV hypertrophy and RWT >0.42), concentric hypertrophy (LV hypertrophy and RWT >0.42), and eccentric hypertrophy (LV hypertrophy and RWT ≤0.42). Left atrial size was indexed to BSA (15). In additional analyses, we investigated whether microvascular complications were associated with diastolic dysfunction defined as e′ septal <8 and/or e′ lateral<10 and E/A ≥0.8 and/or deceleration time ≤200 and/or E/e′ ≥9 (16).

Outcomes

The primary outcome of this study was a composite of all-cause death or HF rehospitalization at 1 year. A total of 5,831 (90.6%) participants had outcomes data available, whereas 607 (9.4%) participants were lost to follow-up. Participants with <1 year of outcomes available were censored at their last known visit date. Secondary outcomes were all-cause mortality alone and HF hospitalization alone.

Statistical Analysis

Differences between participants with DM with and without microvascular complications were tested with Student *t* test, χ^2 test, or the Mann-Whitney *U* test depending on the nature and distribution of the variable. Multivariable association between microvascular complications and HFrEF/HFpEF (as the dependent variable) was tested using multivariable logistic regression, correcting for age, sex, history of CAD, previous stroke, peripheral artery disease, hypertension, atrial fibrillation, ethnicity, NYHA class, duration of HF, BMI, usage of β-blockers, ACE inhibitors (ACEi)/ angiotensin receptor blockers (ARBs), insulin, oral antidiabetes medications, creatinine, hemoglobin, type of DM, and duration of DM in years. The association between microvascular disease and echocardiographic variables was tested using multivariable logistic regression with subjects with DM without microvascular complications as a reference. Kaplan-Meier curves stratified by group membership were depicted, with differences between groups tested using the log-rank test for survival. Multivariable analyses were performed using Cox regression analysis correcting for the aforementioned model. When analyzing the secondary outcome of HF hospitalizations, we used all-cause mortality as a competing risk. All tests were performed two sided, and *P* values of <0.05 were considered statistically significant. Statistical analyses were performed using STATA 15.0 (StataCorp, College Station, TX).

RESULTS

Baseline Characteristics

Among the 6,438 participants in the ASIAN-HF registry, 2,800 participants had DM, of whom 601 (21%) had microvascular complications. Among 2,800 participants with DM, those with HFpEF had a higher prevalence (27%) of microvascular complications compared with those with HFrEF (20%; $P = 0.001$) (Fig. 1*A*). After adjustment for age, sex, ethnicity, history of coronary artery disease, atrial fibrillation, previous stroke, peripheral arterial disease, hypertension, NYHA class, duration of HF, HF medications, serum creatinine, hemoglobin, DM type, DM medication, and duration of DM, participants with any (one or more) microvascular complications were more likely to have HFpEF (odds ratio [OR] 1.70 [95% CI 1.15–2.50]; $P = 0.008$). Following further correction for systolic blood pressure at baseline, participants with microvascular complications were more likely to have HFpEF (1.80 [95% CI 1.22–2.65]; $P = 0.003$). Furthermore, there was a linear increase in the OR of having HFpEF for participants with an increasing number of microvascular complications (Fig. 1*B*) ($P_{trend} < 0.001$), which remained statistically significant in the fully corrected model ($P < 0.01$ for all). Among participants with microvascular complications, diabetic nephropathy was the most prevalent (71%) followed by retinopathy (42%) and neuropathy (28%). Each of neuropathy, retinopathy, and nephropathy were all more prevalent among participants with HFpEF compared with participants with HFrEF in both univariable and the fully corrected models (Fig. 1*A*). Participants with microvascular complications had higher blood pressure and worse signs and symptoms and were more often in NYHA class III/IV compared with participants with DM without microvascular complications and were more often on insulin and had a longer duration of DM (Table 1).

Echocardiography

HF type was a significant effect modifier for the association of microvascular complications with LV mass ($P_{interaction} < 0.001$). In participants with DM and HFrEF, a greater number of microvascular complications was associated with a decrease in LV hypertrophy (Fig. 1*C* and Supplementary Table 1). In contrast, among participants with DM and HFpEF, those with microvascular complications had a higher LV mass indexed to BSA (Supplementary Table 1). Furthermore, the prevalence of LV hypertrophy increased with an increasing number of microvascular complications in HFpEF, with 41% having LV hypertrophy among participants with HFpEF, DM, and no microvascular complications and 76% having LV hypertrophy among participants with DM, HFpEF, and three microvascular complications ($P_{trend} < 0.001$) (Fig. 1*C*). In addition, the presence of DM microvascular complications was associated with higher LV filling pressures (E/e′ ≥14: OR 1.71 [95% CI 1.14–2.56]; $P = 0.009$) regardless of HF type ($P_{interaction} > 0.1$). In addition, microvascular complications were associated with more diastolic dysfunction (OR 3.83 [95% CI 1.1–12.9]; $P = 0.029$).

Clinical Outcomes

Participants with and without follow-up data available were not different in terms of age, sex, comorbidities, or medication use, but those lost to follow-up had higher systolic and diastolic blood pressures and were more often in NYHA class III/IV (Supplementary Table 2). Of 2,567 participants with DM and follow-up data available, 609 (23.7%) participants died or were hospitalized for HF within 1 year. In multivariable analyses compared with participants with DM without microvascular complications, participants with DM microvascular complications had higher rates of the primary combined outcome (HR 1.34 [95% CI 1.06–1.69]; $P = 0.015$) after correction for age, sex, NYHA class, duration of HF, history of coronary artery disease, previous stroke, peripheral artery disease, hypertension, atrial fibrillation, ethnicity, BMI, usage of β-blockers, ACEi/ARBs, insulin, oral antidiabetes medications, creatinine, hemoglobin, and type of DM (Table 2). After further correction for systolic blood pressure at baseline, microvascular complications were still independently associated with the primary combined outcome (HR 1.37 [95% CI 1.09–1.73]; $P = 0.008$). Diabetic nephropathy showed the strongest association with adverse outcomes (Supplementary Table 3). No significant interaction was observed between microvascular complication subtype and HF type for the composite outcome ($P_{interaction}$ for all >0.2).

Quality of Life

Participants with DM microvascular complications had worse quality of life as reflected by lower KCCQ scores across various domains, with social limitation, total symptoms, and physical

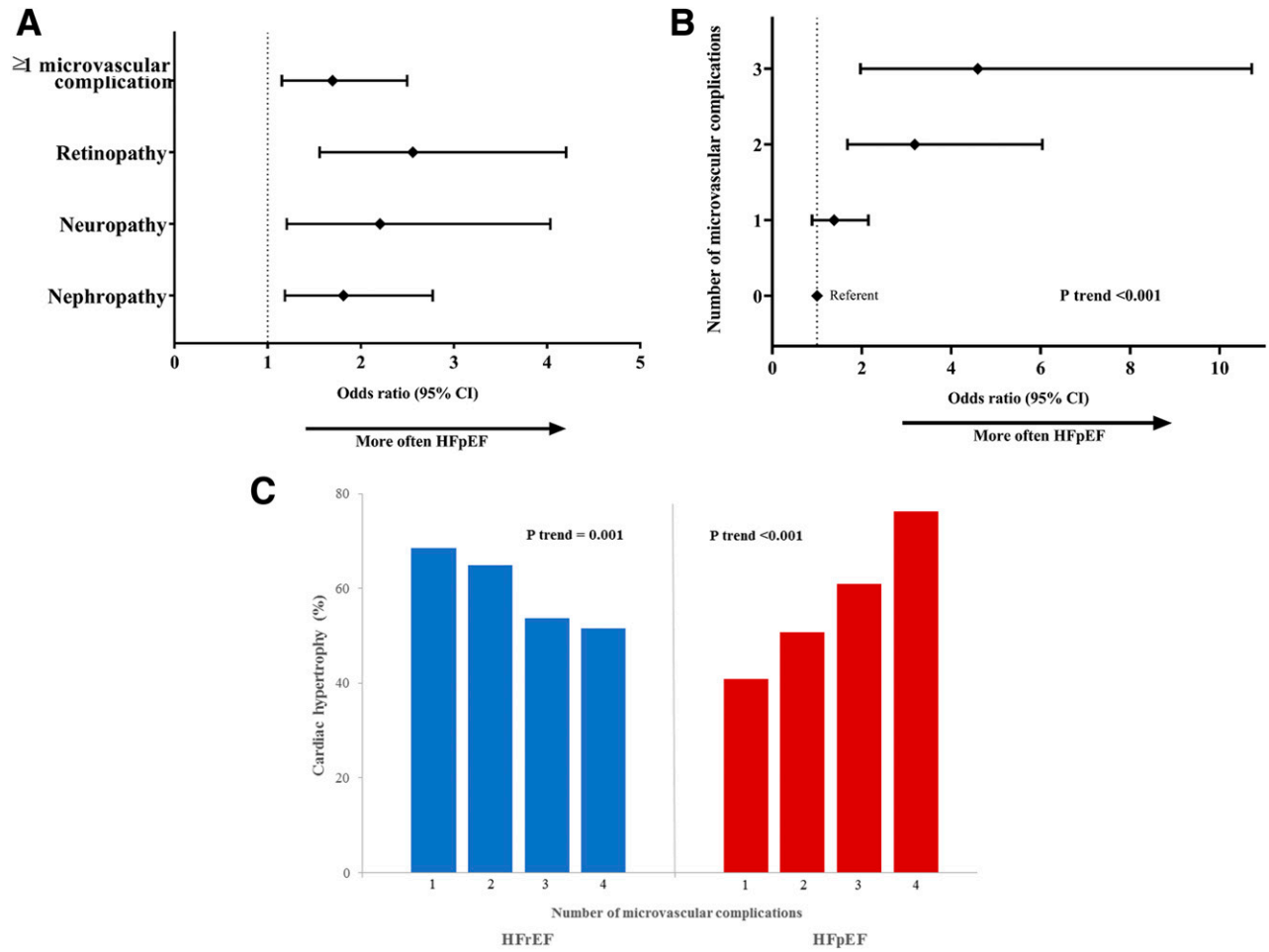

Figure 1—Odds ratios adjusted for age, sex, history of CAD, previous stroke, peripheral artery disease, hypertension, atrial fibrillation, ethnicity, NYHA class, duration of HF, BMI, usage of beta-blockers, ACEi/ARBs, insulin, oral anti-diabetic medications, creatinine, hemoglobin. *A* and *B*: Forest plot with ORs and 95% CI for having HFpEF stratified according to microvascular complication (*A*) and number of microvascular complications (*B*). *C*: Percentage of participants with cardiac hypertrophy stratified according to number of microvascular complications and HF subtype.

limitation being most severely affected (Supplementary Table 4). Compared with participants without microvascular complications, those with HFpEF and diabetic microvascular complications reported a larger reduction in overall KCCQ scores than participants with HFrEF and microvascular complications ($P_{interaction} < 0.001$) (Fig. 2*D*).

CONCLUSIONS

In this first comparison of diabetic microvascular complications between HFpEF and HFrEF from the same study population, we found that DM microvascular complications were more prevalent in participants with DM and HFpEF (27%) than in participants with DM and HFrEF (20%), a finding also true for each individual microvascular complication. Diabetic nephropathy was the most common manifestation of microvascular involvement (present in 71% of participants with at least one microvascular complication), followed by retinopathy (42%) and neuropathy (28%). Diabetic microvascular disease was related to greater LV hypertrophy and worse quality of life in participants with DM and HFpEF than HFrEF. Participants with microvascular disease had higher LV filling pressures and more adverse clinical outcomes regardless of the HF type. These findings suggest that HFpEF may be a clinical manifestation of microvascular disease in patients with DM.

The prevalence of microvascular complications among participants with DM in ASIAN-HF (21%) was lower than that observed in participants with DM from the TOPCAT trial (32%) and BEST (32%) (4,5). This lower prevalence may be explained by a shorter duration of DM in ASIAN-HF, where participants with DM were almost a decade younger than their counterparts from BEST and TOPCAT (4–6,9). In addition, the percentage of participants with DM on insulins was less than half in ASIAN-HF (16%) compared with BEST (41%) and TOPCAT (38%), suggesting a lesser severity of DM. Furthermore, diabetic nephropathy was the most common microvascular complication compared with diabetic neuropathy in TOPCAT and BEST (4,5). Ethnicity has an important influence on the prevalence and distribution of types of microvascular complications (17–23). Asians with DM are at higher risk for developing diabetic nephropathy compared with Europeans (20,21). A separate study found that Indo-Asian immigrants with DM in the Netherlands had a 40-fold higher risk of end-stage kidney disease and that overall renal disease progression is faster than in the indigenous Dutch

Table 1—Baseline characteristics according to complication status

	DM without microvascular complications (*N* = 2,199)	DM with microvascular complications (*N* = 601)	*P* value
Age (years)	63.0 (11.4)	64.3 (10.8)	0.012
Women	586 (26.6)	175 (29.1)	0.23
Ethnicity			<0.001
Chinese	767 (34.9)	180 (30.0)	
Indian	673 (30.6)	182 (30.3)	
Malay	415 (18.9)	119 (19.8)	
Japanese	145 (6.6)	73 (12.1)	
Korean	103 (4.7)	10 (1.7)	
Thai	43 (2.0)	27 (4.5)	
Filipino	12 (0.5)	5 (0.8)	
Indigenous SEA	34 (1.5)	4 (0.7)	
Others	6 (0.3)	1 (0.2)	
NYHA class			<0.001
I	289 (14.9)	50 (9.0)	
II	1,035 (53.4)	286 (51.6)	
III	523 (27.0)	195 (35.2)	
IV	93 (4.8)	23 (4.2)	
Systolic BP (mmHg)	122.6 (20.9)	127.1 (22.6)	<0.001
Diastolic BP (mmHg)	72.4 (12.4)	71.1 (12.0)	0.019
BMI (kg/m^2)	26.0 (5.1)	26.3 (5.7)	0.16
Heart rate (bpm)	80.1 (16.1)	78.1 (13.9)	<0.001
eGFR (mL/min/1.73 m^2)	63.6 (27.4)	46.7 (25.5)	<0.001
LVEF (%)	33.8 (14.9)	35.9 (15.5)	0.002
HFpEF (%)	411 (18.7)	150 (24.9)	0.001
Ischemic etiology	1,202 (58.5)	372 (64.4)	0.011
Duration of HF, years			0.02
<1	988 (47.1)	229 (40.2)	
1–5	621 (29.3)	196 (34.4)	
5–10	317 (14.9)	97 (17.0)	
≥10	185 (8.7)	48 (8.4)	
Signs and symptoms			
Shortness of breath on exertion	1,531 (69.7)	470 (78.2)	<0.001
Angina	266 (12.1)	56 (9.3)	0.058
Elevated JVP	359 (16.3)	132 (22.0)	0.001
Peripheral edema	636 (28.9)	224 (37.3)	<0.001
Pulmonary Rales	391 (17.8)	165 (27.5)	<0.001
Medical history			
Obese	380 (18.7)	115 (20.6)	0.329
CAD	1,263 (57.5)	383 (63.7)	0.006
CKD (eGFR <60 mL/min/1.73 m^2)	877 (48.7)	375 (75.0)	<0.001
Prior stroke	166 (7.6)	67 (11.1)	0.005
Atrial fibrillation/flutter	399 (18.2)	104 (17.3)	0.63
Hypertension	1,532 (69.7)	448 (74.5)	0.022
Type of DM			0.214
Type 1	60 (2.7)	11 (1.8)	
Type 2	2,139 (97.3)	590 (98.2)	
Duration of DM (years)	7 (3, 12)	11 (6, 20)	<0.001
Peripheral arterial disease	73 (3.3)	63 (10.5)	<0.001
Medication and device use			
ACEi or ARB	1,560 (73.2)	392 (66.4)	0.001
β-Blockers	1,616 (75.8)	457 (77.5)	0.41
MRA	1,078 (50.6)	206 (34.9)	<0.001
Any diuretics	1,771 (83.1)	489 (82.9)	0.9
Any oral antidiabetes medication	1,291 (60.6)	320 (54.6)	0.008
Insulin	335 (15.7)	139 (23.7)	<0.001
Device use			0.372
None	1,932 (88.0)	539 (89.7)	
ICD/CRT-D	177 (8.0)	45 (7.5)	
Pacer/pacemaker	87 (4.0)	17 (2.8)	

Continued on p. 6

Table 1—Continued

	DM without microvascular complications (*N* = 2,199)	DM with microvascular complications (*N* = 601)	*P* value
Laboratory (median + interquartile range)			
Potassium (mmol/L)	4.2 (3.8, 4.6)	4.3 (3.9, 4.6)	0.008
Sodium (mmol/L)	138.0 (136.0, 140.0)	138.0 (136.0, 141.0)	0.88
Creatinine (mg/dL)	1.1 (0.9, 1.5)	1.5 (1.2, 2.2)	<0.001

Data are *n* (%). BP, blood pressure; CKD, chronic kidney disease; CRT-D, cardiac resynchronization therapy defibrillator; HR, heart rate; JVP, jugular venous pressure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SEA, Southeast Asia.

population (18,19). Additionally, diabetic neuropathy is considerably less common in Asians, which could be explained by a smaller stature (22,23). Ethnic differences might also potentially influence the association between microvascular complications and HFpEF. However, recent results from the PROMIS-HFpEF (PRevalence Of MIcrovascular dySfunction in Heart Failure with Preserved Ejection Fraction) study showed only marginal ethnic differences in the prevalence of microvascular disease in HFpEF (3).

In a study using U.S. Medicare claims, patients with DM and diabetic nephropathy had a higher risk of developing HF (24). A study from the U.K. Clinical Practice Research Datalink showed that DM microvascular complications were associated with a higher risk of developing HF (25). This is further supported by results from the Atherosclerosis Risk In Communities (ARIC) study, where diabetic retinopathy was associated with an excess risk of developing HF (26). The current study extends on these previous findings and suggests that microvascular disease in DM may portend an excess risk for developing HFpEF specifically (rather than HFrEF). Indeed, data from the Multiethnic Study of Atherosclerosis (MESA) also showed that microvascular complications were associated with more concentric hypertrophy on echocardiography, a hallmark of HFpEF (27,28). Finally, our findings are also consistent with recently reported results of the PROMIS-HFpEF study (3)—a large prospective multicenter study showing a high prevalence of coronary microvascular dysfunction in HFpEF in the absence of unrevascularized macrovascular coronary artery disease. The PROMIS-HFpEF study also showed that microvascular dysfunction in HFpEF was likely to be systemic, with evidence of reduced peripheral reactive hyperemia index and increased urinary albumin-to-creatinine ratio. Collectively, these data support the notion that microvascular dysfunction may be a promising composite risk marker and therapeutic target in HFpEF whether in the presence or absence of DM.

Microvascular disease was similarly associated with adverse outcomes in both participants with HFrEF and HFpEF, in keeping with prior observations in BEST and TOPCAT (4,5). However, this is the first report directly comparing the predictive value of microvascular disease in participants with HFrEF and HFpEF enrolled simultaneously in the same cohort. Interestingly, microvascular disease had a stronger association with HF hospitalizations than all-cause mortality. This could be explained by the lower statistical power in the mortality analysis. This is plausible given the significant association between microvascular disease and all-cause mortality alone in participants with DM and HF as previously reported (4,5). Another potential explanation is the relatively large contribution of diabetic nephropathy to microvascular events in the ASIAN-HF study. Renal dysfunction in particular is associated with sodium and water retention, which leads to worsening of HF and subsequent hospitalization.

The clinical implications of this study are twofold. First of all, results of this study suggest that HFpEF might be a clinical manifestation of microvascular disease in patients with DM. Thus, in the routine screening for microvascular

Table 2—Crude and adjusted associations of microvascular complications with 1-year outcomes

	Composite outcome		All-cause mortality		HF hospitalizations	
	No. at risk	No. of events (%)	No. at risk	No. of events (%)	No. at risk	No. of events (%)
DM without microvascular complications (referent for HR)	2,024	437 (21.6)	2,024	209 (10.3)	2,024	271 (13.4)
DM with microvascular complications	543	172 (31.7)	543	76 (14.0)	543	114 (21.0)
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Univariable	1.55 (1.32–1.94)	<0.001	1.39 (1.07–1.81)	0.014	1.63 (1.31–2.02)	<0.001
Model 1	1.60 (1.34–1.92)	<0.001	1.42 (1.08–1.88)	0.012	1.59 (1.24–2.04)	<0.001
Model 2	1.52 (1.25–1.86)	<0.001	1.43 (1.07–1.91)	0.015	1.46 (1.13–1.90)	0.004
Model 3	1.34 (1.06–1.69)	0.015	1.12 (0.78–1.60)	0.536	1.43 (1.06–1.93)	0.019
Model 4	1.35 (1.04–1.76)	0.024	1.16 (0.78–1.73)	0.456	1.49 (1.06–2.09)	0.020

Model 1: age, sex, ethnicity, New York Heart Association class, HF subtype (HFrEF/HFpEF), duration of HF. Model 2: model 1 + BMI, history of hypertension, atrial fibrillation, CAD, usage of insulins, and oral DM drugs. Model 3: model 2 + usage of ACEi/ARB, β-blockers, mineralocorticoid receptor antagonist, creatinine levels, hemoglobin levels, type of DM. Model 4: model 3 + duration of DM.

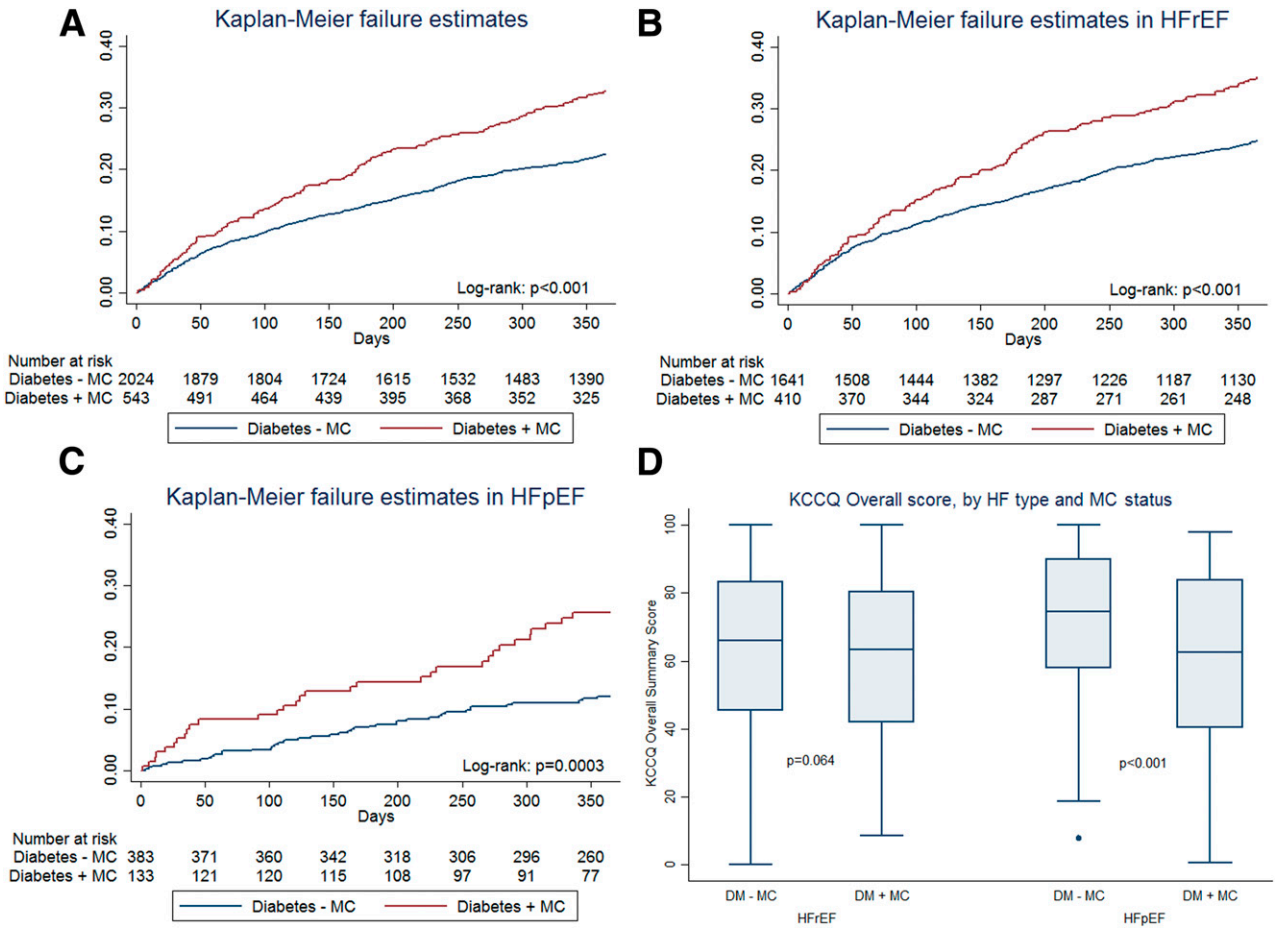

Figure 2—*A–C*: Kaplan-Meier curves according to microvascular status for the combined outcome of all-cause mortality or HF hospitalization for the total population (*A*), HFrEF only (*B*), and HFpEF only (*C*). *D*: Box plot of quality of life status (KCCQ overall scores) stratified according to HF type and microvascular complication (MC) status.

complications in patients with DM, physicians may also consider evaluating the heart for structural/ functional changes and not only the eyes, kidneys, and peripheral nerves. Conversely, given that microvascular complications are associated with greater LV hypertrophy and reduction in quality of life among patients with HFpEF, the optimal management of patients with HFpEF may also include screening for microvascular complications in other organ systems and optimizing antidiabetes medication to prevent microvascular complications.

Limitations

The presence of DM and microvascular complications was determined by history and review of medical records, without the use of glycated hemoglobin levels, disease-specific questionnaires, or specialist testing. Despite rigorous attempts to identify all participants with DM and microvascular complications, some of these participants might have been missed. However, this is more likely to underestimate the impact of DM and microvascular complications on outcomes rather than introduce significant bias. We were also unable to account for DM severity due to the lack of glycated hemoglobin levels. Several uncaptured factors including quality of health care services, fitness level, and quality of self-care (adherence to medication, water and dietary restriction, and others) might have led to residual confounding not accounted for in our analyses. Urinary albumin-to-creatinine ratio (UACR) would have provided additional insights into concurrent microvascular disease in the kidneys; however, this was not available in ASIAN-HF. Nonetheless, UACR has recently been shown to directly correlate with coronary microvascular disease (measured as coronary flow reserve) in HFpEF (3). Furthermore, we did not have longitudinal assessments of cardiovascular risk factor control (e.g., lipids, blood pressure, glucose). Finally, ASIAN-HF only included participants of Asian descent; generalizability to other regions and ethnicities is unclear.

Conclusion

DM microvascular complications are more common and are associated with greater LV remodeling and worse quality of life in patients with HFpEF compared with HFrEF from Asia. Microvascular disease portends worse clinical outcomes regardless of HF subtype. Our findings suggest that HFpEF may be a clinical manifestation of microvascular disease in DM. Further investigation is needed to validate our findings in a multiethnic study and to determine optimal management strategies in patients with HFpEF and DM.

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