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Association of type 2 diabetes mellitus with the development of new-onset atrial fibrillation in patients with non-ischemic dilated cardiomyopathy

-Impact of SGLT2 inhibitors-

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Abstract

Purpose: The aim of this study was to investigate the association of type 2 diabetes mellitus (T2DM) with the development of new-onset atrial fibrillation (AF) for non-ischemic dilated cardiomyopathy (DCM) patients. We also tested the hypothesis that sodium glucose cotransporter type 2 (SGLT2) inhibitors reduce the risk of development of new-onset AF for non-ischemic DCM patients.

Methods: We retrospectively studied 210 patients with non-ischemic DCM and sinus rhythm, mean age of 59.0±16.7 years and left ventricular ejection fraction of 31.0±8.2% (all<45%). T2DM was identified in 60 patients (28.6%), and the remaining 150 patients (71.4%) were classified as non-T2DM patients.

Results: New-onset AF occurred in 21 patients (10.0%) over a median follow-up of 6.1 years. Kaplan-Meier curve analysis showed that non-ischemic DCM patients without T2DM experienced fewer occurrences of the development of new-onset AF compared with those with T2DM (log-rank p=0.0003). Furthermore, global longitudinal strain in patients who showed development of new-onset AF was significantly lower than that in those whose sinus rhythm was preserved (6.4±1.4% vs. 7.7±2.2%, p=0.01). Of the 60 non-ischemic DCM patients with T2DM, those treated with SGLT2 inhibitors experienced fewer occurrences of the development of new-onset AF than did those not treated with SGLT2 inhibitors (log-rank p=0.040).

Conclusions: T2DM is associated with the development of new-onset AF in non-ischemic DCM patients, and treatment with SGLT2 inhibitors can significantly reduce the development of new-onset AF. Our findings may thus offer a new insight into the management of non-ischemic DCM patients with T2DM.

Key words: type 2 diabetes mellitus, atrial fibrillation, dilated cardiomyopathy, sodium glucose cotransporter type 2 inhibitors

Introduction

Type 2 diabetes mellitus (T2DM) is associated with increases in both cardiovascular events and cardiovascular mortality [1]. T2DM is also associated with myocardial fibrosis or increased collagen content and myocardial stiffness [2], and is known as a significant factor associated with coronary artery disease and the development of various types of heart failure (HF) [3]. Atrial fibrillation (AF) is the most common heart rhythm disorder and the number of individuals with AF is expected to increase in the future [4]. Importantly, the development of new-onset AF in various types of HF patients was found to be a cause of HF hospitalization and to be associated with poor outcomes [5-7]. In addition, T2DM is reportedly associated with an increased risk of development of new-onset AF, while findings of a previously reported meta-analysis of cohort and case-control studies indicated that patients with T2DM had an approximate 40% greater risk of developing new-onset AF compared to patients without [8].

Sodium glucose cotransporter type 2 (SGLT2) inhibitors represent a new class of anti-hyperglycemic agents for the treatment of T2DM, and act insulin-independently to selectively inhibit renal glucose reabsorption, thereby increasing urinary glucose excretion. Three large clinical trials using a SGLT2 inhibitor, empagliflozin [9], canagliflozin [10] or dapagliflozin [11], found that treatment with SGLT2 inhibitors of T2DM patients without HF who had or were at risk for atherosclerotic cardiovascular disease, resulted in a lower rate of cardiovascular death or hospitalization for HF. In addition, dapagliflozin reduced the risk of HF deterioration or death from cardiovascular causes for patients with HF with reduced ejection fraction (HFrEF) than for those who received a placebo, regardless of the presence or absence of T2DM [12]. More recently, dapagliflozin also was found to reduce by 19% the risk of development of new-onset AF for 17,160 T2DM patients without HF by significantly lowering the time to the first AF event during follow-up[13].

AF is also a common occurrence in HFrEF patients such as those with non-ischemic dilated cardiomyopathy (DCM), and limits cardiovascular capacity, lowers the quality of life and has been

shown to be associated with worsened outcome. However, the association of T2DM with the development of new-onset AF in non-ischemic DCM patients, or the impact of SGLT2 inhibitors on the development of new-onset AF for such patients remains unclear. The aim of this study was thus to investigate the association of T2DM with the development of new-onset AF in non-ischemic DCM patients. We also tested the hypothesis that SGLT2 inhibitors could reduce the risk of the development of new-onset AF for non-ischemic DCM patients.

Materials and Methods

Study population

The retrospective study group consisted of 218 patients with non-ischemic DCM admitted to Kobe University Hospital between June 2010 and March 2019, all of whom were diagnosed with reduced LV ejection fraction (LVEF) (<45%). Patients were excluded from enrolment in this study if they met any of the following criteria: (1) history or suspicion of coronary artery disease; (2) previous history of open-heart surgery and congenital heart disease; (3) undeniable secondary cardiomyopathy; (4) serious renal dysfunction defined as glomerular filtration rate <30mL/min/1.73m^2; (5) uncontrolled hypertension >180/100mmHg; (6) more than moderate primary valvular heart disease other than functional mitral regurgitation; (7) a previous history of electrocardiographically confirmed AF or atrial flutter. Reduced LVEF due to ischemic cardiomyopathy and LV myocardial ischemia were excluded on the basis of results obtained with coronary angiography, coronary computed tomography angiography, treadmill exercise or stress myocardial perfusion scintigraphy. None of the patients showed an ischemic response, and coronary angiography showed no coronary artery disease, defined as >50% stenosis of a major epicardial vessel. Eight patients (3.7%) were excluded from all subsequent analyses because of poor echocardiographic image quality to analyze speckle-tracking strain, so that eventually 210 patients with DCM were enrolled in this study. This study was approved by the local ethics committee of our institution (No. B20014).

Echocardiographic examination

All patients underwent a resting standard echocardiographic examination using a commercially available echocardiography systems (Aplio Artida: Canon Medical Systems, Tochigi, Japan; Vivid 7 or E9: GE Vingmed Ultrasound AS, Horten, Norway; iE33: Philips Medical Systems, Andover, MA). Digital routine grayscale two-dimensional cine loops from three consecutive heart beats were obtained at end-expiratory apnea from standard parasternal and apical views. Sector width was optimized to allow for complete myocardia visualization while maximizing the frame rate. Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography [14].

GLS Analysis

Speckle-tracking strain analysis was performed for each patient with the aid of a single dedicated software to evaluate LV longitudinal function, which was assessed in terms of global longitudinal strain (GLS) (AutoSTRAIN, TOMTEC-ARENA: TOMTEC Imaging Systems GmbH, Munich, Germany). Briefly, apical 4-, 2- and long-axis views, obtained as Digital Imaging and Communications in Medicine (DICOM) formatted file images, were uploaded onto a personal computer for subsequent off-line GLS analysis. Longitudinal speckle-tracking strain was calculated by means of an automated contouring detection algorithm, and manual adjustments of region of interest were performed if necessary. Longitudinal strain results for the individual clips were visualized in color-coded format and combined in a bull's eye plot. GLS was then determined as the averaged peak longitudinal strain of 18 LV segments, and was expressed as an absolute value in accordance with current guidelines [14].

Definitions of primary endpoint

Long-term unfavorable outcome events were pre-specified as primary endpoint of the development of new-onset AF over a median follow-up period of 6.1 years (2.5-7.8 years).

Statistical analysis

Continuous variables were expressed as mean values with standard deviation for normally distributed data and as medians with interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The parameters of the two subgroups were compared by using Student t test or Mann-Whitney U test according to data distribution. Proportional differences were evaluated with Fisher's exact test. Event-free curves showing freedom from the development of new-onset AF were determined with the Kaplan-Meier method and cumulative event rates were compared by using the log-rank test. The intraclass correlation coefficient was used to determine inter- and intra-observer reproducibility for GLS from 20 randomly selected subjects. For all steps, a p value of < 0.05 was considered statistically significant. All the analyses were performed with commercially available software (MedCalc software version 18.1.1.; MedCalc Software, Mariakerke, Belgium).

Results

Baseline characteristics

The baseline clinical and echocardiographic characteristics of the 210 patients with non-ischemic DCM are summarized in Table 1. Their mean age was 59.0±16.7 years, LVEF was 31.0±8.2%, and 70 patients (33.3%) were female. The intraclass correlation coefficients for inter-observer reproducibility of GLS were 0.972 (95% confidential interval: 0.944-0.986), and the corresponding coefficients for intra-observer reproducibility were 0.968 (95% confidential interval: 0.920-0.985).

Comparison of patients with or without T2DM

A comparison of baseline parameters of non-ischemic DCM patients with or without T2DM is summarized in Table 2. T2DM was identified in 60 patients (28.6%), and the remaining 150 patients (71.4%) were classified as non-T2DM patients. Non-ischemic DCM patients with T2DM were more likely to be older and have a lower blood pressure than did those without T2DM.

Association of T2DM with the development of new-onset AF

New-onset AF occurred in 21 patients (10.0%) over a median follow-up of 6.1 years. Fig. 1 shows the result of the Kaplan-Meier curve analysis for the development of new-onset of AF in non-ischemic DCM patients with or without T2DM. Non-ischemic DCM patients without T2DM experienced fewer occurrences of the development of new-onset AF compared with those with T2DM (log-rank p=0.0003).

Comparison of GLS for patients with or without the development of new-onset AF

GLS for patients with the development of new-onset AF was significantly lower than that for patients whose sinus rhythm was preserved (6.4±1.4% vs. 7.7±2.2%, p=0.01; Fig. 2).

Impact of SGLT2 inhibitors on new-onset AF in patients with T2DM

Fig. 3 shows the result of the Kaplan-Meier curve analysis for the development of new-onset AF among 60 non-ischemic DCM patients with T2DM. Of these patients, 32 (53.3%) were treated with SGLT2 inhibitors including 20 with dapagliflozin, 7 with empagliflozin and 5 with canagliflozin. Those treated with SGLT2 inhibitors experienced fewer occurrences of the development of new-onset AF compared with those not treated with SGLT2 inhibitors (log-rank p=0.040).

Fig. 4 shows representative cases of GLS in a bull's eye plot of DCM patients who showed development of new-onset AF and whose sinus rhythm was preserved during follow-up.

Discussion

The findings of our study indicate that the presence of T2DM was associated with the development of new-onset AF in non-ischemic DCM patients. In addition, treatment with SGLT2 inhibitors significantly reduced the development of new-onset AF in non-ischemic DCM patients with T2DM. To the best of our knowledge, this is the first study to show association of T2DM with development of new-onset AF in patients with non-ischemic DCM, and the preventive effect of SGLT2 inhibitors.

Impact of T2DM on AF in HF patients

T2DM is a major cardiovascular risk factor, and its global prevalence is predicted to will have increased from 425 million to 600 million by the year 2045 [15]. The projected number of individuals with AF in the European Union could reach 14-17 million by 2030 [16]. T2DM was identified to be an independent risk factor for the development of AF [8], and patients with T2DM and AF are at high risk of cardiovascular complications [17, 18]. The pathophysiology that may causally link T2DM with risk for AF is complex with several mechanisms having been proposed, including structural, electromechanical, mechanical myocardial remodeling, and an imbalance in the sympathetic-parasympathetic tone [19]. T2DM is also associated with neural remodeling in the atrium, with both parasympathetic and sympathetic denervation, which could lead to AF [20]. Moreover, the presence of hyperglycemia is thought to be leading to left atrial (LA) fibrosis and structural remodeling accompanied by LA dilatation [21]. In fact, a previous meta-analysis of cohort and case-control studies indicated that patients with T2DM are at a 40% higher risk to develop new-onset AF [22] and that the risk of new-onset AF increased gradually with advances of the diabetic stage [23].

It has also been reported that the development of new-onset AF is associated with poor outcome for HF patients. Mogensen et al reported on the association of various types of AF with outcomes for 15,415 HF patients from two large global multicenter randomized trials, the PARADIGM-HF and ATMOSPHERE trials, involving patients with HFrEF (LVEF<35%) [5]. They showed that HFrEF patients with development of new-onset AF were at higher risk of adverse outcomes including cardiovascular death and HF hospitalization compared to those without such development. In addition, HFrEF patients with this development also had a higher adjusted risk of cardiovascular death (hazard ratio: 2.37) and HF hospitalization (hazard ratio: 1.91) than did those with a history of AF at baseline.

Impact of SGLT2 inhibitors on new-onset AF in HF patients

There are several potential mechanisms pertaining to how SGLT2 inhibitors may reduce the risk of AF for patients with T2DM. It was found that SGLT2 inhibitors promote natriuresis and diuresis and thus may reduce atrial dilation, and experimental and clinical data suggest that SGLT2 inhibitors

reduce cardiac remodeling [24]. Findings from the sub-group analyses of the DECLARE-TIMI 58 trial [25] indicate that the SGLT2 inhibitor dapagliflozin reduced the risk of AF events by significantly increasing the time until the first AF event during follow-up by 19% for 17,160 patients with T2DM. They also showed that dapagliflozin did not only reduce the risk of occurrence of the first event but also significantly lowered the total number of AF events that were observed in this trial. Furthermore, our group showed, in a previously reported prospective multicenter study of 58 T2DM patients with stable HF at five institutions in Japan, the beneficial effect of SGLT2 inhibitors, specifically that of dapagliflozin on cardiac remodeling including LA volume index and LV mass index [26]. We found that the LA volume index and LV mass index showed significant reductions from 31 mL/m^2 (23-45) to 26 mL/m^2 (21-32) ($p = 0.001$), and from 75.0 g/m^2 (61.7-92.0) to 67.0 g/m^2 (55.0-81.9) ($p < 0.001$), respectively, 6 months after administration of dapagliflozin. SGLT2 inhibitors have also been shown to lower blood pressure and body weight, as well as reduce inflammation, oxidative stress, and the sympathetic overdrive, all of which play important roles in fostering AF. Furthermore, SGLT2 inhibitors have been linked to a reduction in epicardial fat [27], a biologically highly-active tissue that has been associated with an increase in incidence and severity of AF [19]. Moreover, Shao et al. recently reported that the SGLT2 inhibitor empagliflozin can ameliorate atrial structural and electrical remodeling as well as improve mitochondrial function and mitochondrial biogenesis in T2DM [28]. These findings thus show that SGLT2 inhibitors may be potentially useful for the prevention of T2DM-related AF.

Association of GLS with the development of new-onset AF in non-ischemic DCM patients

In this study, we showed that baseline GLS for patients with the development of new-onset AF was significantly lower than that in patients without. Olsen et al. used multivariable Cox regression analysis of 373 patients during a median follow-up of 5.5 years to show that baseline GLS was an independent predictor of the development of new-onset AF after ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention [29]. Russo et al. found that lower

GLS and an increase in the LA volume index were significantly associated with the development of new-onset AF in a community cohort of 675 subjects during a mean follow-up of 63.6±18.7 months [30]. They also showed that an abnormal GLS of <14.7% was associated with an adjusted hazard ratio of 3.2 for the risk of development of new-onset AF. One likely explanation for the link between GLS and the development of AF is that GLS largely reflects LA reservoir function, and a decrease in GLS is hence a reflection of an impaired LA reservoir function, which has been shown to be associated with the development of AF [31]. Furthermore, we recently reported finding that the SGLT2 inhibitor dapagliflozin was associated with improvement in GLS, which led to further improvement in the LV diastolic function of T2DM patients with stable HF [32]. Thus, SGLT2 inhibitors may possibly be used for the prevention of development of AF as a result of improvement in GLS, so that GLS-guided management may lead to more effective management of non-ischemic DCM patients with T2DM.

Clinical implications

In addition to previous studies using T2DM patients without HF, we demonstrated for the first time the association of T2DM with the development of new-onset AF in non-ischemic DCM patients (LVEF<45%). We also newly showed the association of low GLS with the development of new-onset AF in non-ischemic DCM patients. Dublin et al. reported that T2DM was associated with higher risk of developing new-onset AF, and that this risk became higher as treatment of T2DM lasted longer and glycemic control deteriorated [33]. Although it is not known whether permanent hyperglycemia or wide fluctuations in glucose levels, which are commonly seen in T2DM, was associated with the development of new-onset AF, they can be therapeutic targets for the prevention of new-onset AF in non-ischemic DCM patients with T2DM. Since previous studies also indicated that low GLS was strongly associated with poor outcome in patients with HFrEF[34, 35], treatment with SGLT2 inhibitors may have a significant impact on outcome by reducing the risk of development of new-onset AF in non-ischemic DCM patients with T2DM. especially those with low GLS.

Study limitations

This study covered a relatively small number of patients in a retrospective single-center study, so that T2DM patients were not randomized into patients with or without treated with SGLT2 inhibitors. Thus, further studies with larger patient populations will be needed to validate our findings. Furthermore, serial electrocardiography and Holter monitoring were not part of this study. Thus, occurrences of asymptomatic episodes or transient episodes of AF occurring after the study was completed may therefore have resulted in some underdiagnosis of new-onset AF. The causes of new-onset AF such as cardiac and/or non-cardiac were also unknown in this study. However, careful monitoring for development of new-onset AF was carried out by at least two senior cardiologists. Another limitation was that speckle-tracking analysis depends on the echocardiographic image quality. In fact, 3.7% of patients were excluded from speckle-tracking analysis due to poor echocardiographic image quality in this study. Finally, new-onset AF occurred in only 21 patients during follow-up so that it may effect on in-depth statistical analyses.

Conclusions

T2DM is associated with the development of new-onset AF in non-ischemic DCM patients, and treatment with SGLT2 inhibitors can significantly reduce the development of new-onset AF. Our findings may thus offer a new insight into the management of non-ischemic DCM patients with T2DM.

Compliance with Ethical Standards

Conflict of interest:

Hidekazu Tanaka declares that he has no conflict of interest. Kazuhiro Tatsumi declares that he has no conflict of interest. Hiroki Matsuzoe declares that he has no conflict of interest. Fumitaka Soga declares that he has no conflict of interest. Kensuke Matsumoto declares that he has no conflict of interest. Ken-ichi Hirata declares that he has no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals

performed by any of the authors.

Figure Legends

Figure 1: Kaplan-Meier curve shows that non-ischemic DCM patients without T2DM experienced fewer occurrences of development of new-onset AF compared with those with T2DM.

Figure 2: Box plot of GLS for T2DM patients with non-ischemic DCM and with development of new-onset AF and preservation of sinus rhythm, showing significantly lower GLS for T2DM DCM patients with development of new-onset AF.

Figure 3: Kaplan-Meier curve analysis of 60 T2DM patients with non-ischemic DCM shows that patients treated with SGLT2 inhibitors experienced fewer occurrences of development of new-onset AF compared with those not treated with SGLT2 inhibitors.

Figure 4: Representative cases of GLS in a bull's eye plot of DCM patients with development of new-onset AF and preservation of sinus rhythm during follow-up.

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Table 1

Baseline Characteristics of non-ischemic DCM Patients

	Non-ischemic DCM patients (n=210)
Clinical data	
Age, years	59.0±16.7
Female, n (%)	70 (33.3)
Body surface area, m^2	1.6±0.2
Systolic blood pressure, mmHg	108.0±19.5
Heart rate, bpm	68.6±15.5
T2DM, n (%)	60 (28.6)
Hypertension, n (%)	44 (21.0)
Dyslipidemia, n (%)	61 (29.0)
Electrocardiogram	
QRS duration, msec	114.0±23.4
Blood examination	
HbA1c, %	6.0±0.7
BNP, pg/dL	111.0 (54.0-202.4)
eGFR, mL/min/1.73m^2	63.0±19.5
Medical treatment, n (%)	
ACEI/ARB	205 (97.6)
β-blocker	206 (98.1)
MRA	97 (46.2)
Loop diuretics	108 (51.4)
Medical treatment (for T2DM), n (%)	
Insulin	4 (1.9)
DPP-4 inhibitor	36 (17.1)
GLP-1RA	2 (0.5)
Sulfonylurea	9 (4.3)
α-GI	6 (2.9)
Thiazolidine	1 (0.5)
Metformin	35 (16.7)
SGLT2 inhibitor	32 (15.2)
Echocardiography	
LV end-diastolic volume, mL	172.7±61.1
LV end-systolic volume, mL	121.0±52.3
LV ejection fraction, %	31.0±8.2
LA volume index, mL/m^2	50.3±19.7

LV mass index, g/m^2	131.1±39.6
E/e’	13.6±7.2
MR ≥moderate, n (%)	66 (32)

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%).

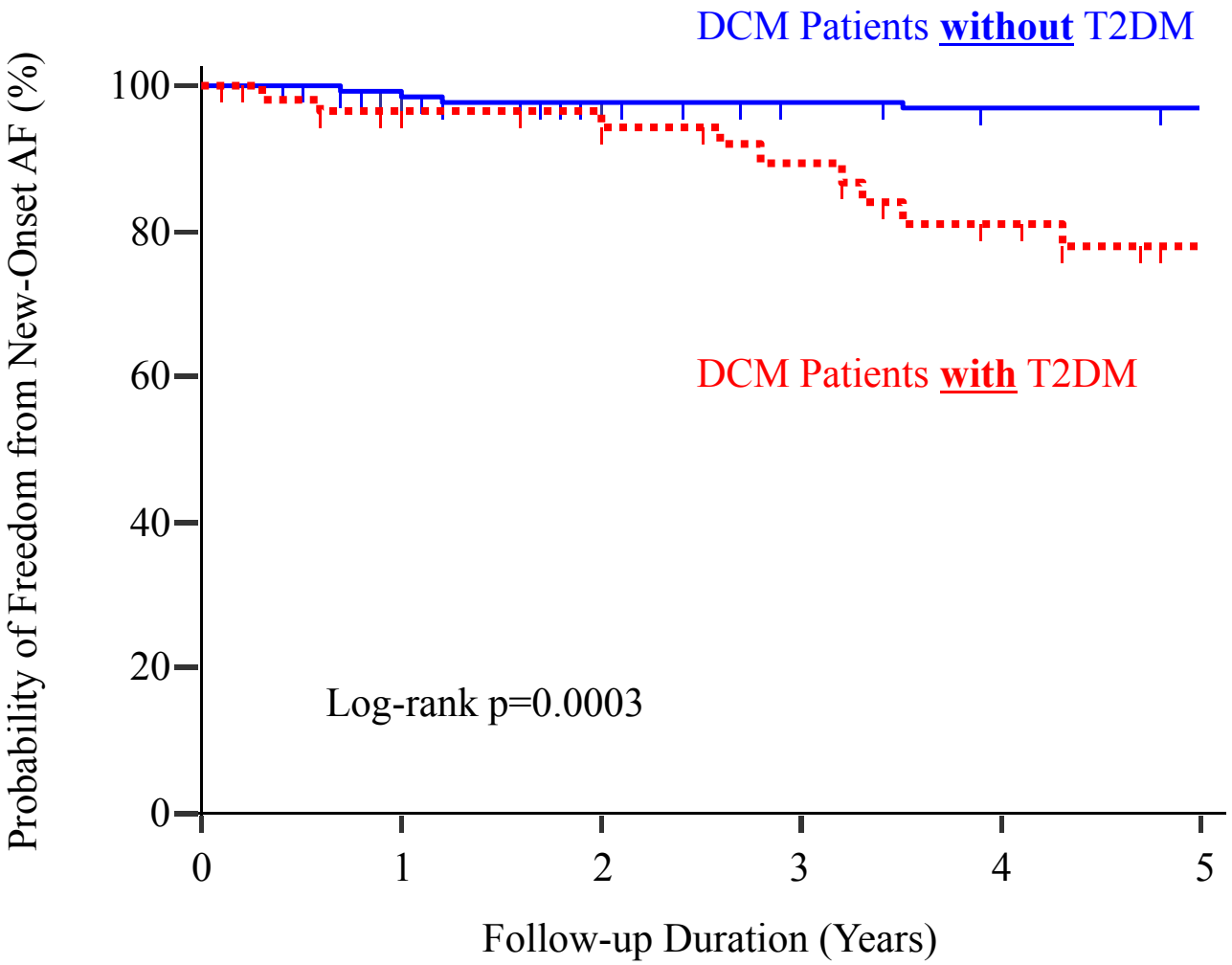
DCM, dilated cardiomyopathy; T2DM, type 2 diabetes mellitus; BNP. brain natriuretic peptide; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonists; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon like peptide-1receptor agonist; α-GI, α-glucosidase inhibitor; SGLT, sodium glucose cotransporter; LV, left ventricular; LA, left atrial; E, peak early diastolic mitral flow velocity; e’, spectral pulsed-wave Doppler–derived early diastolic velocity from the septal mitral annulus; MR, mitral regurgitation

Table 2
Comparison of patients with or without T2DM

Clinical data	Non-ischemic DCM patients **with** T2DM (n=60)	Non-ischemic DCM patients **without** T2DM (n=150)	P value
Age, years	63.1±14.9	57.3±14.1	0.02
Female, n (%)	19 (31.7)	51 (34.0)	0.75
Body surface area, m^2	1.6±0.2	1.6±0.2	0.65
Systolic blood pressure, mmHg	103.6±17.2	109.8±20.2	0.04
Heart rate, bpm	67.5±14.1	69.1±16.1	0.52
T2DM, n (%)	60 (100)	0 (0)	-
Hypertension, n (%)	10 (16.7)	34 (22.7)	0.36
Dyslipidemia, n (%)	22 (36.7)	39(26.0)	0.13
Electrocardiogram			
QRS duration, msec	118.9±22.4	112.1±23.6	0.05
Blood examination			
HbA1c, %	6.8±0.9	5.7±0.4	<0.0001
BNP, pg/dL	81.5 (48.5-202.0)	121.0 (54.0-202.0)	0.22
eGFR, mL/min/1.73m^2	59.1±16.0	64.6±20.5	0.06
Medical treatment, n (%)			
ACEI/ARB	59 (98.3)	147 (98.0)	1.0
β-blocker	59 (98.3)	147 (98.0)	1.0
MRA	31 (51.7)	66 (44.0)	0.36

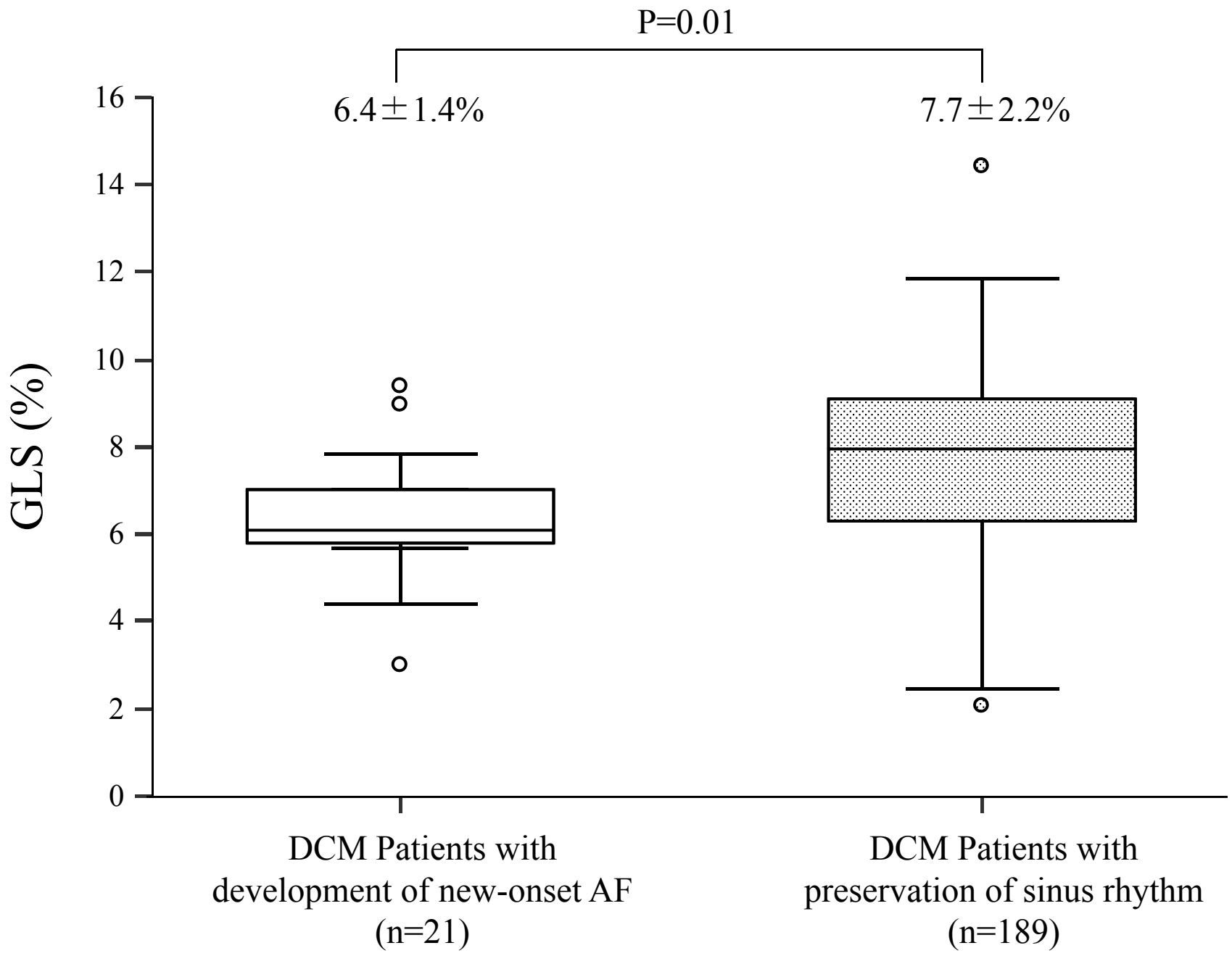
Loop diuretics	37 (61.7)	71(47.3)	0.07
Medical treatment (for T2DM), n (%)			
Insulin	4 (6.7)	0 (0)	-
DPP-4 inhibitor	36 (60.0)	0 (0)	-
GLP-1RA	2 (3.3)	0 (0)	-
Sulfonylurea	9 (15.0)	0 (0)	-
α-GI	6 (10.0)	0 (0)	-
Thiazolidine	1 (1.7)	0 (0)	-
Metformin	35 (58.3)	0 (0)	-
SGLT2 inhibitor	32 (53.3)	0 (0)	-
Echocardiography			
LV end-diastolic volume, mL	176.6±62.7	171.2±60.5	0.56
LV end-systolic volume, mL	125.9±51.8	119.0±52.6	0.39
LV ejection fraction, %	29.8±8.0	31.4±8.2	0.20
LA volume index, mL/m^2	52.4±25.2	49.5±17.0	0.34
LV mass index, g/m^2	125.1±34.1	133.5±41.4	0.17
E/e’	13.7±6.9	13.6±7.1	0.88
MR ≥moderate, n (%)	21 (35.0)	39 (26.0)	0.24

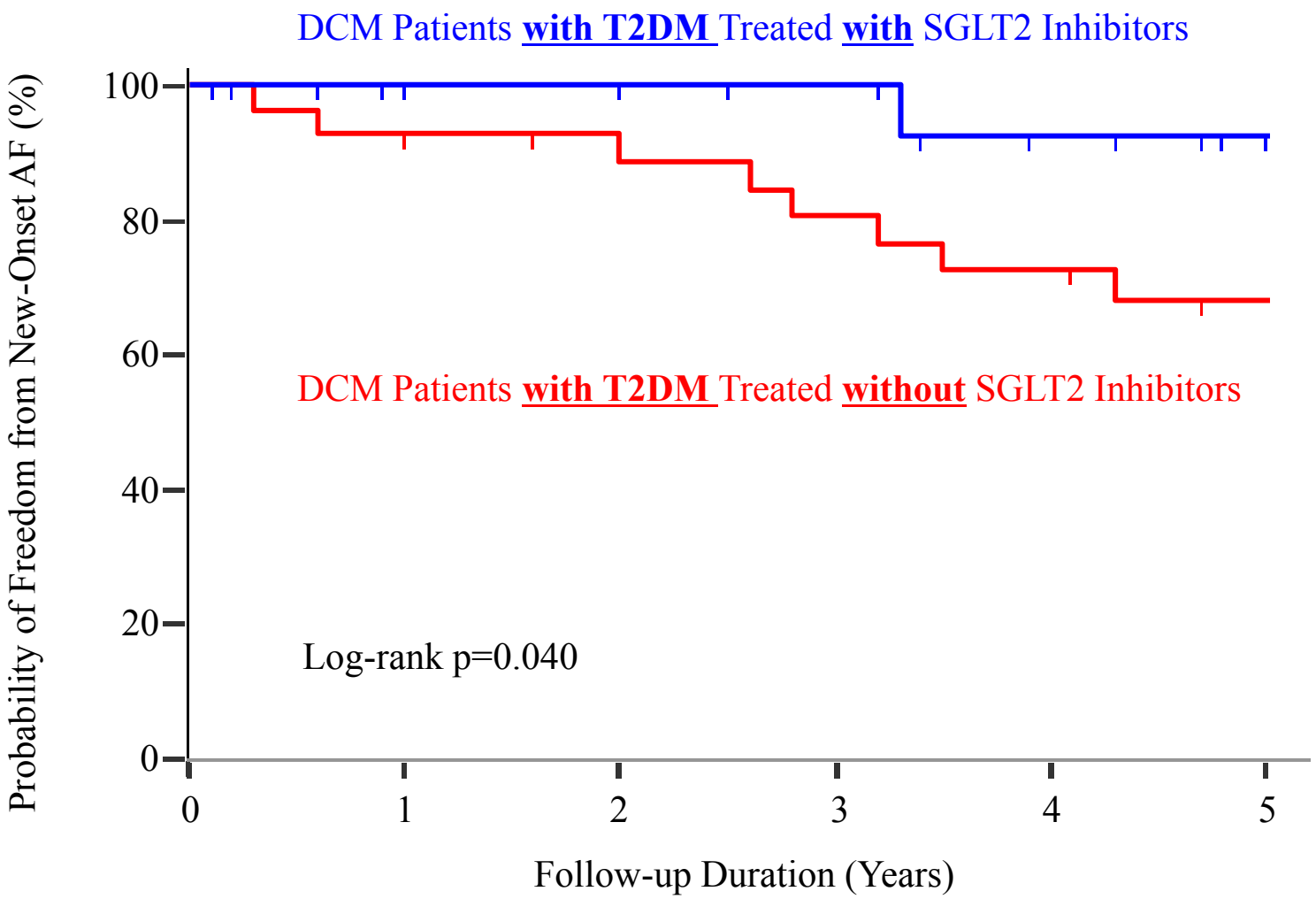
Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%). Abbreviation as in Table 1.



Number at risk

DCM Patients **without** T2DM					
150	137	126	115	112	110
DCM Patients **with** T2DM					
60	50	39	34	28	19


P=0.01
6.4±1.4%
7.7±2.2%
GLS (%)
16
14
12
10
8
6
4
2
0
DCM Patients with development of new-onset AF (n=21)
DCM Patients with preservation of sinus rhythm (n=189)

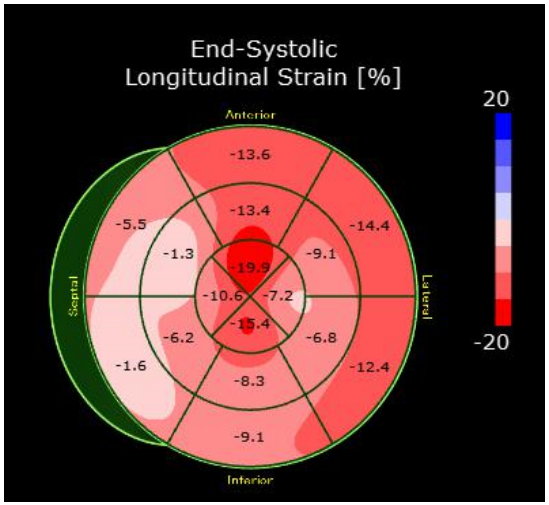


Number at risk

DCM Patients **with T2DM** Treated **with** SGLT2 Inhibitors	28	24	22	20	18	14
DCM Patients **with T2DM** Treated **without** SGLT2 Inhibitors	32	26	17	14	10	5

DCM patients **without** T2DM

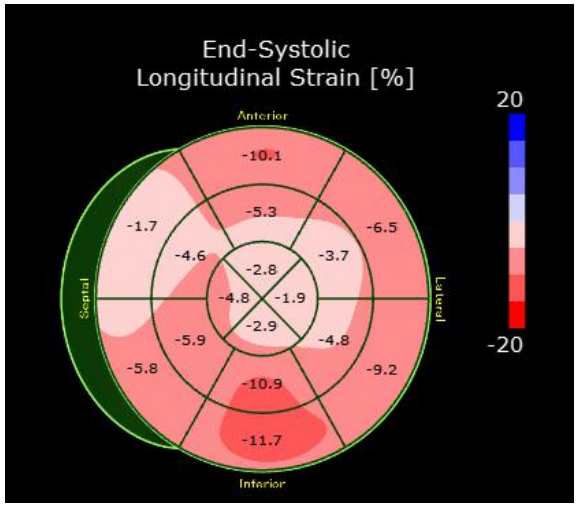
- ✓ 62-year-old male
- ✓ GLS=9.8%
- ✓ LVEF=31%



Preservation of sinus rhythm
for 5.0 years

DCM patients **with** T2DM

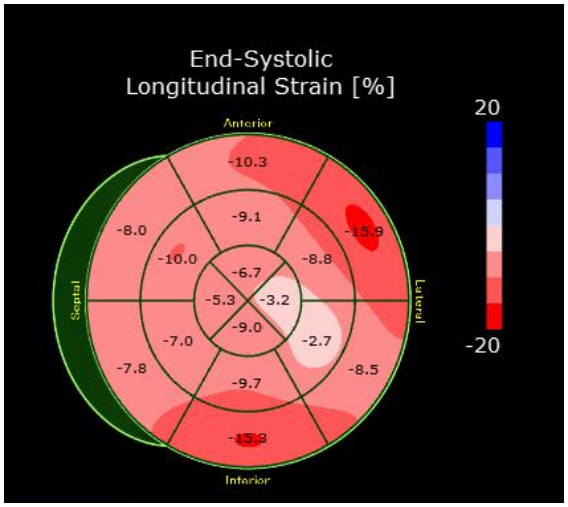
- ✓ 65-year-old male
- ✓ GLS=5.5%
- ✓ LVEF=35%
- ✓ Treated **without** an SGLT2 inhibitor



Development of new-onset AF
after 3.0 years

DCM patients **with** T2DM

- ✓ 67-year-old male
- ✓ GLS=7.9%
- ✓ LVEF=32%
- ✓ Treated **with** an SGLT2 inhibitor



Maintenance of sinus rhythm
for 4.5 years