Longitudinal Development of Left Ventricular Diastolic Function in Patients With Type 2 Diabetes

Laura Venskutonyte, Christina Jarnert, Lars Rydén, and Barbro Kjellström

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OBJECTIVE

Left ventricular diastolic dysfunction (LVDD) is considered to be common in patients with type 2 diabetes mellitus (T2DM), but information on its progression over time is lacking. We studied the longitudinal development of left ventricular diastolic function (LVDF) and myocardial blood flow reserve in patients with T2DM who were free from clinically detectable cardiovascular disease.

RESEARCH DESIGN AND METHODS

The LVDF was assessed in 73 patients with T2DM (mean age 67 ± 7 years; males 51%) on two occasions separated by 6.4 ± 0.8 years.

RESULTS

At baseline, LVDD was observed in 23 of the patients (32%). During follow-up, the LVDF normalized in 10 of these patients (43%) and remained unchanged in 13 of them (57%). Of the 50 patients (68%) with normal LVDF at baseline, LVDD developed in 9 (18%). Paired evaluation of myocardial blood volume index was available from 22 patients with LVDD and remained unchanged over time.

CONCLUSIONS

The condition of the majority of the investigated patients with LVDD improved or remained stable over a period of 6 years.

Myocardial dysfunction, in particular relaxation disturbances, occurs in patients with type 2 diabetes even in the absence of such conditions as hypertension and coronary artery disease (1). The background structural and functional changes relate to glucometabolic perturbations (2,3), but factors such as increasing age, obesity, hypertension, and coronary artery disease may also contribute to myocardial stiffness (4), and often coexist in patients with diabetes.

Left ventricular diastolic dysfunction (LVDD) is characterized by echocardiographic indices of impaired early diastolic filling, prolonged isovolumetric relaxation (5), and also, in more advanced stages, increased atrial volume (6). It has been referred to as a progressive condition increasing the risk for subsequent overt heart failure and compromised survival (7,8). The prevalence of LVDD in patients with type 2 diabetes has been estimated to be between 35% and 60% (9–11). The wide range is mainly explained by varying definitions of LVDD, applied echocardiographic techniques, and population characteristics. Considering the rather high prevalence of LVDD, a better understanding of its time-dependent development may identify high-risk populations as well as create opportunities to prevent or at least delay its progression. However, longitudinal studies of the natural course of left ventricular diastolic function (LVDF) in patients with type 2 diabetes who were free

Cardiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

Corresponding author: Laura Venskutonyte, laura.venskutonyte@ki.se.

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from apparent cardiovascular disease need to be presented before this can be accomplished.

The aim of the Diabetes Mellitus and Diastolic Dysfunction Follow-Up (DADD-FU) study was to investigate the progress of LVDF and myocardial blood flow reserve over time in patients with type 2 diabetes who were free from clinically detectable cardiovascular disease.

RESEARCH DESIGN AND METHODS

Patient Population

During 2004–2007, 121 patients with type 2 diabetes from the general population were screened by means of a clinical investigation and echocardiography for participation in the Diabetes Mellitus and Diastolic Dysfunction (DADD) study (12) (Fig. 1). To be included in the study, patients had to fulfill the following criteria: type 2 diabetes (fasting plasma glucose level ≥7.0 mmol/L or glycated hemoglobin [HbA_{1c}] level ≥6.5% [Diabetes Control and Complications Trial units]); age 40–70 years; normal systolic function; and impaired diastolic function, defined according to criteria outlined by the Mayo clinic (13–15). Exclusion criteria were as follows: ongoing insulin treatment, history of or clinical signs of ischemic heart disease (angina pectoris or myocardial infarction), peripheral vascular disease, heart failure, atrial fibrillation, clinically significant valvular disease, poorly controlled hypertension, left ventricular (LV) hypertrophy (septal wall thickness >13 mm or electrocardiogram signs indicating LV hypertrophy), or echocardiographic recordings of poor quality. Forty-one patients who were included in the DADD study and another 54 patients who met all inclusion criteria, apart from having LVDD at the time of the DADD study, were reinvestigated within the context of the present longitudinal analysis (Fig. 1), which were conducted from September 2010 to March 2012.

Study Investigations and Laboratory Tests

All patients underwent baseline examinations, including a brief medical history, blood tests (measurements of fasting plasma glucose and HbA_{1c} levels, and glomerular filtration rate), transthoracic Doppler echocardiography, and tissue Doppler imaging (TDI). The 54 patients screened but not included in the DADD study did not undergo a full clinical examination at baseline, while the study participants were investigated with a full medical history, physical examination, and some further blood tests (measurement of lipids and brain natriuretic peptide). During the DADD-FU study, all patients underwent the full investigation.

All blood analyses were performed at the central laboratory at the Karolinska University Hospital. HbA_{1c} levels were analyzed by high-performance liquid chromatography and presented as Diabetes Control and Complications Trial units (16).

Assessment of Diastolic Myocardial Dysfunction

A detailed description of the echocardiographic methods used in the study has been presented elsewhere (12). In brief, the echocardiograms, including the Doppler recordings, were obtained according to the standards of the American Society of Echocardiography (17). All investigations were performed by a single analyst with the same equipment on both occasions (Sequoia c512, rev 8.0, Siemens Medical Systems, Mountain View, CA). LV systolic function was assessed by calculating the wall motion index using a 17-segment model (18) and was considered normal if the wall motion index was ≤1.1. Left atrial volume index (in milliliters per square meter) (19) was measured by two-dimensional echocardiography in the apical four-chamber view (20). Early (E) and late (A) peak diastolic velocities (in centimeters per second) across the mitral valve were measured by pulsed Doppler echocardiography in the apical four-chamber view. Early (e′) and late (a′) myocardial velocities were measured by TDI. Diastolic function was assessed according to the following criteria: mild E/A ratio ≤0.75 and E/e′ ratio <10; moderate E/A ratio >0.75 and <2 in combination with an E/e′ ratio ≥10; and severe E/A ratio >2 and E/e′ ratio ≥10 (21).

Myocardial Contrast Echocardiography

Low–mechanical index myocardial contrast echocardiography was performed at rest and during maximal dipyridamole-induced vasodilatation (12). The contrast agent (SonoVue; Bracco, Milan, Italy) was administered intravenously with a parallel saline solution infusion. Image acquisition started after at least 2 min of contrast infusion. Microbubble replenishment images were recorded in

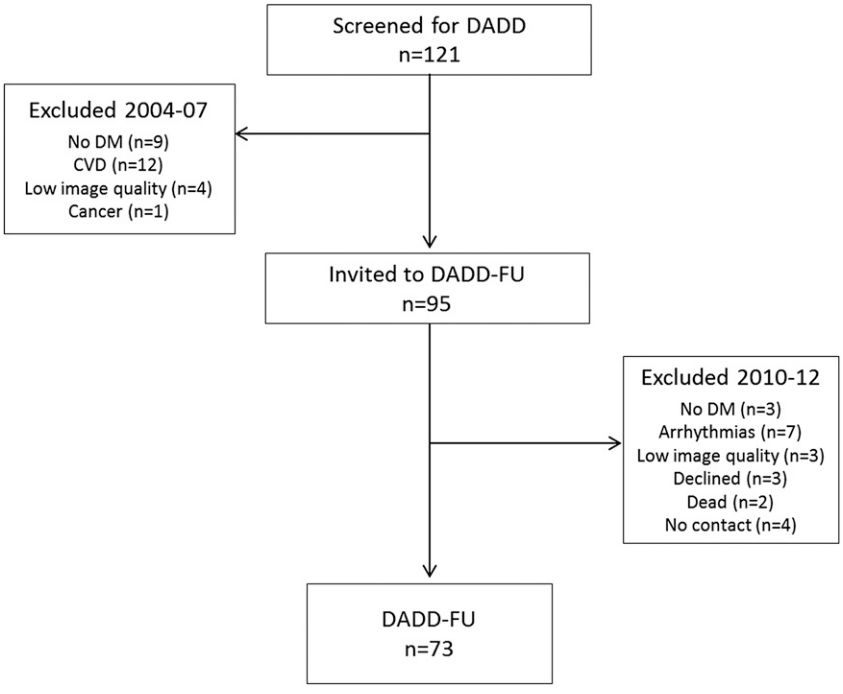

Figure 1—Flowchart of study population. Of the originally screened 121 patients, 95 were invited to participate in the follow-up study whereof 73 were eligible and subsequently included. CVD, cardiovascular disease; DM, diabetes mellitus.

the apical four-chamber view. Quantitative analysis was performed offline by a single analyst on a workstation (Research-Arena 1.0; TomTec Imaging Systems, Munich, Germany) with dedicated software (Axius Auto-Tracking Contrast Quantification; Siemens Medical Systems). Region of interest was manually traced at end-systolic frames in the four-chamber view. Signal intensity (SI) was expressed as log compressed data, giving the two primary components of myocardial flow: the initial slope, providing a measure of flow velocity, and the plateau SI, which correlates with myocardial capillary blood volume (22). An additional region of interest was placed in the LV cavity to measure the blood pool SI. After log decompression, the plateau SI was normalized for the blood pool SI to obtain a myocardial blood volume index (MBVI).

Ethics

The study was conducted according to the Declaration of Helsinki, and the protocol was approved by the Regional Ethics Committee. Following the provision of written and oral information to all patients, they gave their informed consent to study participation.

Data Analysis and Statistical Methods

Patient characteristics are summarized as the mean ± SD for continuous variables, and as counts and proportions for categorical variables. The Wilcoxon Mann-Whitney rank sum test was used for the comparison of continuous variables and the Fisher exact test for categorical variables. Change over time was determined using the Student *t* test. A two-sided *P* value of <0.05 was considered statistically significant. Data were analyzed using Minitab version 13.32.

To control for interindividual variability in echocardiographic assessment, the current analyst reassessed nine randomly selected echocardiograms from the baseline measurements. The following variables were analyzed: E, A, E/A ratio, e′, a′, E/e′ ratio, and MBVI. The Student *t* test was used to evaluate the interindividual variability, confirming that the reassessed data did not differ from the original observations (E/A ratio $P = 0.315$; E/e′ $P = 0.397$; resting MBVI $P = 0.077$; and stress MBVI $P = 0.627$).

RESULTS

Seventy-three of 95 invited patients participated in the DADD-FU study (Fig. 1). The mean time of follow-up was 6.4 ± 0.8 years (range 5.7–7.3 years). Pertinent clinical characteristics of the participants are shown in Table 1. None of the patients had reported any cardiovascular events during the period between the original screening and the follow-up, and none had been revascularized. Except for being older and having a longer duration of diabetes at follow-up, there were no differences in the characteristics of the study population over time. Men had lower mean BMI (28 ± 4 vs. 30 ± 5 kg/m^2; $P = 0.008$) and total cholesterol levels (4.3 ± 1.1 vs. 4.7 ± 0.9 mmol/L; $P = 0.017$) than women at follow-up. Patients with signs of LVDD at both study visits were older, had a higher systolic blood pressure, and received more intense glucose-lowering treatment (Table 2) compared with patients with a remaining normal LVDF. Compared with patients whose LVDF had normalized at follow-up, patients with remaining LVDD had a higher BMI.

Echo-Doppler Imaging and TDI Data

At baseline, 23 patients (32%) showed signs of LVDD, and a similar number was seen at follow-up (Fig. 2). At baseline, 57% of patients were graded as having mild LVDD, and 43% as having

Table 1—Patient characteristics at baseline and follow-up

Variables	Baseline (*n* = 73)	Follow-up (*n* = 73)	*P* value
Age (years)	60 ± 7	67 ± 7	<0.001
Male sex	37 (51)	37 (51)	
Diabetes duration (years)	6 ± 5	12 ± 5	<0.001
BMI (kg/m^2)	28 ± 4	28 ± 5	0.101
Blood pressure (mmHg)			
Systolic	143 ± 17*	146 ± 15	
Diastolic	80 ± 7*	81 ± 8	
Treated hypertension	14 (42)*	44 (60)	
Smokers	3 (9)*	5 (7)	
Cardiovascular treatment			
β-Blockers	7 (21)*	11 (15)	
ACE-i/ARBs	11 (33)*	36 (50)	
Calcium antagonists	5 (15)*	13 (18)	
Diuretics	8 (24)*	17 (23)	
Statins	10 (30)*	40 (55)	
Glucose-lowering treatment			
No treatment	2 (3)	0	0.159
Diet	32 (48)	9 (12)	<0.001
Oral	33 (49)	46 (63)	0.068
Insulin	0	18 (25)	<0.001
Unknown	7 (9)	0	0.013
Laboratory tests			
Fasting plasma glucose (mmol/L)	8.0 ± 2.8	7.7 ± 2.5	0.515
HbA_{1c} (%)	6.9 ± 1.3	7.1 ± 1.0	0.178
GFR (mL/min)	105 ± 28	99 ± 32	0.003
NT-proBNP (ng/L)	80 ± 96*	69 ± 62	
HDL cholesterol (mmol/L)	1.4 ± 0.6*	1.3 ± 0.4	
LDL cholesterol (mmol/L)	3.0 ± 0.9*	2.6 ± 0.9	
Triglycerides (mmol/L)	1.4 ± 1.0*	1.3 ± 0.9	
Echocardiographic measurements			
E (cm/s)	72 ± 16	70 ± 14	0.166
A (cm/s)	71 ± 17	78 ± 15	<0.001
E/A ratio	1.1 ± 0.2	0.9 ± 0.2	<0.001
e′ (cm/s)	9.4 ± 2.0	11.0 ± 2.4	<0.001
a′ (cm/s)	11.6 ± 1.7	13.1 ± 2.5	<0.001
E/e′ ratio	7.8 ± 2.0	6.5 ± 2.8	<0.001
LAVI (mL/m^2)	29 ± 7	21 ± 4	<0.001

Data are the mean ± SD or number (%), unless otherwise indicated. ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; LAVI, left atrial volume index; NT-proBNP, brain natriuretic peptide. *n = 33 (the patients included in the original DADD study).

Table 2—Patient characteristics and echocardiographic measurements at follow-up presented in groups representing the change in LVDD from baseline

	LVDD			
Variables	Normal (n = 41)	Dysfunction (n = 13)	Normalized (n = 10)	Worsened (n = 9)
Age (years)	64 ± 7	70 ± 6*	68 ± 7	68 ± 4
Male sex	23 (56)	5 (39)	4 (40)	5 (56)
Diabetes duration (years)	11 ± 4	11 ± 5	13 ± 7	14 ± 7
BMI (kg/m^2)	28 ± 5	30 ± 5	26 ± 5†	29 ± 5
Blood pressure (mmHg)				
Systolic	142 ± 16	153 ± 14*	155 ± 10	145 ± 13
Diastolic	80 ± 9	82 ± 8	81 ± 8	82 ± 9
Smokers	5 (12)	0	0	0
Cardiovascular treatment				
β-Blockers	4 (10)	4 (31)	1 (10)	2 (22)
ACE-i/ARB	16 (39)	9 (69)	7 (70)	4 (44)
Calcium antagonists	5 (12)	4 (31)	3 (30)	1 (11)
Diuretics	6 (15)	5 (39)	4 (40)	2 (22)
Statins	23 (56)	8 (62)	4 (40)	5 (56)
Glucose-lowering treatment				
Diet	8 (19)	0	0	1 (11)
Oral	27 (66)	7 (54)	6 (60)	6 (67)
Insulin	6 (15)	6 (46)*	4 (40)	2 (22)
Laboratory tests				
Fasting plasma glucose (mmol/L)	8.1 ± 2.8	7.7 ± 2.0	6.1 ± 1.5	7.6 ± 1.6
HbA_{1c} (%)	7.2 ± 1.2	7.3 ± 0.9	6.7 ± 0.7	7.0 ± 0.8
GFR (mL/min)	105 ± 33	89 ± 28	90 ± 40	99 ± 26
NT-proBNP (ng/L)	69 ± 69	72 ± 62	85 ± 51	45 ± 26
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.2 ± 0.5	1.5 ± 0.5	1.4 ± 0.4
LDL cholesterol (mmol/L)	2.5 ± 1.0	2.6 ± 0.4	3.0 ± 1.1	2.4 ± 0.9
Triglycerides (mmol/L)	1.5 ± 1.1	1.1 ± 0.8*	1.0 ± 0.5	1.1 ± 0.3
Echocardiographic measurements				
E/A ratio	1.0 ± 0.2	0.7 ± 0.1*	1.0 ± 0.3†	0.8 ± 0.3‡,§
E/e′ ratio	6.7 ± 1.7	6.0 ± 2.3	7.1 ± 0.9	6.1 ± 2.0§
LAVI (mL/m^2)	21 ± 4	21 ± 3	24 ± 5	22 ± 5

Data are the mean ± SD or number (%), unless otherwise indicated. ACE-I, ACE inhibitor; ARB, angiotensin receptor blockers; FPG, fasting plasma glucose; GFR, glomerular filtration rate; LAVI, left atrial volume index; NT-proBNP, brain natriuretic peptide. *$P < 0.05$ remained normal LV function vs. remained LVDD. †$P < 0.05$ LV function normalized vs. remained LVDD. ‡$P < 0.005$ remained LVDD vs. LV function worsened. §$P < 0.05$ LV function normalized vs. LV function worsened.

moderate LVDD, while at follow-up the corresponding numbers were 91% and 9%, respectively. No patient had severe LVDD. At baseline, 39% of the women and 24% of the men had signs of LVDD, and comparable numbers were seen at follow-up.

Mean E/A and E/e′ ratios decreased significantly over time for the whole group (Table 1). The left atrial volume index was within the normal range at baseline and follow-up. Baseline E/e′ was higher in women than in men (8.3 vs. 7.2, P = 0.015) but decreased more over time; thus, at follow-up there was no sex difference in diastolic function. MBVI data were available from 22 patients with LVDD at baseline and follow-up, and did not change over time.

CONCLUSIONS

Over a 6-year period, LVDF remained unchanged or normalized in a majority of the present population of patients with type 2 diabetes who were free from apparent cardiovascular disease at their baseline investigation. Moreover, signs of LVDD developed in only a small proportion of those patients with an initially normal LVDF during this time period.

This study confirms that LVDD exists in patients with type 2 diabetes in whom there is no evidence of structural heart disease. The present prevalence of LVDD of ~30% in patients at the baseline investigation is, however, lower than that in several previous reports (9,10). Two apparent reasons for this discrepancy are that patient selection and the definition for assessing LVDF differ between studies. In the current study, the mitral inflow velocity curves and TDI evidence of mitral annular motion were used (21). The use of additional criteria has been suggested (23) and, if, for example, left atrial size had been incorporated into the present algorithm, the prevalence of LVDD would have been even lower. The normal left atrial volume index seen in the present investigation are in line with the majority of patients having normal LVDF or mild LVDD. An increase in left atrial volume reflects elevated LV filling pressures. Patients with mild LVDD may have normal or increased left atrial volume index that worsens with the progression of LVDD (24). In the current study, a majority of patients had mild LVDD that improved or remained stable, which may explain the observed decrease in left atrial volume index. In summary, this favors the assumption that in a population of patients with well-controlled diabetes and no signs of cardiovascular disease the prevalence of LVDD is rather low. Patients in the current study had well-controlled glycemia, blood pressure, and BMI at follow-up, which might have contributed to the continued low prevalence of LVDD at follow-up, and to the improvement of LVDF in 21% of the patients and the deterioration of LVDF in only 12% of patients. The investigation of myocardial blood flow in a subgroup of the current study population showed no change over time, which further supports the lack of ischemic heart disease.

Most previous studies (25,26) examining the longitudinal effect of diabetes on LVDF have included patients with cardiovascular disease, which certainly will affect the development of LVDD over time compared with the current study. A strong correlation between the severity of LVDD and diabetes duration was shown in 486 patients with diabetes and LVDD without symptoms of heart failure (24). However, this study included patients with type 1 diabetes and valvular disease, and did not screen for coronary artery disease, which makes it difficult to eliminate synergistic effects on LVDF. In addition, when healthy individuals from the general population were investigated, it was shown that the conditions of patients

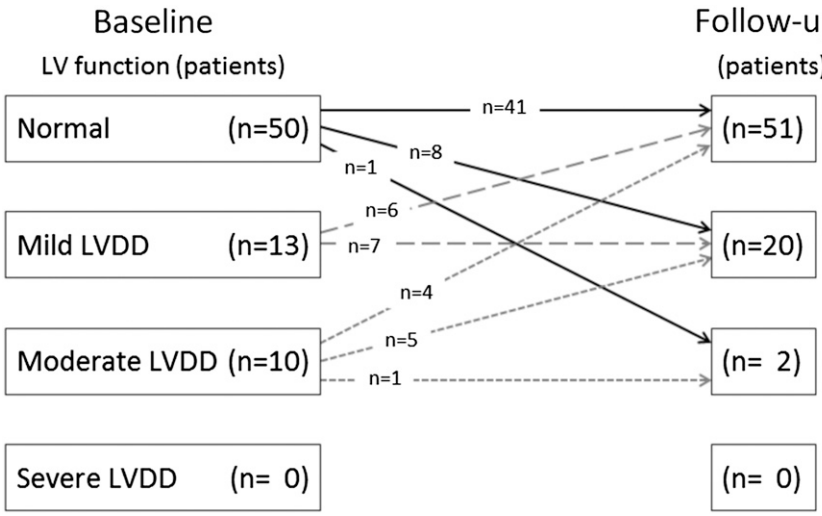

Figure 2—Change in LV function from baseline to follow-up visit. Numbers in parentheses are the number of patients at each stage with normal to severe LVDD. Numbers on the lines show how many patients moved in the direction of the arrow.

with LVDF may deteriorate over time (26). It was assumed that aging associated with decreased peripheral elasticity and LV stiffness may be independent risk factors affecting diastolic function. This assumption is questioned by the results of the current study, with LVDD developing in only 20% of patients over time and >50% of those patients initially identified as having mild-to-moderate LVDD having LVDF return to normal despite their growing 6 years older. The present findings extend observations made over 2 years by Roos et al. (27), who followed a similar group of 112 patients with type 2 diabetes who did not show symptoms of cardiovascular disease. Their LVDF was studied by means of two-dimensional speckle-tracking echocardiography, which showed only very mild changes over time. Moreover, Aljaroudi et al. (8) showed that LVDD could regress to normal if cardiovascular risk factors were well managed. Also, a relationship between glycemic control and LVDD has been reported (2,28), suggesting that myocardial alterations may be affected by poor glycemic control (29). Thus, one may speculate that in the early stage of LVDD, progressive myocardial changes develop slowly and might even be reversible. In this context, a reasonable explanation for the present findings is that treating concomitant conditions of importance for the development of diastolic dysfunction, such as hypertension and untoward glycemia, prevents progression. Another possibility may be that the relatively small changes seen are an expression of natural fluctuations in diastolic function.

In addition, the proportion of patients with new onset of LVDD might be lower than previously reported in patients whose conditions were adequately managed in a multifactorial way (30).

Study Limitations

Although all patients had preserved LV systolic function and no apparent symptoms or signs of ischemic heart disease, the investigations performed may be insufficient to completely exclude the presence of coronary artery disease. LV mass index might have been a better tool to exclude LV hypertrophy than the determination of septal wall thickness. However, it seems that the inferiority of septal wall thickness versus LV mass index is less when only excluding rather than grading LV hypertrophy severity (31).

Risk factors that may affect LVDF were recorded only at baseline and at follow-up 6 years later. Thus, control of glycemia, hypertension, weight, and hyperlipidemia is not known during the intermediate period. Finally, the screening part of the study did not include a full baseline clinical examination of all participants.

Conclusion

The prevalence of LVDD was relatively low, and LVDF improved or remained stable over an observation period of 6 years in a majority of the investigated patients with type 2 diabetes and no apparent cardiovascular disease. Thus, our study supports the conclusion that, without an impact of concomitant disease (e.g., hypertension with hypertrophy or coronary artery disease), diabetes does not necessarily relate to diastolic dysfunction or increase the risk for progressive myocardial involvement.

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Author Contributions. L.V. enrolled patients, analyzed the research data, performed statistical analysis, and wrote the manuscript. C.J. enrolled patients and reviewed and edited the manuscript. L.R. provided the study concept and design, supervised the protocol development and the research, contributed to the discussion, and reviewed and edited the manuscript. B.K. contributed to the analysis of the research data, the statistical analysis, and the discussion and reviewed and edited the manuscript. L.V. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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