JACC: HEART FAILURE
VOL. 5, NO. 1, 2017

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2016.09.015

Prevalence and Clinical Significance of Diabetes in Asian Versus White Patients With Heart Failure

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ABSTRACT

OBJECTIVES The study sought to compare the prevalence, clinical correlates and prognostic impact of diabetes in Southeast Asian versus white patients with heart failure (HF) with preserved or reduced ejection fraction.

BACKGROUND Diabetes mellitus is common in HF and is associated with impaired prognosis. Asia is home to the majority of the world's diabetic population, yet data on the prevalence and clinical significance of diabetes in Asian patients with HF are sparse, and no studies have directly compared Asian and white patients.

METHODS Two contemporary population-based HF cohorts were combined: from Singapore (n = 1,002, median [25th to 75th percentile] age 62 [54 to 70] years, 76% men, 19.5% obesity) and Sweden (n = 19,537, 77 [68 to 84] years, 60% men, 24.8% obesity). The modifying effect of ethnicity on the relationship between diabetes and clinical correlates or prognosis (HF hospitalization and all-cause mortality) was examined using interaction terms.

RESULTS Diabetes was present in 569 (57%) Asian patients versus 4,680 (24%) white patients ($p < 0.001$). Adjusting for clinical covariates, obesity was more strongly associated with diabetes in white patients (odds ratio [OR]: 3.45; 95% confidence interval [CI]: 2.86 to 4.17) than in Asian patients (OR: 1.82; 95% CI: 1.13 to 2.96; $p_{interaction} = 0.026$). Diabetes was more strongly associated with increased HF hospitalization and all-cause mortality in Asian patients (hazard ratio: 1.50; 95% CI: 1.21 to 1.87) than in white patients (hazard ratio: 1.29; 95% CI: 1.22 to 1.36; $p_{interaction} = 0.045$).

CONCLUSIONS Diabetes was 3-fold more common in Southeast Asian compared to white patients with HF, despite younger age and less obesity, and more strongly associated with poor outcomes in Asian patients than white patients. These results underscore the importance of ethnicity-tailored aggressive strategies to prevent diabetes and its complications. (J Am Coll Cardiol HF 2017;5:14–24) © 2017 by the American College of Cardiology Foundation.

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A wealth of data from clinical trials and epidemiologic studies in Western populations have established that diabetes mellitus is a common comorbidity in patients with heart failure (HF) regardless of ejection fraction (EF), and portends a worse short- and long-term prognosis (1–3). More than one-half of the patients with diabetes in the world live in Asia, where there are currently >72 million of such people in Southeast Asia alone (versus ~24 million in the United States and ~56 million in Europe), and where the prevalence of diabetes is increasing more rapidly than elsewhere (4). Yet, there are few data describing the prevalence of HF in Asia (5), and also few data describing the prevalence of diabetes in Southeast Asian patients with HF and its association with clinical covariates and impact on prognosis.

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Ethnic differences not only in prevalence of diabetes, but also in consequences of diabetes are increasingly recognized. The UKPDS (United Kingdom Prospective Diabetes Study) study showed that Asian Indian patients with diabetes living in the United Kingdom were at higher risk of diabetes-related outcomes (including HF) compared to white patients with diabetes, but at lower risk of mortality (6). In the SABRE (Southall and Brent REvisited) study cohort from London, diabetes was associated with a lower left ventricular EF in Asian patients than in white patients (7). Although the preceding studies compared Asian and white patients, both ethnic groups were from Western geographic regions and did not have HF.

In 32 population-based cohorts from the Asia-Pacific Region, diabetes had a weaker association with HF mortality risk in Asian patients than in Australian patients (8). Significant heterogeneity in the diagnosis and reporting of HF, and over-representation of Japanese historical cohorts, were acknowledged limitations. The relative prevalence, clinical correlates, and prognostic impact of diabetes in Asian patients versus white patients with HF with preserved EF (HFpEF) versus HF with reduced EF (HFrEF) thus remain unknown.

By combining data from the contemporary, prospective, population-based HF cohorts of the SwedeHF (Swedish Heart Failure Registry) registry (9) and the SHOP (Singapore Heart Failure Outcomes and Phenotypes) study (10), we aimed to compare the prevalence, clinical correlates, and prognostic impact of diabetes in Southeast Asian patients versus white patients with HFpEF and HFrEF.

We hypothesized that the prevalence of diabetes would be higher among Southeast Asian patients with HF from Singapore, despite younger age and less obesity, compared to predominantly white patients from Sweden (11). Moreover, given our prior observations in patients with coronary artery disease (CAD) (12) and myocardial infarction (13), we hypothesized that there would be ethnic differences in the association between diabetes risk of HF hospitalization and all-cause mortality, and that these differences would be accentuated in ischemic versus nonischemic patients with HF with diabetes, and in Asian women versus Asian men with diabetes.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CAD = coronary artery disease

CI = confidence interval

EF = ejection fraction

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

IQR = interquartile range

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

OR = odds ratio

METHODS

STUDY POPULATION. Two HF cohorts were combined, from the SHOP study (10) and the SwedeHF registry (9)—both contemporary population-based observational HF studies recruiting patients with HF regardless of EF, from either in-hospital (hospitalization with [primary] diagnosis of HF) or outpatient (visit related to HF management) settings.

The SHOP study protocol has been described in detail before (10). In brief, patients were enrolled from 6 centers: National University Hospital, Khoo Teck Puat Hospital, National Heart Center, Tan Tock Seng Hospital, Changi General Hospital, and

Dr. Richards has served on the advisory board for Roche Diagnostics and Novartis; and has received speaker honoraria from Alere and Roche Diagnostics; and has received support in kind from Roche Diagnostics, Thermo Fisher, Critical Diagnostics, and Abbott Diagnostics. Dr. Dahlström has served as a consultant for and received honoraria from Novartis. Dr. Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Thermo Fisher, Medtronic, and Vifor Pharma; and has served as a consultant for Bayer, Novartis, Takeda, Merck, AstraZeneca, Janssen Research & Development, Menarini, Boehringer Ingelheim, and Abbott Diagnostics. Dr. Lund has received research grant support from AstraZeneca (to his institution), Boston Scientific (to his institution), and Novartis; has served as a consultant for AstraZeneca, Novartis, Relypsa, and Vifor Pharma; and has received consulting and speaker honoraria from AstraZeneca, Novartis, Bayer, Servier, and Vifor Pharma. These funding sources in no way influenced the analyses or the content of this manuscript. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Bank and Gijsberts contributed equally to this work. Drs. Lam and Lund contributed equally to this work.

Manuscript received August 17, 2016; revised manuscript received September 22, 2016, accepted September 29, 2016.

TABLE 1 Baseline Characteristics of Asian and White Patients With HF With and Without Diabetes

	Patients Without Diabetes			Patients With Diabetes			% Missing
	Asian	White	p Value	Asian	White	p Value	SHOP/SwedeHF
n	433	14,857		569	4,680		
Age, yrs*	61.0 (52.0-72.0)	78.0 (68.0-85.0)	<0.001	62.0 (55.0-69.0)	76 (68.0-82.0)‡	<0.001	0/0
Female, %*	22.9	40.6	<0.001	24.4	37.8†	<0.001	0/0
EF, %*			<0.001	†	†	<0.001	5.0/15.5
<30%	51.7	28.3		47.0	25.8		
30%-39%	17.1	26.9		21.6	27.1		
40%-49%	13.3	21.5		9.0	21.2		
≥50%	17.9	23.3		22.4	25.9		
Height, cm*	162.6 ± 8.5	171.2 ± 10.1	<0.001	162.2 ± 8.7	170.8 ± 9.7	<0.001	1.7/53.6
Weight, kg*	66.2 (57.1-76.5)	75.0 (64.8-87.0)	<0.001	68.0 (60.1-80.0)†	83.0 (72.0-96.2)‡	<0.001	1.4/8.7
BMI, %*	24.8 (21.9-28.5)	25.6 (22.7-29.0)	0.004	25.9 (23.2-29.6)‡	28.6 (25.2-32.4)‡	<0.001	2.0/54.1
Obesity, BMI ≥30 kg/m^2	16.3	20.0	0.075	21.8†	39.4‡	<0.001	
Obesity, BMI ≥27.5 kg/m^2	30.7	34.0	0.183	38.6†	56.6‡	<0.001	
SBP, mm Hg*	124.7 ± 22.3	127.7 ± 20.9	0.003	125.8 ± 22.6	130.7 ± 21.0‡	<0.001	0.4/1.4
DBP, mm Hg*	73.1 ± 13.6	73.8 ± 12.3	0.277	70.3 ± 12.4†	72.5 ± 12.0‡	<0.001	0.4/1.5
Hypertension, %*	61.5	50.8	<0.001	80.4‡	70.6‡	<0.001	0.1/2.0
Diabetes type						<0.001	46.2/0
1	-	-		7.5	3.2		
2	-	-		92.5	96.8		
Smoking, %*			<0.001	†	‡	<0.001	0.3/23.2
Current smoker	44.1	46.1		48.2	41.3		
Ex-smoker	27.9	40.3		32.9	46.5		
Nonsmoker	27.9	13.7		18.9	12.3		
History of CAD, %*	44.2	41.3	0.258	63.8‡	55.4‡	<0.001	3.9/5.2
History of PCI, %*	15.8	14.5	0.496	23.7†	19.7‡	0.030	2.1/0
History of CABG, %*	8.9	19.3	<0.001	20.1‡	31.2‡	<0.001	0.5/0
History of valve surgery, %*	0.7	5.7	<0.001	0.7	5.1	<0.001	0.5/1.2
History of AF, %*	28.8	53.8	<0.001	20.7†	51.8†	<0.001	1.1/0
History of stroke, %*	9.0	18.0	<0.001	12.7†	21.9‡	<0.001	0.3/0
History of PAD, %*	1.6	9.3	<0.001	6.7‡	15.4‡	<0.001	0.8/0
NYHA functional class, %*			<0.001		‡	<0.001	1.5/37.5
I	26.7	12.5		24.8	8.6		
II	58.3	49.9		58.6	42.4		
III	13.1	33.9		15.4	43.6		
IV	1.9	3.7		1.2	5.4		
NT-proBNP, pg/ml*	1,971 (703.0-4,134)	2,670 (1,150-5,819)	<0.001	2,138 (904.0-4,776)	2,800 (1,279-6,000)	<0.001	2.6/58.8
Creatinine clearance, ml/min*	61.9 (43.8-85.4)	58.4 (40.6-83.2)	0.131	54.1 (37.4-82.5)†	59.3 (41.4-83.8)	0.010	4.6/9.3
Hb, g/dl*	13.4 ± 2.0	13.3 ± 1.7	0.055	12.6 ± 2.2‡	12.8 ± 1.7‡	0.024	14.1/0
HF >6 months, %*	39.1	43.1	0.111	41.7	52.3‡	<0.001	1.1/2.0
QRS duration, ms*§	102 (92.0-116.0)	100 (88.0-122.0)	0.145	100 (89.0-116.0)	102 (90.0-126.0)†	0.016	0.5/29.9
QRS duration ≥120 ms, %§	22.2	27.2	0.025	22.3	30.3	<0.001	
HR, beats/min*	74 (65.0-82.0)	72 (63.0-82)	0.133	74 (66.0-85.0)	72 (64.0-82.0)†	0.009	0.03/3.1
LBBB, %*	7.8	16.9	<0.001	7.0	16.8	<0.001	2.1/13.0
Device, %			<0.001		†	<0.001	0/1.2
CRT with ICD	1.4	1.2		0.9	1.6		
CRT without ICD	0.5	0.8		0.7	1.0		
ICD without CRT	3.2	1.6		4.4	1.6		
PM	2.8	8.6		2.5	9.5		

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Singapore General Hospital. A total of 1,099 patients were enrolled between June 2010 and July 2014.

Patients with HF from the SHOP study cohort were residents of Singapore with Chinese (63%), Malay (26%), Indian (10%), and Eurasian (1%) ancestry, reflecting the Southeast Asian ethnicities of the region. For the purpose of this study, we refer to this cohort as Asian/Southeast Asian.

Patients with HF from the SwedeHF registry cohort were residents of Sweden and predominantly of

TABLE 1 Continued

	Patients Without Diabetes			Patients With Diabetes			% Missing
	Asian	White	p Value	Asian	White	p Value	SHOP/SwedeHF
Beta-blocker, %*	87.5	85.1	0.183	87.9	86.6†	0.439	0.2/0.6
ACE inhibitor, %*	63.4	63.2	0.969	57.7	58.0‡	0.927	0.2/0.5
ARB, %*	10.4	20.2	<0.001	13.9	27.8‡	<0.001	0.2/1.2
Diuretic agents, %*	88.0	77.1	<0.001	91.0	87.5‡	0.018	0.2/0.7
Statins, %*	76.6	40.0	<0.001	89.3‡	64.0‡	<0.001	0.2/0.5
Antiplatelet, %*	67.6	46.2	<0.001	83.6‡	56.5‡	<0.001	0.2/0.6

Values are median (interquartile range) or mean ± SD unless otherwise indicated. *Variables used in the SwedeHF (Swedish Heart Failure Registry) registry imputation model. †$p < 0.05$ versus patients without diabetes of same ethnicity. ‡$p < 0.001$ versus patients without diabetes of same ethnicity. §In the SwedeHF registry, QRS duration is only registered for patients without a device (we do not have data on QRS duration for patients with a device).

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CRT = cardiac resynchronization therapy; DBP = diastolic blood pressure; EF = ejection fraction; Hb = hemoglobin; HF = heart failure; HR = heart rate; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PM = pacemaker; SBP = systolic blood pressure; SHOP = Singapore Heart Failure Outcomes and Phenotypes study.

white European ancestry. For the purpose of this study, we refer to this cohort as white. The protocol of the SwedeHF registry (for details, see Eklin-Cervenka et al. [14]) encompasses enrollment of patients with HF starting in 2000. For the current analysis we applied the same time limits to the SwedeHF registry cohort as the SHOP study cohort, and thus only included patients enrolled from 2010 onward (excluding the first 30,987 patients enrolled from 2000 to 2009, n = 20,073).

Patients with missing information on follow-up or who died during the index event were excluded from analysis (n = 462 white patients, n = 91 Asian patients). Information about diabetic state was missing in 6 Asian patients and 74 white patients, who were also excluded from analysis, leaving 1,002 Asian patients and 19,537 white patients for the current study.

DEFINITION OF DIABETES. The presence of diabetes was recorded at baseline. Diabetes was defined as the presence of the clinical diagnosis (fasting plasma glucose ≥7 mmol/l or random plasma glucose ≥11.1 mmol/l or glycosylated hemoglobin ≥6.5%) or receiving antidiabetic therapy.

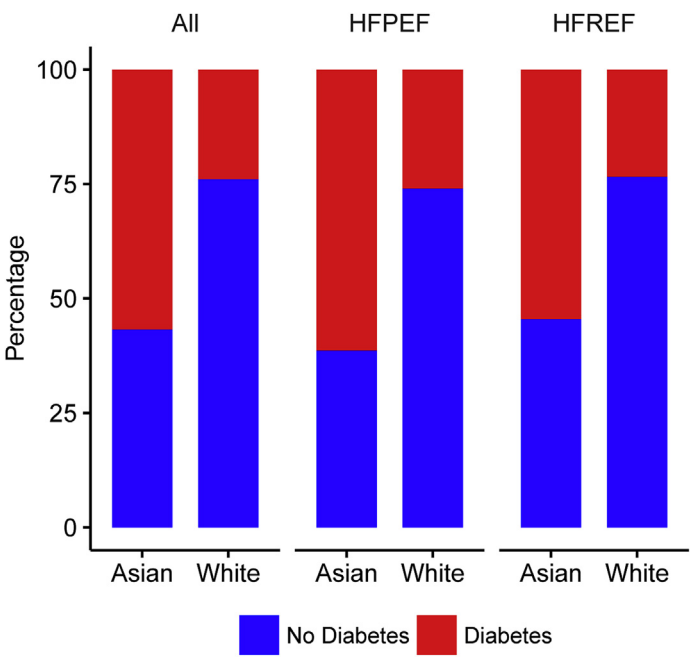
HFrEF AND HFpEF. HFrEF was defined as clinical features of HF with an echocardiographic EF lower than 50%. HFrEF was further categorized according to EF 40% to 49%, 30% to 39%, and <30%. HFpEF was defined as clinical features of HF with an echocardiographic EF ≥50%.

OUTCOMES. Outcomes included all-cause mortality and the composite of mortality and HF hospitalizations. Mortality was obtained by checking the Singapore's Registry of Births and Deaths and the Population Registry in Sweden. HF hospitalizations were obtained from the International Classification of Diseases-Tenth Edition code registrations in the main (first) position in the Patient Registry in Sweden and by follow-up visits or telephone follow-up in Singapore.

STATISTICAL ANALYSIS. Baseline characteristics were stratified by diabetic status and ethnicity. Continuous, normally distributed data are presented as mean ± SD and compared using a Student *t* test. Non-normally distributed data are presented as median (interquartile range [IQR]) and compared using the Kruskal-Wallis test. Categorical data are reported as number and percentages and compared by the chi-square test. In multivariable analysis, missing covariates were multiply imputed (m = 10) per cohort using the MICE package for R (R Development Core Team, Vienna, Austria) (15) to avoid bias due to information missing not completely at random. Covariates used for imputation are indicated with an asterisk in **Table 1**. Outcome variables (baseline diabetes and events during follow-up) were not missing and not imputed. The results of regression analyses are pooled results from analyses on 10 imputed datasets.

First, we evaluated whether ethnicity modified the relationship between clinical characteristics (age, sex, body mass index [BMI], history of CAD, duration of HF [>6 or ≤6 months], EF, New York Heart Association [NYHA] functional class, N-terminal pro-B-type natriuretic peptide [NT-proBNP] levels, and creatinine clearance [calculated with the Cockcroft-Gault formula]) and diabetes in logistic regression models by means of interaction terms between ethnicity and the respective clinical characteristic. Restricted cubic splines were used to test whether clinical characteristics measured on a continuous scale had a linear association with the log odds of the outcome. Age, BMI, and NT-proBNP levels violated this model assumption and were therefore categorized according to clinically relevant cutoffs. The overall significance of the interaction terms was assessed using the Wald

FIGURE 1 Diabetes Prevalence in Asian Patients and White Patients With Heart Failure



The prevalence of diabetes was higher among Asian patients than white patients, in both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFPEF) ($p < 0.001$).

test. Covariates for multivariable adjustment were clinically selected as follows: age, sex, BMI, hypertension, smoking, history of CAD, history of valve surgery, atrial fibrillation, left bundle branch block, creatinine clearance, duration of HF, heart rate, beta-blocker use, angiotensin-converting enzyme inhibitor use, angiotensin receptor blocker use, diuretic agent use, statin use, antiplatelet medication use, NT-proBNP levels, NYHA functional class, and EF. Restricted cubic splines were used for continuous variables.

Second, we examined the modifying effect of ethnicity on the relationship of diabetes with outcome (HF hospitalizations and mortality) in a Cox proportional hazard model, before and after adjusting for the previously listed covariates. The predictors angiotensin receptor blocker use and NYHA functional class were modeled using strata because the proportional hazard assumption was violated. Continuous variables were modeled using restricted cubic splines.

Finally, given our specific hypotheses that ethnic differences in the risk of HF hospitalization and all-cause mortality would be accentuated in ischemic versus nonischemic HF, and in Asian women versus Asian men, we tested the 3-way interaction terms among diabetes, ethnicity, and sex as well as diabetes, ethnicity, and history of CAD.

All analyses were performed using Rstudio and R software for statistical computing version 3.1.2 (R Development Core Team). A p value of <0.05 was considered statistically significant and all p values were 2-sided.

RESULTS

PREVALENCE OF DIABETES. The prevalence of diabetes was strikingly higher among Asian patients compared to white patients with HF (57% vs. 24%; $p < 0.001$) and in both HFpEF and HFrEF (Figure 1). Compared to white patients, Asian patients were younger, more predominantly men, more likely to have a history of hypertension and CAD, and more likely to be current smokers, but less likely to have a history of coronary artery bypass grafting, valve surgery, atrial fibrillation, peripheral arterial disease, or stroke (Table 1). Adjusting for these baseline inter-ethnic differences, the adjusted odds of diabetes were 3.1 times higher in Asian patients than white patients (odds ratio [OR]: 3.1; 95% confidence interval [CI]: 2.6 to 3.6; $p < 0.001$).

CLINICAL CORRELATES OF DIABETES. In the 2 cohorts combined, compared to patients without diabetes, patients with diabetes were slightly younger, more predominantly male, had a higher BMI (median 27.9 kg/m^2 [IQR: 24.7 to 31.9 kg/m^2] vs. 25.5 kg/m^2 [IQR: 22.6 to 29.0 kg/m^2]; $p < 0.001$), and were more likely to have a history of hypertension (71.7% vs. 51.1%; $p < 0.001$), CAD (56.3% vs. 41.4%; $p < 0.001$), previous coronary artery bypass grafting (30% vs. 19%; $p < 0.001$), and previous percutaneous coronary intervention (20% vs. 15%; $p < 0.001$). Despite similar NT-proBNP levels and better EF, patients with diabetes had worse NYHA functional class. Patients with diabetes were treated more often with diuretic agents, beta-blockers, angiotensin receptor blockers, statins, and antiplatelet agents, whereas angiotensin-converting enzyme inhibitors were more often used in patients without diabetes. There was no difference in device therapy use. Within the separate cohorts, these patterns were generally replicated (Table 1).

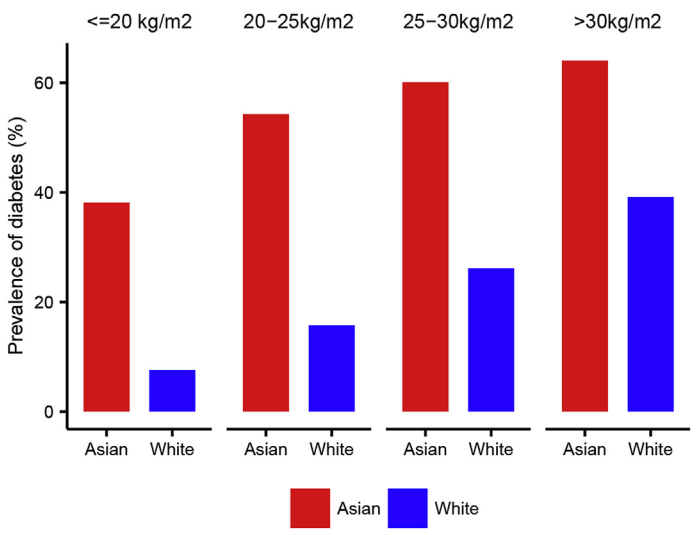
ETHNIC DIFFERENCES IN THE CLINICAL CORRELATES OF DIABETES. Patient demographics. Although diabetes was associated with higher BMI in both cohorts, overweight and obesity had a stronger association with diabetes in white patients than in Asian patients (multivariable $p_{interaction} = 0.026$) (Figure 2). The OR for having diabetes when being overweight (BMI 25 to 30 kg/m^2) compared to normal weight

(BMI 20 to 25 kg/m^2) was 1.90 (95% CI: 1.61 to 2.23) in white patients and 1.32 (95% CI: 0.92 to 1.92) in Asian patients. The OR for having diabetes when being obese (BMI >30 kg/m^2) compared to normal weight was 3.45 (95% CI: 2.86 to 4.17) in white patients versus 1.82 (95% CI: 1.13 to 2.96) in Asian patients. When defining overweight and obesity in the Asian patients with HF according to the World Health Organization's lower BMI cutoff for overweight (BMI 23 to 27.5 kg/m^2) and obesity (BMI ≥27.5 kg/m^2) in Singapore, comparable ethnic differences were observed. Ethnicity significantly modified the relationship between age and diabetes, but this attenuated after multivariable correction ($p_{interaction}$ = 0.790). Although the proportion of women was overall greater in white patients, this was similarly true in patients with and without diabetes (nonsignificant interactions).

Heart failure characteristics. There were no ethnic differences in the associations of diabetes with HF duration, left ventricular EF, NYHA functional class, and NT-proBNP (nonsignificant interactions) (Figure 3). In univariable analysis, there was no significant ethnic difference in the relationship between history of CAD and diabetes; however, after multivariable adjustment, a stronger relationship between history of CAD and diabetes was found in Asian patients compared to white patients (OR: 1.81 [95% CI: 1.30 to 2.52] vs. OR: 1.21 [95% CI: 1.11 to 1.31]; $p_{interaction}$ 0.014). A stronger negative association was observed between diabetes and renal function in Asian patients with HF compared to their white counterparts. However, this ethnic disparity attenuated after multivariable adjustment.

Ethnic differences in the impact of diabetes on outcome. In the combined cohort, diabetes was independently related to the composite outcome of all-cause mortality and HF hospitalization (adjusted hazard ratio [HR]: 1.31 [95% CI: 1.21 to 1.38]; $p < 0.001$), and to all-cause mortality alone (adjusted HR: 1.33 [95% CI: 1.24 to 1.43]; $p < 0.001$). The impact of diabetes on the composite outcome was stronger in Asian patients (adjusted HR: 1.50 [95% CI: 1.21 to 1.87]) compared to white patients (HR: 1.29 [95% CI: 1.22 to 1.36]; $p_{interaction}$ = 0.045) (Figure 4). No difference was found for all-cause mortality alone (adjusted HR: 1.32 [95% CI: 0.87 to 1.98] in Asian patients vs. HR: 1.34 [95% CI: 1.24 to 1.44] in white patients; $p_{interaction}$ = 0.761). Although there were ethnic differences in the association between diabetes and the composite endpoint of HF admissions and all-cause mortality, they were not accentuated in ischemic versus nonischemic HF (multivariable $p_{interaction}$ = 0.674 and 0.292, respectively), or in Asian women versus men (multivariable $p_{interaction}$ = 0.377 and 0.969, respectively) (Figure 5).

FIGURE 2 Relation of Body Mass Index With Diabetes in Asian and White Patients With Heart Failure



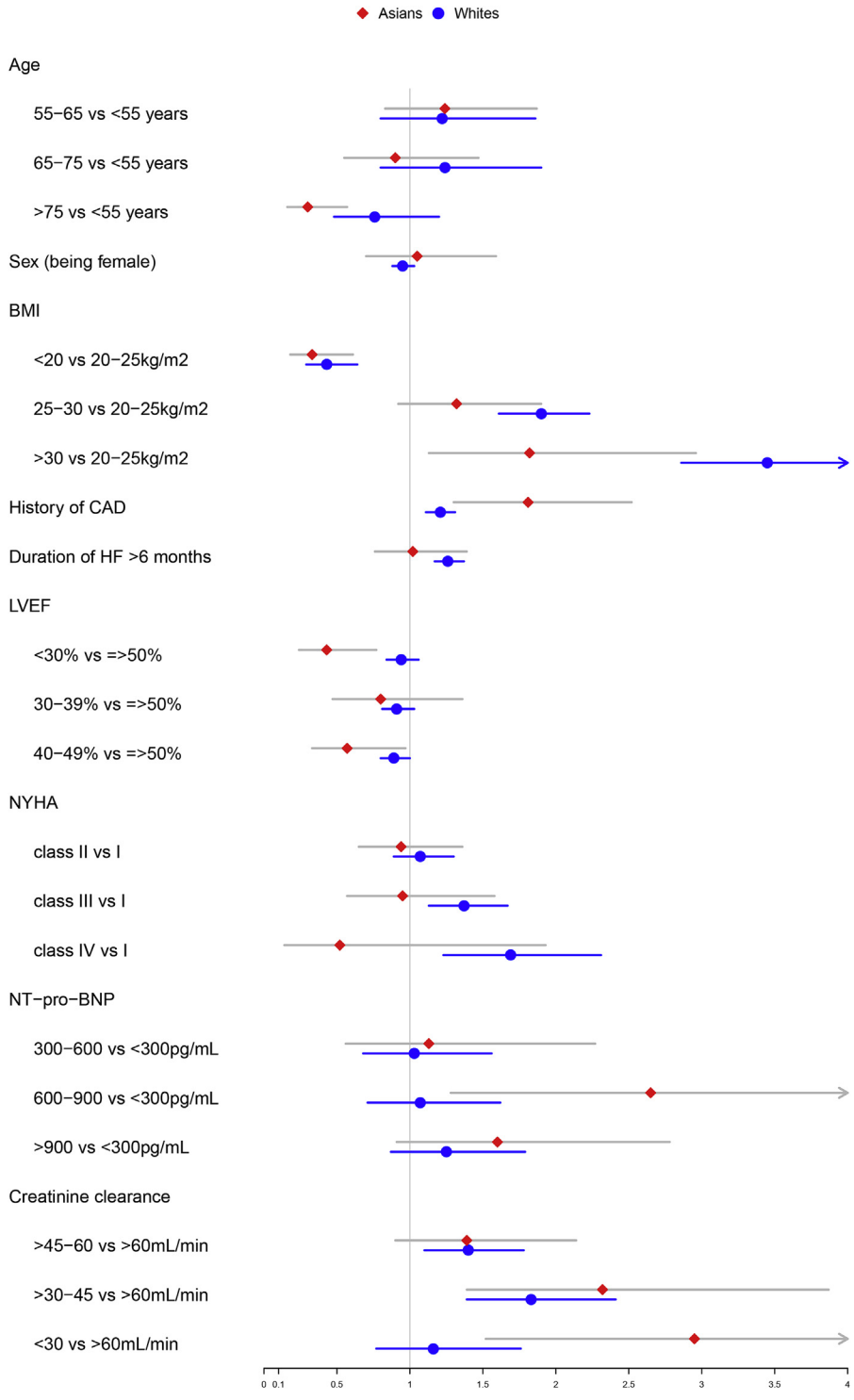
The prevalence of diabetes is illustrated per body mass index category. This relation was significantly stronger in white patients than in Asian patients (adjusted $p_{interaction}$ = 0.026).

DISCUSSION

These data from contemporary, prospective, population-based cohorts of white and Southeast Asian patients with HF showed notable ethnic differences in the prevalence and clinical correlates of diabetes in HF regardless of EF. Despite being more than a decade younger and with lower BMI, diabetes was present in 57% of Asian patients versus 24% of white patients. After adjustment for covariates, Asian patients with HF had 3.1 times higher odds of having diabetes compared to white patients. Significant ethnic interactions were found: diabetes was more strongly related to overweight and obesity in white patients than in Asian patients, whereas diabetes had a stronger negative impact on the composite outcome of HF hospitalizations and all-cause mortality in Asian patients than in white patients.

PREVALENCE OF DIABETES IN HF. Our findings of a higher prevalence of diabetes among Asian patients compared to white patients with HF corroborate a prior study in the United Kingdom, where 46% of South Asian (predominantly Indian) patients had diabetes, compared to 18% of white patients (16). Similarly, diabetes was highly prevalent (45%) among patients in the ADHERE (Acute Decompensated

FIGURE 3 Differences in Clinical Correlates of Diabetes in Asian and White Patients With HF: Results Interaction Analysis

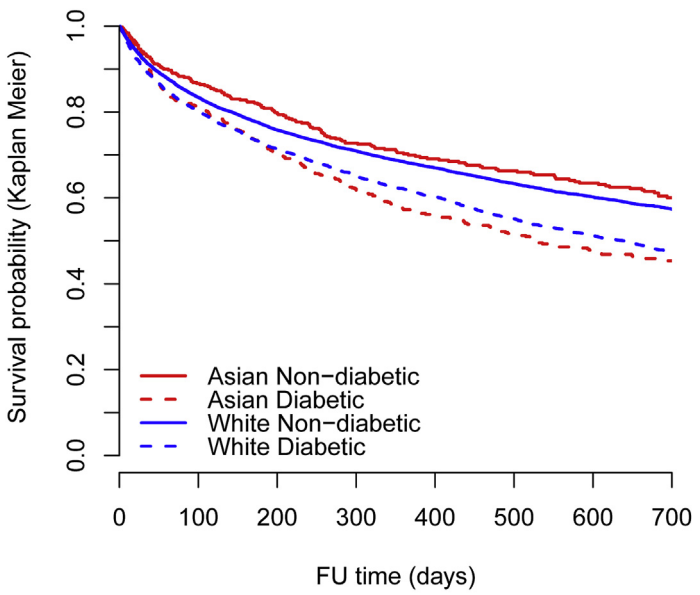


Adjusted odds ratios (and 95% confidence intervals) for concomitant diabetes with the respective clinical characteristic, stratified by ethnicity. BMI = body mass index; CAD = coronary artery disease; HF = heart failure; LVEF = left ventricular ejection fraction; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

Heart Failure Registry)-Asia Pacific study, which included patients from Australia, Hong Kong, Taiwan, Malaysia, Thailand, Philippines, Indonesia, and Singapore. The even higher prevalence of diabetes (57%) observed in the SHOP study cohort suggests that heterogeneity may exist among different Asian populations. The remarkably higher prevalence of diabetes in Asian patients with HF versus white patients with HF in the current study likely reflects the high and increasing prevalence of diabetes in Singapore's general population. In 2011, the prevalence of diabetes among Singaporean adults 20 to 79 years of age was 9.8%, higher than the Organization for Economic Cooperation and Development average of 6.9%. Indeed, diabetes is the largest single cause of total disease burden in Singapore (10.4% of total Disability-Adjusted Life-Years in 2010), a burden that increased by 4.6% from 2004 to 2010. These startling figures have been attributed to population aging, increased high-caloric food consumption and more sedentary lifestyle associated with the rapid transition from a developing to a developed country. Although diabetes is known to be a risk factor for developing HF (17), studies have further suggested that diabetes conveys a larger risk of left ventricular systolic and diastolic dysfunction, as well as future cardiovascular events, specifically in Asian patients compared to white patients (7,12).

CORRELATIONS WITH DIABETES. The much higher prevalence of diabetes in Asian patients despite lower prevalence of obesity is noteworthy. Obesity is well recognized as a major risk factor for type 2 diabetes, yet considerable variation in BMI has been reported in patients with diabetes. In fact, stratifying patients with diabetes by BMI into "lean" patients with diabetes (BMI <25 kg/m^2) versus obese patients with diabetes (BMI ≥30 kg/m^2) (18) revealed novel genetic variants (e.g., rs8090011 in the LAMA1 gene) associated with susceptibility to type 2 diabetes, and provided evidence that lean patients with diabetes may have a stronger genetic predisposition to type 2 diabetes than obese cases. Intriguingly, ethnic differences have been observed in the association of diabetes with fat mass and obesity-associated (FTO) gene polymorphisms and obesity, when comparing white patients and African American patients (19). Also, the strong association of FTO variant rs8050136 with diabetes in European patients appeared to be mediated by obesity (20), whereas this association was independent of BMI among Japanese patients with diabetes (21). Asian patients have been shown to have a different body composition with greater abdominal and visceral fat compared to white

FIGURE 4 The Relationship Between Diabetes and Outcomes for Asian and White Patients With Heart Failure

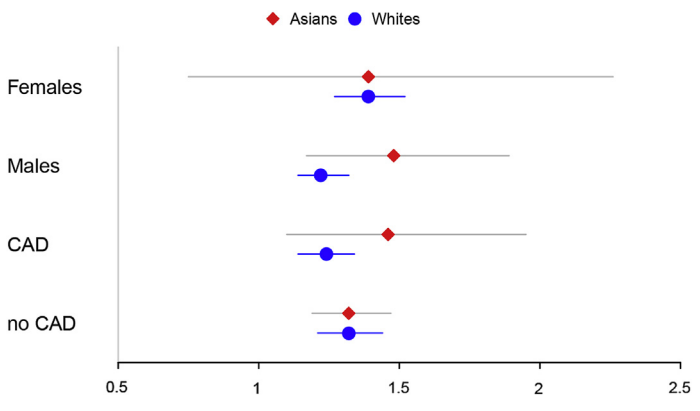


Number of patients at risk

Asians	1001	806	705	630	479	423	396	334
Whites	19537	14809	12250	10224	8407	6674	5341	3884

Kaplan-Meier curves of event-free survival probabilities are shown for Asian and white patients with heart failure with and without diabetes for the composite endpoint of heart failure hospitalizations and all-cause mortality. FU = follow-up.

FIGURE 5 The Impact of the Presence of Diabetes on Heart Failure Hospitalizations and Mortality in Pre-Specified Subgroups



The figure shows the hazard ratio with 95% confidence interval for each subgroup. CAD = coronary artery disease.

patients of similar BMI (22), potentially explaining their increased metabolic risk for obesity-related diseases such as diabetes, even in the absence of obesity. High waist circumference or waist-to-hip ratio, or the World Health Organization's proposed lower BMI cutoff for defining obesity (BMI ≥27.5 kg/m^2) in Asian patients (23), may better reflect increased metabolic risk in the Asian population. Furthermore, recent data provided insight into the molecular basis of diabetes in lean patients; subcutaneous and visceral adipose tissues displayed adipocyte hypertrophy, shortened telomeres, and hypoadiponectinemia reflecting a state of metabolic obesity (24). In a study of Singaporean Chinese, although some known genetic variants from European cohorts were replicated, most of the risk of diabetes remained unexplained, suggesting an important role of environmental factors and gene by environment interactions (25).

ASSOCIATION BETWEEN DIABETES AND OUTCOMES. Diabetes had a larger detrimental impact on the composite outcome of HF hospitalizations and all-cause mortality in Asian patients with HF compared to their white counterparts. This difference was driven by HF hospitalizations, as no difference was observed in all-cause mortality alone. The ethnic disparity was not explained by differences in age, severity of HF, use of HF medications, or renal function. Beyond glomerular filtration rate, more subtle differences in renal injury from diabetes, reflected by microalbuminuria, may have been present. Prior studies showed a greater predisposition to albuminuria in Asian patients compared to white European patients (26), and a strikingly high prevalence of microalbuminuria (44%) among Asian adults with type 2 diabetes without known proteinuria or nondiabetic kidney disease (27).

Unmeasured factors that may have contributed to the more profound impact of diabetes on HF hospitalizations in Singaporean patients with HF include the following: a longer disease history of diabetes or more severe diabetes, suboptimal glucose control (increasing the risk of macro- and microvascular complications) (28), subtle renal dysfunction (manifested as microalbuminuria rather than changes in creatinine clearance), possible differences in use of antidiabetic medications that may adversely affect myocardial function (29), and possible differences in nonadherence to prescribed diet and medications, self-monitoring and use of home care monitoring programs. Unfortunately, these data, and changes over time, were not uniformly available in both cohorts. Nonetheless, prior reports have suggested suboptimal glycemic control (glycosylated hemoglobin >7.0%) in the majority of Singaporeans with diabetes (30).

STUDY LIMITATIONS. Data collection occurred through separate albeit similar protocols in the SwedeHF registry and SHOP study; thus, some differences in data are likely. However, the majority of the merged data were standard HF variables that are uniformly assessed globally, and ours is a unique combined database of population-based HF from European and Asian countries. Unquantified differences, including cultural attitude, health care consumption or access, and glycemic control may have accounted for some of the observed differences. Furthermore, the cross-sectional correlations of diabetes with HF characteristics do not allow determination of causality. We did not measure molecular data to unravel the underlying mechanism for greater odds of diabetes in Asian patients with HF despite being lean. Also, we did not correct for multiple comparisons, but this would not change our overall conclusions.

The Singaporean and Swedish patients in this study, although representative of the respective HF populations in Singapore and Sweden, may not be universally representative of Asian and White patients with HF. We acknowledge the complexities of terminology for race, ethnicity, and culture (31) and oversimplification in our assignment of the terms *Asian* and *white* to refer to our groups. Our results may not be generalizable to patients with HF from other ethnicities (e.g. black or Latino). Furthermore, this analysis does not investigate potential inter-ethnic differences among the Asian ethnicities (Chinese, Malay, Indian, Eurasian) in Singapore, due to limited numbers in the subgroups. Disparities among Asian ethnicities with regard to diabetes control and cardiovascular risk have been described (30,32). Nonetheless, Singapore's HF population is representative of patients of Southeast Asian ancestry in a developed society, and Singapore's advanced health care system allows meaningful comparisons with patients in other developed and medically advanced societies.

CLINICAL IMPLICATIONS. Diabetes is increasing in prevalence in Asia; therefore, the relationship between HF and diabetes as well as the clinical characteristics and outcomes of these patients have major public health implications (32). The strikingly high prevalence of diabetes in Asian patients with HF means that the population attributable risk of diabetes is far greater in Asian populations compared to European populations, given the same relative risk (5,33). Furthermore, the younger age among

Asian HF populations with diabetes implies greater economic impact of the disease compared to European HF populations. Notably, the risk of diabetes-related cardiovascular complications and death has been reported to be even higher in younger than in older patients (33). As timely recognition of (pre-) diabetes and strict glycemic control are key in preventing diabetes-related complications, our data have important implications for early screening of patients for diabetes, and early aggressive glycemic control. In particular, our results suggest that even young and nonobese individuals in Singapore should be actively screened for diabetes—groups that are traditionally considered low risk in European populations.

CONCLUSIONS

These population-based data from Singapore and Sweden show that Asian patients with HF have more than 3 times higher odds of diabetes despite lower BMI and being a decade younger on average. Overweight and obesity were more strongly related to diabetes in white patients than in Asian patients. The negative impact of diabetes on outcomes was more profound in Asian patients. These findings further underscore the importance of seeking a better understanding of ethnicity-specific underlying mechanisms for incident diabetes and poor outcomes with prevalent diabetes, and of ethnicity-tailored aggressive preventive and treatment strategies for diabetes and its complications.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Diabetes is 3-fold more common in Southeast Asian with HF patients compared to white patients with HF, despite younger age and less obesity, and more strongly associates with poor outcomes in Asian patients than in white patients.

TRANSLATIONAL OUTLOOK: These data underscore the need for ethnic-specific approaches to diabetes in patients with heart failure.

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KEY WORDS **diabetes mellitus, global disease patterns, global health, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction**