

Does diabetes increase the risk of cardiovascular events in patients with negative treadmill stress echocardiography?

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Abstract. Cardiovascular morbidity and mortality rates are considered to be high in patients with diabetes despite negative stress test results; however, little data are available to support this supposition. We compared the long-term cardiovascular events between patients with diabetes and those without diabetes with negative treadmill stress echocardiography and evaluated the predictors for cardiovascular events in patients with diabetes. A total of 1,243 consecutive patients (mean age, 56 ± 10 years; non-diabetics: diabetics, 975:268; mean follow-up of 5 years) with negative treadmill stress echocardiography were evaluated. Clinical data were examined, and major adverse cardiovascular events (MACEs, a composite of coronary revascularization, acute myocardial infarction, and cardiovascular death) were compared between the non-diabetic and diabetic groups. In the population matched by clinical characteristics, the diabetic and non-diabetic groups had similar occurrence of MACEs (non-diabetics vs. diabetics = 5% versus 7%; $p = 0.329$) and event-free survival. MACEs in the diabetic group were associated with elevated early diastolic velocity of the mitral inflow/mitral annulus (E/e') ratio, indicative of diastolic dysfunction. The absence of statin and dipeptidyl peptidase-4 inhibitor use and use of sulfonylureas were also predictors of more MACEs. In conclusion, long-term cardiovascular events in patients with diabetes and negative stress echocardiography were comparable to those in patients without diabetes. However, appropriate monitoring of diastolic dysfunction, statin use, and individualized antidiabetic drug selection are required to reduce the cardiovascular risk in patients with diabetes.

Key words: Diabetes mellitus, Prognosis, Stress echocardiography

EXERCISE STRESS ECHOCARDIOGRAPHY is one of the non-invasive methods available for diagnosing significant coronary artery disease (CAD). Therefore, patients with negative stress echocardiography usually have good prognosis [1]. However, patients with diabetes, the elderly, and patients with low exercise capacity are considered to have substantial risks of cardiovascular morbidity and mortality despite negative stress echocardiography [2]. Moreover, the European Society of Cardiology and European Atherosclerosis Society commented that the cardiovascular risk in patients with diabetes is higher than moderate, similar to the risk in patients with CAD [3]. Thus, it has been considered that patients with diabetes should be monitored carefully even when stress test findings for diagnosing CAD are negative. However,

there is paucity of data from direct comparison studies to ascertain whether cardiovascular events occur more frequently in patients with diabetes than in those without diabetes in the general population with negative stress test findings. Previous studies focused on demonstrating cardiac outcomes in high-risk diabetic patients with several comorbidities, including a history of CAD and heart failure [4, 5]. Meanwhile, diastolic dysfunction in patients with diabetes has been considered a surrogate marker of cardiac events. Indeed, it was associated with subclinical CAD, risk of developing heart failure, and cardiovascular mortality in several previous reports [6-9].

In this study, we compared the long-term cardiovascular events in patients with diabetes with those in patients without diabetes in a symptomatic population with negative treadmill stress echocardiography. Furthermore, we investigated prognostic markers for cardiovascular events among baseline clinical characteristics and medical, laboratory, treadmill, and echocardiographic parameters.

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Methods

Study population

We evaluated consecutive patients who had chest pain or chest discomfort and a negative treadmill stress echocardiography from November 2006 to June 2018 in a cardiology center (Kyung Hee University Hospital at Gangdong, Seoul, Korea). The patients were divided into diabetic (DM) and non-diabetic (non-DM) groups. Diabetes was diagnosed if the individual used hypoglycemic agents, had a fasting plasma glucose level of ≥ 126 mg/dL, had a 2-hour 75 g oral glucose tolerance test result of ≥ 200 mg/dL plasma glucose, or had a blood glycosylated hemoglobin of $\geq 6.5\%$ [10].

We excluded patients aged < 20 years and those who had a history of percutaneous coronary intervention, cardiac artery bypass graft, or stroke; resting regional wall motion abnormalities indicative of previous CAD; significant cardiomyopathy including hypertrophic and dilated cardiomyopathies; systolic dysfunction with an ejection fraction $< 40\%$; significant valvular disease over moderate grade; type 1 diabetes; significant systemic disease including chronic kidney disease (estimated glomerular filtration rate < 45 mL/min); liver cirrhosis; and chronic obstructive pulmonary disease more than moderate grade. Verbal informed consent was obtained during a telephonic interview, and the recorded data were collected. This study was approved by the hospital's ethics committee (KHNMC 202003063).

Treadmill stress echocardiography

Before exercise, all patients underwent baseline echocardiography, including complete 2-dimensional, color, pulsed, and continuous wave Doppler imaging, according to the standard techniques [11]. Treadmill testing was performed with symptom-limited exercise cessation according to the standard Bruce protocol under monitoring of twelve-lead electrocardiography (ECG), blood pressure (BP), and heart rate. After exercise, the patients were placed in the left decubitus position to estimate regional wall motion abnormalities. Failure to achieve the target heart rate was defined as $< 85\%$ of the age-predictive maximal heart rate ($220 - \text{age}$). The Duke treadmill score was calculated as follows: exercise time (min) $- 5 \times$ maximal ST depression (mm) $- 4 \times$ angina index (0, no angina during exercise; 1, non-limited angina; 2, exercise limited angina) [12]. Angina during the exercise test was defined as the development of exertional chest pain, dyspnea, or chest discomfort following the exercise test. Left ventricular (LV) ejection fraction was assessed using modified Simpson's method. LV mass indexed to body surface area (LVMI) and relative wall thickness (RWTd) were estimated using LV cavity dimension and

wall thickness at end-diastole. This estimation used the formula: LV mass = $0.8(1.04 ([\text{LV dimension} + \text{interventricular septal thickness} + \text{posterior wall thickness}]^3 - [\text{LV dimension}]^3)) + 0.6$ g; RWTd = $2(\text{posterior wall thickness})/(\text{LV dimension})$ [13]. LV diastolic function was estimated using several traditional parameters [14, 15]. LV diastolic dysfunction grades were also determined according to the American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACVI) recommendations (updated in 2016) using the following four variables [15]: septal annular velocity $e' < 7$ cm/s (or lateral < 10 cm/s), average $E/e' > 14$ (or septal > 15), left atrial maximal volume index > 34 mL/m², and peak tricuspid regurgitation velocity > 2.8 m/s. Grades were divided into three groups: normal, abnormal variables $< 50\%$; indeterminate, abnormal variables 50% ; and diastolic dysfunction, abnormal variables $> 50\%$.

Data acquisition, patient follow-up, and cardiovascular events

Clinical characteristics, medication history, laboratory test results, treadmill stress echocardiography results, and follow-up data were obtained from medical records and telephonic interviews. Cardiovascular events were estimated using major adverse cardiovascular events (MACEs), defined as a composite of coronary revascularization, acute myocardial infarction, and cardiovascular death. Acute myocardial infarction was defined as significant cardiac enzyme elevation with appropriate symptoms and ECG changes.

Statistical analysis

Statistical analyses were performed using R software, version 3.6.2. Continuous variables are expressed as mean \pm standard deviation (or median and interquartile range for variables with skewed data). Categorical variables are expressed as group percentages. Student's *t*-test (or the Mann-Whitney test for variables with skewed data) was used to compare continuous variables between the two groups, and the chi-square test (or Fisher's exact test for cell counts less than 5) was used to compare categorical variables. Between-group comparison of clinical and treadmill-related variables was performed in the overall and propensity score-matched populations. This was necessary because baseline clinical characteristics, including age, sex, body mass index, history of smoking, and incidence of hypertension, were substantially different between the groups. Propensity score matching for balancing covariates was performed using the nearest-neighbor method. Standardized differences after matching were within 0.1 for all variables. Cumulative MACEs incident curves of both groups were described using

Kaplan-Meier plots and compared using the log-rank test in both the overall and propensity score-matched populations. Univariate and multivariate Cox proportional hazard models were used to identify the predictors of MACEs. Association between predictors and clinical data was assessed using linear and logistic regression models according to predictor characteristics. A p -value <0.05 was considered statistically significant.

Results

Of the 1,823 people who underwent treadmill stress echocardiography, 580 were excluded, including 272 according to the exclusion criteria, 167 with positive stress echocardiography, and 141 who were unable to conduct a telephonic interview for follow-up information (e.g., withdrawn consent or lack of contact) (Supplemental Fig. 1). Thus, a total of 1,243 people were finally enrolled: 975 without diabetes (non-DM group) and 268 with diabetes (DM group). The mean follow-up period for MACEs was 4.8 ± 2.7 years (4.9 ± 2.7 years in the non-DM group, 4.6 ± 2.8 years in the DM group; $p = 0.132$).

Clinical data and MACEs between the non-DM and DM groups

In the overall population (Table 1), patients in the DM group were older, predominantly male, had a higher body mass index, and a higher incidence of smoking and hypertension than those in the non-DM group. After matching the baseline clinical characteristics (Table 2), patients in the DM group were found to take more angiotensin converting enzyme inhibitors or angiotensin-receptor blockers and statins and to have lower total cholesterol and low-density lipoprotein cholesterol levels, higher baseline heart rate and peak systolic BP, lower peak heart rate, higher percentage of failure to achieve the target heart rate, lower exercise capacity, thicker RWTd, lower maximal diastolic mitral inflow velocity of early wave/late wave (E/A) ratio, elevated early diastolic velocity of mitral inflow/early diastolic velocity of mitral annulus (E/e') ratio, and more advanced grade of diastolic dysfunction than those in the non-DM group.

The incidence of MACEs in the overall population was higher in the DM group than in the non-DM group ($p = 0.025$, Table 1; $p = 0.021$, Fig. 1A). However, in the propensity score-matched population, the DM group had a similar incidence of MACEs ($p = 0.329$, Table 2; $p = 0.289$, Fig. 1B) as the non-DM group, and advanced age, failure to achieve the target heart rate, angina occurrence during the exercise test, and increased LVMI were identified as independent predictors of MACEs (Table 3).

Table 1 Baseline clinical characteristics and MACEs of the non-DM and DM groups in the overall population

Overall population ($n = 1,243$)	Non-DM ($n = 975$)	DM ($n = 268$)	p value
Baseline clinical characteristics			
Age, years	55 ± 10	59 ± 10	<0.001
Male, n (%)	502 (51)	175 (65)	<0.001
Body mass index, kg/m^2	25 ± 3	26 ± 3	<0.001
Smoking, n (%)	190 (19)	67 (25)	0.040
Hypertension, n (%)	344 (35)	153 (57)	<0.001
MACEs, n (%)	35 (3.6)	18 (6.7)	0.025
Coronary revascularization	31	17	
AMI, non-fatal	3	1	
Cardiovascular death	1	0	

MACEs, major adverse cardiovascular events; DM, diabetic mellitus; AMI, acute myocardial infarction

Predictors of MACEs in each group

Univariate predictors of MACEs in the DM group (Table 4) were the incidence of hypertension, absence of statin and dipeptidyl peptidase-4 (DPP-4) inhibitor use, use of sulfonylureas, failure to achieve the target heart rate, and elevated E/e' ratio. After adjusting for significant parameters, except antidiabetic drugs (model 1), MACEs in the DM group were associated with the absence of statin use, failure to achieve the target heart rate, and elevated E/e' ratio. After adjusting for all significant parameters, including antidiabetic drugs (model 2), absence of statin and DPP-4 inhibitor use, use of sulfonylureas, and failure to achieve the target heart rate were independent predictors of MACEs in the DM group. Sulfonylurea users had higher blood glycosylated hemoglobin level ($7.5 \pm 1.5\%$ versus $7.1 \pm 1.3\%$; $p = 0.100$) and longer duration of diabetes (9.1 ± 8.7 years versus 7.6 ± 6.5 years; $p = 0.174$), but not significant, and DPP-4 inhibitor users had lower blood glycosylated hemoglobin level ($7.1 \pm 1.2\%$ versus $7.4 \pm 1.5\%$; $p = 0.185$) and shorter duration of diabetes (7.9 ± 7.2 years versus 8.2 ± 7.4 years; $p = 0.756$), but not significant, than users of other drugs.

Independent predictors of MACEs in the non-DM group were advanced age, angina occurrence during the exercise test, lower Duke treadmill score, and increased LVMI (Supplemental Table 1).

Clinical data associated with diastolic dysfunction in patients with diabetes

Elevated E/e' ratio in patients with diabetes was correlated with advanced age, female sex, history of non-smoking, incidence of hypertension, and longer duration of diabetes (Table 5). Among these, elevated E/e' ratio was independently associated with advanced age, female

Table 2 Clinical and treadmill stress echocardiography-related variables and MACEs between the non-DM and DM groups in the propensity score-matched population

Propensity score-matched population (<i>n</i> = 792)	Non-DM (<i>n</i> = 528)	DM (<i>n</i> = 264)	<i>p</i> value	<i>d</i> _{after}
Baseline clinical characteristics				
Age, years	58 ± 9	59 ± 10	0.396	0.062
Male, <i>n</i> (%)	347 (66)	174 (66)	1.000	-0.004
Body mass index, kg/m ²	26 ± 3	26 ± 3	0.328	0.072
Smoking, <i>n</i> (%)	128 (24)	67 (25)	0.793	0.026
Hypertension, <i>n</i> (%)	276 (52)	149 (56)	0.302	0.084
Medications				
Beta-blocker, <i>n</i> (%)	63 (12)	39 (15)	0.227	
CCB, <i>n</i> (%)	94 (18)	59 (23)	0.102	
ACEI or ARB, <i>n</i> (%)	100 (19)	134 (54)	<0.001	
Statin, <i>n</i> (%)	135 (26)	179 (71)	<0.001	
Metformin, <i>n</i> (%)		212 (88)		
SU, <i>n</i> (%)		78 (33)		
DPP-4 inhibitor, <i>n</i> (%)		93 (39)		
Insulin, <i>n</i> (%)		47 (20)		
Laboratory tests				
TC, mg/dL	196 ± 36	171 ± 41	<0.001	
TG, mg/dL	164 ± 127	169 ± 120	0.675	
HDL-C, mg/dL	49 ± 12	47 ± 12	0.079	
LDL-C, mg/dL	120 ± 34	98 ± 34	<0.001	
HbA1c, %		7.2 ± 1.4		
Hemodynamic and TMT data				
baseline SBP, mmHg	117 ± 15	119 ± 15	0.060	
baseline DBP, mmHg	69 ± 11	68 ± 10	0.380	
baseline heart rate, /min	70 ± 11	74 ± 12	<0.001	
peak SBP, mmHg	160 ± 31	171 ± 30	<0.001	
peak DBP, mmHg	78 ± 17	75 ± 16	0.071	
peak heart rate, /min	159 ± 18	155 ± 19	0.002	
Failure to target heart rate, <i>n</i> (%)	36 (7)	29 (11)	0.044	
MET	11.6 ± 2.1	10.8 ± 2.4	<0.001	
Duke treadmill score	6.9 ± 5.4	6.6 ± 5.7	0.312	
Angina during exercise, <i>n</i> (%)	247 (49)	131 (52)	0.442	
Echocardiographic findings				
EF, %	66 ± 4	66 ± 5	0.212	
LVMI, g/m ³	79.9 ± 17.9	80.7 ± 19.5	0.596	
RWTd	0.36 ± 0.06	0.38 ± 0.08	<0.001	
E/A	1.14 ± 0.39	0.91 ± 0.24	<0.001	
Septal E/e'	9.7 ± 2.4	10.7 ± 3.3	<0.001	
Grades of diastolic dysfunction			0.017	
<i>Normal</i>	488 (92.6)	228 (86.7)		
<i>Indeterminate</i>	34 (6.5)	27 (10.3)		
<i>Dysfunction</i>	5 (0.9)	8 (3.0)		
MACEs, <i>n</i> (%)	27 (5.1)	18 (6.8)	0.329	
Coronary revascularization	23	17		
AMI, non-fatal	3	1		
Cardiovascular death	1	0		

MACEs, major adverse cardiovascular events; DM, diabetic mellitus; *d*, standardized difference; CCB, calcium channel blocker; ACEI or ARB, angiotensin converting enzyme inhibitor or angiotensin-receptor blocker; SU, sulfonylurea; DPP-4, dipeptidyl peptidase-4; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, blood glycated hemoglobin; TMT, treadmill test; SBP, systolic blood pressure; DBP, diastolic blood pressure; MET, metabolic equivalent of tasks; EF, ejection fraction; LVMI, left ventricular mass index; RWTd, relative wall thickness; E/A, maximal diastolic mitral inflow velocity of early wave/late wave; E/e', early diastolic velocity of mitral inflow/early diastolic velocity of mitral annulus; AMI, acute myocardial infarction

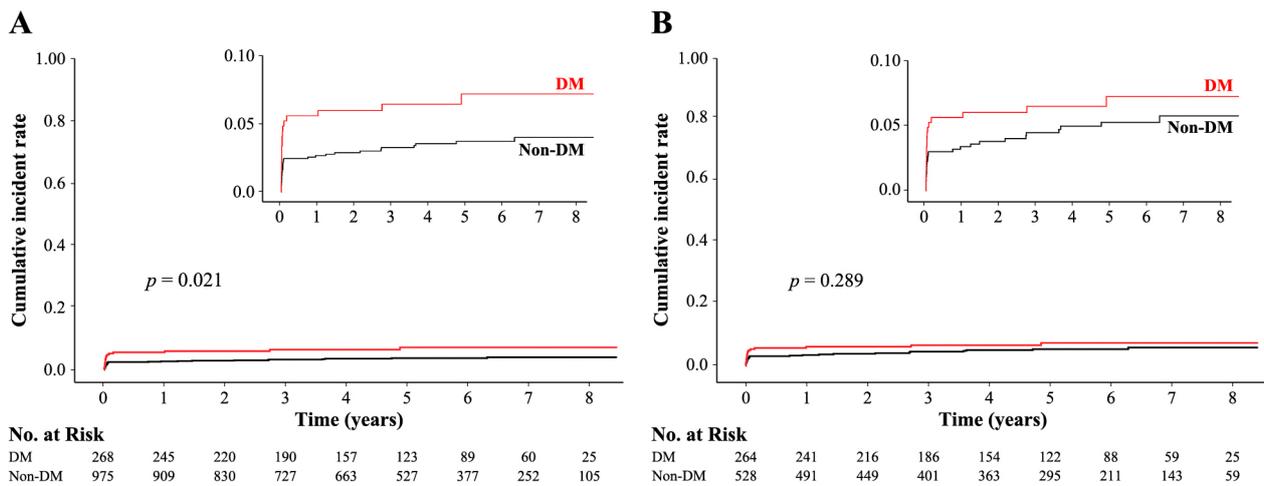


Fig. 1 Kaplan-Meier curves of MACEs: (A) observed curve (B) curve after matching for age, sex, body mass index, and history of smoking and hypertension. *p* values were estimated using the *log-rank* method; MACEs, major adverse cardiovascular events; DM, diabetes mellitus.

sex, incidence of hypertension, and longer duration of diabetes.

Discussion

Cardiovascular events between the non-DM and DM groups

In our study, patients with diabetes had cardiovascular events similar to those without diabetes when treadmill stress echocardiography was negative. Haffner *et al.* [16] reported that the risk in patients with diabetes and no history of myocardial infarction was comparable to that in patients with non-diabetes and a history of myocardial infarction. Several researchers have also shown that diabetes is a major independent risk factor for cardiovascular events [3, 17]. Moreover, Chaowalit *et al.* showed that diabetes accompanied by advanced age, history of CAD, or failure to achieve the target heart rate had a poorer prognosis despite negative dobutamine stress echocardiography [2]. However, this research group evaluated diabetes as a risk factor without directly comparing between patients with and without diabetes. Kamalesh *et al.* demonstrated that the prognosis of patients with diabetes and negative stress echocardiography was poorer than that of patients with non-diabetes and negative stress echocardiography [5]. However, their study population was based on veterans of a high-risk cohort including advanced age (mean age, 64 ± 11 years), high percentage of male participants (98%), high incidence of previous CAD (60%), existing regional wall motion abnormality (38%), and lower ejection fraction of <35% (4%), subsequently skewed. Therefore, it is not surprising that cardiac events in their study were high despite the relatively short follow-up period (20% of

patients with diabetes and 10% of patients without diabetes during a mean follow-up of 2 years). In addition, their data do not represent the primary cardiovascular risk of patients with diabetes because patients with heart disease were already enrolled in a high proportion and the primary cardiovascular risk assessment is different from the secondary risk assessment. Conversely, McCulley's study showed that diabetes is not a risk factor for cardiac events in patients with negative exercise echocardiography and that patients with diabetes have a benign course akin to patients without diabetes [4]. However, this group's enrolled sample of diabetic patients was only 6% (80 people); moreover, there was a relatively short mean follow-up period of 2 years. Our study enrolled more diabetic patients (264 persons) and directly compared cardiovascular events between patients with and without diabetes during a long-term follow-up of 5 years. We concluded that the estimated cardiovascular risk in patients with diabetes was comparable to that in patients without diabetes when treadmill stress echocardiography was negative. This finding also demonstrates that treadmill stress echocardiography can effectively stratify the risk in patients with diabetes.

Diastolic dysfunction as a predictor for cardiovascular events in patients with diabetes

After the introduction of the updated recommendations of ASE/EACVI (2016) for the assessment of diastolic dysfunction, Sanchis *et al.* reported that half of the patients diagnosed with grade 1 diastolic dysfunction under the 2009 recommendations were reassessed as having normal diastolic function under the new guidelines [18]. Like this, the estimation of diastolic function is complex and conflicting because numerous parameters

Table 3 Univariate and multivariate predictors of the occurrence of MACEs in the propensity score-matched population

Analyses	Univariate		Multivariate	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Clinical characteristics				
Age	1.049 (1.014–1.085)	0.005	1.059 (1.008–1.113)	0.023
Male	2.436 (1.135–5.232)	0.022	2.725 (0.909–8.164)	0.073
Body mass index	0.985 (0.895–1.082)	0.747	—	—
Smoking	1.393 (0.741–2.619)	0.303	—	—
Hypertension	1.571 (0.853–2.892)	0.147	—	—
DM	1.379 (0.759–2.504)	0.291	—	—
Medications				
Beta-blocker	0.630 (0.225–1.763)	0.379	—	—
CCB	0.767 (0.342–1.721)	0.521	—	—
ACEI or ARB	1.536 (0.846–2.788)	0.159	—	—
Statin	0.514 (0.266–0.996)	0.049	0.461 (0.185–1.147)	0.096
Laboratory tests				
TC	1.000 (0.992–1.008)	0.970	—	—
TG	1.000 (0.998–1.002)	0.831	—	—
HDL-C	0.982 (0.955–1.010)	0.196	—	—
LDL-C	1.002 (0.994–1.011)	0.566	—	—
TMT data				
Failure to target heart rate	2.533 (1.179–5.440)	0.017	3.110 (1.033–9.365)	0.044
MET	0.926 (0.818–1.048)	0.223	—	—
Angina during exercise	2.722 (1.354–5.470)	0.005	3.380 (1.336–8.549)	0.010
Duke treadmill score	0.951 (0.906–0.997)	0.039	0.947 (0.892–1.005)	0.071
Echocardiographic findings				
EF	0.982 (0.921–1.048)	0.589	—	—
LVMI	1.025 (1.013–1.037)	<0.001	1.027 (1.007–1.047)	0.007
RWTd (×10)	1.046 (0.684–1.601)	0.835	—	—
E/A	0.628 (0.178–2.216)	0.469	—	—
Septal E/e'	1.131 (1.039–1.231)	0.005	0.973 (0.839–1.128)	0.718
Diastolic dysfunction grade				
Normal (reference)	1		—	—
Indeterminate	1.853 (0.783–4.386)	0.160	—	—

MACEs, major adverse cardiovascular events; DM, diabetic mellitus; HR, hazard ratio; CI, confidence interval; CCB, calcium channel blocker; ACEI or ARB, angiotensin converting enzyme inhibitor or angiotensin-receptor blocker; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TMT, treadmill test; MET, metabolic equivalent of tasks; EF, ejection fraction; LVMI, left ventricular mass index; RWTd, relative wall thickness; E/A, maximal diastolic mitral inflow velocity of early wave/late wave; E/e', early diastolic velocity of mitral inflow/early diastolic velocity of mitral annulus

and definitions have been introduced. Among them, the E/e' ratio is linearly correlated with LV diastolic pressure; thus, elevated E/e' ratio has traditionally and most strongly of any single parameter been indicative of diastolic dysfunction [19]. In our study, elevated E/e' ratio in patients with diabetes was associated with more MACEs. Diastolic dysfunction is a common finding in diabetes [6, 9] and tends to increase rapidly over time [20]. Indeed, diastolic dysfunction was more common in the DM

group than in the non-DM group and was associated with increasing age and duration of diabetes in the DM group. Diastolic dysfunction is also considered an early sign of diabetic and ischemic cardiomyopathy [6-8] and has been known to be associated with increased cardiovascular morbidity and mortality in several reports [7, 21]. Several researchers suggest that chronic hyperglycemia-associated pathogenic mechanisms cause diastolic dysfunction in patients with diabetes, subsequently associated

Table 4 Univariate and multivariate predictors of the occurrence of MACEs in patients with diabetes

Analyses	Univariate		Multivariate (model 1)		Multivariate (model 2)	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Clinical characteristics						
Age	1.031 (0.981–1.084)	0.232	—	—	—	—
Male	1.006 (0.378–2.681)	0.990	—	—	—	—
Body mass index	1.019 (0.888–1.170)	0.784	—	—	—	—
Smoking	0.821 (0.270–2.493)	0.727	—	—	—	—
Hypertension	4.024 (1.165–13.901)	0.028	3.114 (0.885–10.949)	0.077	3.455 (0.977–12.214)	0.054
DM duration	0.982 (0.916–1.052)	0.599	—	—	—	—
Medications						
Beta-blocker	0.719 (0.164–3.148)	0.662	—	—	—	—
CCB	1.772 (0.665–4.722)	0.252	—	—	—	—
ACEI or ARB	1.772 (0.665–4.722)	0.252	—	—	—	—
Statin	0.378 (0.150–0.952)	0.039	0.297 (0.115–0.769)	0.012	0.360 (0.139–0.932)	0.035
Metformin	0.616 (0.178–2.128)	0.443	—	—	—	—
SU	2.581 (1.018–6.540)	0.046	—	—	3.110 (1.142–8.467)	0.026
DPP-4 inhibitors	0.090 (0.012–0.680)	0.020	—	—	0.125 (0.016–0.965)	0.046
Insulin	0.510 (0.117–2.217)	0.369	—	—	—	—
Laboratory tests						
TC	1.007 (0.996–1.017)	0.225	—	—	—	—
TG	1.000 (0.997–1.004)	0.812	—	—	—	—
HDL-C	0.982 (0.942–1.023)	0.387	—	—	—	—
LDL-C	1.008 (0.995–1.020)	0.235	—	—	—	—
HbA1c	0.505 (0.153–1.674)	0.264	—	—	—	—
TMT data						
Failure to target heart rate	3.281 (1.169–9.206)	0.024	2.924 (1.009–8.473)	0.048	3.860 (1.270–11.729)	0.017
MET	0.898 (0.750–1.074)	0.238	—	—	—	—
Angina during exercise	2.782 (0.885–8.744)	0.080	—	—	—	—
Duke treadmill score	1.000 (0.911–1.096)	0.992	—	—	—	—
Echocardiographic findings						
EF	1.008 (0.916–1.109)	0.868	—	—	—	—
LVMI	1.018 (1.000–1.036)	0.050	—	—	—	—
RWTd ($\times 10$)	0.926 (0.490–1.752)	0.814	—	—	—	—
E/A	0.954 (0.168–5.430)	0.958	—	—	—	—
Septal E/e'	1.169 (1.052–1.298)	0.004	1.143 (1.012–1.291)	0.031	1.127 (0.989–1.284)	0.074
Diastolic dysfunction grade						
<i>Normal (reference)</i>	1		—	—	—	—
<i>Indeterminate</i>	2.690 (0.876–8.258)	0.084	—	—	—	—

MACEs, major adverse cardiovascular events; DM, diabetic mellitus; HR, hazard ratio; CI, confidence interval; CCB, calcium channel blocker; ACEI or ARB, angiotensin converting enzyme inhibitor or angiotensin-receptor blocker; SU, sulfonylurea; DPP-4, dipeptidyl peptidase-4; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, blood glycosylated hemoglobin; TMT, treadmill test; MET, metabolic equivalent of tasks; EF, ejection fraction; LVMI, left ventricular mass index; RWTd, relative wall thickness; E/A, maximal diastolic mitral inflow velocity of early wave/late wave; E/e', early diastolic velocity of mitral inflow/early diastolic velocity of mitral annulus

with worse cardiovascular outcomes [22, 23]. In contrast, diastolic dysfunction in patients without diabetes was not an independent predictor of MACEs in the present study. The association between diastolic dysfunction and cardi-

ovascular outcomes is not a specific finding observed only in patients with diabetes. Diastolic dysfunction is also a surrogate marker for predicting the cardiovascular morbidity and mortality in advanced age, hypertension,

Table 5 Clinical data associated with the E/e' ratio in patients with diabetes: univariate and multivariate analyses

Analyses	Univariate			Multivariate		
	$\beta \pm SE$	$st\beta$	<i>p</i> value	$\beta \pm SE$	$st\beta$	<i>p</i> value
Age	0.117 \pm 0.019	0.349	<0.001	0.078 \pm 0.020	0.235	<0.001
Male	-2.477 \pm 0.399	-0.358	<0.001	-2.294 \pm 0.407	-0.336	<0.001
Body mass index	0.042 \pm 0.062	0.041	0.507	—	—	—
Smoking	-1.023 \pm 0.461	-0.136	0.027	0.567 \pm 0.447	0.077	0.206
Hypertension	1.535 \pm 0.397	0.232	<0.001	0.854 \pm 0.368	0.131	0.021
Duration of DM	0.098 \pm 0.027	0.220	<0.001	0.063 \pm 0.026	0.142	0.014
HbA1c	-0.049 \pm 0.179	-0.021	0.784	—	—	—

E/e', early diastolic velocity of mitral inflow/early diastolic velocity of mitral annulus; β , unstandardized coefficients; SE, standardized error; $st\beta$, standardized coefficients; DM, diabetic mellitus; HbA1c, blood glycated hemoglobin

and ischemic heart disease in the general population [24-27]. However, because patients with CAD were excluded from this study and the propensity score-matched age range was relatively narrow, diastolic dysfunction in patients without diabetes may have not been a predictor of cardiovascular events in our study. Instead, other well-known risk factors [27-30] such as advanced age, exertional angina occurrence, lower Duke treadmill score, and increased LV hypertrophy were predictors of cardiovascular events in patients without diabetes.

Medications as predictors for cardiovascular events in patients with diabetes

Statins are one of the most commonly used drugs against cardiovascular events. In our study, a cardioprotective effect of statin use was observed in patients with diabetes. Indeed, statin use was higher in patients with diabetes than in those without diabetes, and this may have had an effect on lowering MACEs in patients with diabetes. On the other hand, interpreting the association between the use of antidiabetic drugs and cardiovascular events in patients with diabetes is more complex and may be controversial. In our study, sulfonylurea use was associated with more MACEs, whereas DPP-4 inhibitor use was associated with fewer MACEs. Several previous randomized controlled trials and their meta-analyses, including CAROLINA (CARDiovascular Outcome study of LINAgliptin *versus* glimepiride in patients with type 2 diabetes) and CARMELINA (the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin) trials, have reported neutral cardiovascular outcomes for sulfonylureas and DPP-4 inhibitors [31-35]. Conversely, meta-analyses of observational studies have argued about the cardiovascular risk of sulfonylureas [33, 36, 37]. This discrepancy may be due to the selection and indication bias inherent in observational studies, including disease severity; glucose-lowering efficacy; duration of diabetes; physician preference; and social, economic, and other

confounding factors. This would have worked similarly to the present study. Nevertheless, because the risk of hypoglycemia and weight gain from sulfonylurea use may increase cardiovascular events, the individual cardiovascular risks should be estimated and appropriate anti-diabetic drugs should be selected accordingly.

Limitations

This study has several limitations. First, this was a retrospective study conducted at a single center. Second, the overall number of events was relatively small, including severe cardiovascular events of myocardial infarction or cardiovascular death. This may be because treadmill stress echocardiography tends to be performed in relatively healthy patients who can exercise compared with pharmacologic stress echocardiography. Indeed, several previous studies using dobutamine stress echocardiography or perfusion scan tests [2, 5] had more severe cardiovascular events, whereas McCully's study [4] using exercise stress echocardiography had fewer clinical events. Third, we had no event of hospitalization for heart failure during follow-up probably because patients with definite diastolic dysfunction were fewer and patients with diabetes were well-managed (median blood glycated hemoglobin level, 6.7% [5.4;8.0]) and had a relatively short duration of diabetes (median duration, 7 years [0;12]) on the index day (Supplemental Fig. 2). Fourth, we did not exclude patients with early cardiac events within 30 days to evaluate the overall predictive value of patients with negative stress echocardiography, as in the real clinical setting. Thus, we included patients with false-negative stress echocardiography results. Indeed, 30 patients underwent coronary revascularization within 30 days, which was higher in patients with diabetes than in those without diabetes, although the difference was not significant [14 (5.3%) in the DM group *versus* 16 (3.0%) in the non-DM group; *p* = 0.114]. Conversely, this finding suggests that long-term cardiovascular

outcomes in patients with diabetes are better than those mentioned above when short-term cardiac events within 30 days were excluded (cardiac event rate per person-year: 0.4% in the non-DM group and 0.3% in the DM group; $p = 0.680$). Fifth, we cannot guarantee that the same drug treatment was continued during follow-up because this study had an observational design. Finally, because the sample size to taking antidiabetic drugs was small and many patients were taking multiple antidiabetic drugs, it could not be estimated whether the severity of diabetes affecting cardiovascular events was significantly different for each antidiabetic drug.

Conclusion

Cardiovascular events in patients with diabetes were comparable to those in patients without diabetes during the long-term follow-up when treadmill stress echocardiography was negative. In particular, the popular use of

statins in patients with diabetes may contribute to reducing cardiovascular events. However, patients with diabetes and diastolic dysfunction should be managed with caution because diastolic dysfunction is an independent risk factor for cardiovascular events. In addition, the use of antidiabetic drugs should be selected according to individual risks because the inherent side effects of specific drugs, such as hypoglycemia and weight gain, affect cardiovascular events.

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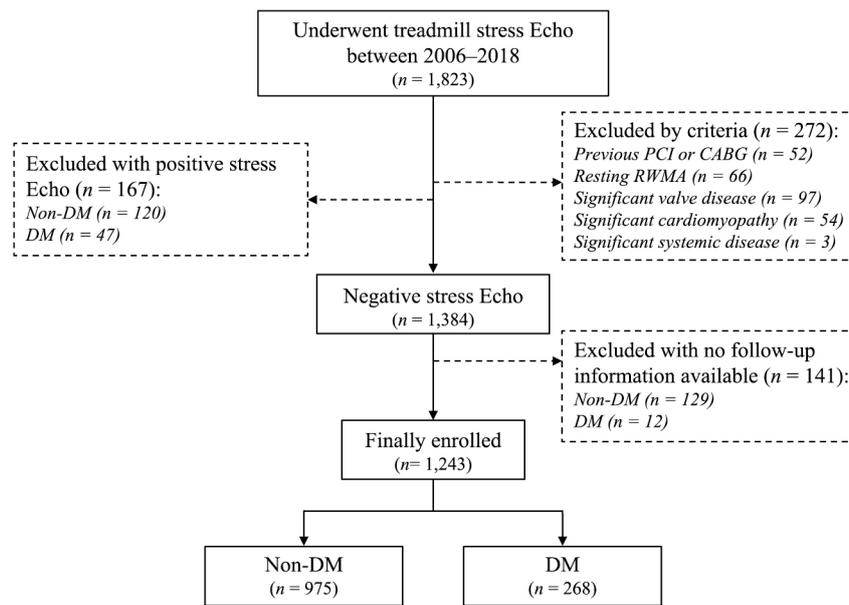
Conflict of Interest

None declared.

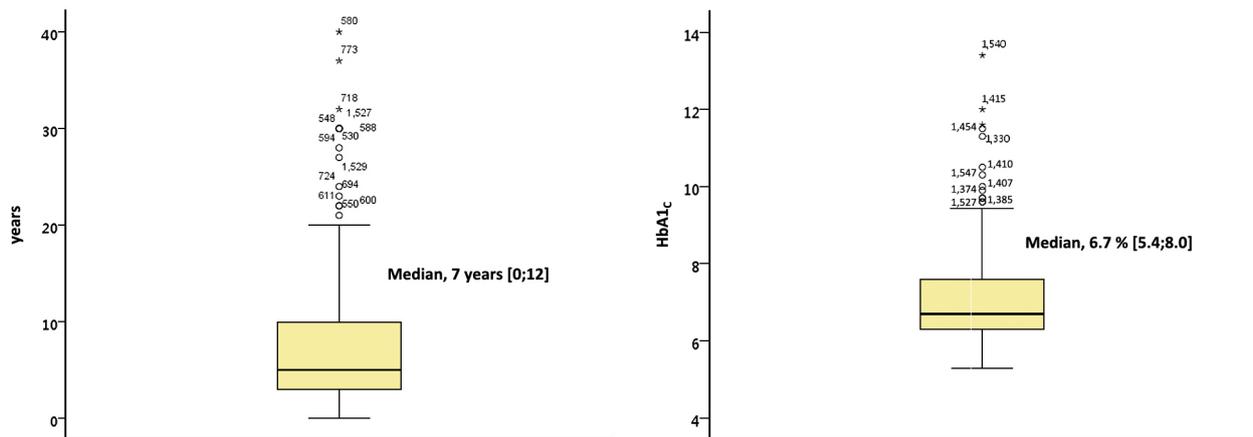
Supplemental Table 1 Univariate and multivariate predictors of the occurrence of MACEs in patients without diabetes

Analyses	Univariate		Multivariate	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Clinical characteristics				
Age	1.081 (1.042–1.122)	<0.001	1.086 (1.019–1.156)	0.010
Male	3.253 (1.478–7.161)	0.003	6.503 (0.829–51.000)	0.075
Body mass index	1.027 (0.937–1.125)	0.573	—	—
Smoking	1.921 (0.941–3.921)	0.073	—	—
Hypertension	1.714 (0.883–3.327)	0.111	—	—
Medications				
Beta-blocker	0.544 (0.129–2.298)	0.408	—	—
CCB	0.548 (0.165–1.821)	0.326	—	—
ACEI or ARB	1.141 (0.460–2.829)	0.776	—	—
Statin	0.336 (0.101–1.115)	0.075	—	—
TMT data				
Failure to target heart rate	1.405 (0.430–4.587)	0.574	—	—
MET	0.909 (0.780–1.060)	0.225	—	—
Angina during exercise	2.615 (1.197–5.712)	0.016	3.274 (1.046–10.250)	0.042
Duke treadmill score	0.923 (0.879–0.970)	0.002	0.916 (0.857–0.979)	0.010
Echocardiographic findings				
EF	0.966 (0.899–1.038)	0.350	—	—
LVMI	1.039 (1.021–1.057)	<0.001	1.032 (1.006–1.059)	0.015
RWTd ($\times 10$)	1.223 (0.722–2.073)	0.454	—	—
E/A	0.216 (0.040–1.163)	0.074	—	—
Septal E/e'	1.095 (1.025–1.171)	0.007	0.895 (0.738–1.086)	0.261
Diastolic dysfunction grade			—	—
<i>Normal (reference)</i>	1			
<i>Indeterminate</i>	2.630 (0.928–7.454)	0.069	—	—

MACEs, major adverse cardiovascular events; HR, hazard ratio; CI, confidence interval; CCB, calcium channel blocker; ACEI or ARB, angiotensin converting enzyme inhibitor or angiotensin-receptor blocker; TMT, treadmill test; MET, metabolic equivalent of tasks; EF, ejection fraction; LVMI, left ventricular mass index; RWTd, relative wall thickness; E/A, maximal diastolic mitral inflow velocity of early wave/late wave; E/e', early diastolic velocity of mitral inflow/early diastolic velocity of mitral annulus



Supplemental Fig. 1 A study flowchart. Echo, echocardiography; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; RWMA, regional wall motion abnormalities; DM, diabetes mellitus



Supplemental Fig. 2 Left, median disease duration of diabetes; Right, blood glycosylated hemoglobin (HbA1c) level

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