Cardiovascular Diabetology

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Relationship between NT-proBNP, echocardiographic abnormalities and functional status in patients with subclinical siabetic cardiomyopathy

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Abstract

Introduction Persons with diabetes are at risk for developing a cardiomyopathy through several pathophysiological mechanisms independent of traditional risk factors for heart failure. Among those with diabetic cardiomyopathy (DbCM), the relationship between natriuretic peptides, cardiac structural abnormalities and functional capacity is largely unknown.

Methods In this prespecified subgroup analysis of the Aldose Reductase Inhibition for Stabilization of Exercise Capacity in Heart Failure (ARISE-HF) trial, 685 participants with asymptomatic DbCM underwent baseline echocardiography data, laboratory investigations, and functional assessments. Participants were stratified by N-terminal pro-B type natriuretic peptide (NT-proBNP) quartiles, and correlation with echocardiographic and functional parameters were assessed using Spearman correlation test.

Results The median NT-proBNP was 71 (Q1, Q3: 33, 135) ng/L. No association was observed between NT-proBNP concentrations and echocardiographic parameters of either diastolic or systolic dysfunction including global longitudinal strain, left ventricular ejection fraction, left ventricular mass index, left atrial volume index, E/E', or right ventricular systolic pressure. In contrast, NT-proBNP was significantly correlated with overall Kansas City Cardiomyopathy Questionnaire score (rho = −0.10; $p=0.007$), the Physical Activity Scale in the Elderly (rho = −0.12; $p=0.004$), duration of cardiopulmonary exercise testing (rho = −0.28; $p<0.001$), peak VO^2 (rho = −0.26; $p<0.001$), and ratio of minute ventilation/carbon dioxide production (rho = 0.12; $p=0.002$). After adjustment for known confounders, the correlation with Physical Activity Scale in the Elderly and overall Kansas City Cardiomyopathy Questionnaire score was no longer significant.

Conclusion Among patients with subclinical DbCM, elevated NT-proBNP concentrations are associated with worse health status, lower activity levels, and reduced functional capacity, but not with cardiac structural abnormalities.

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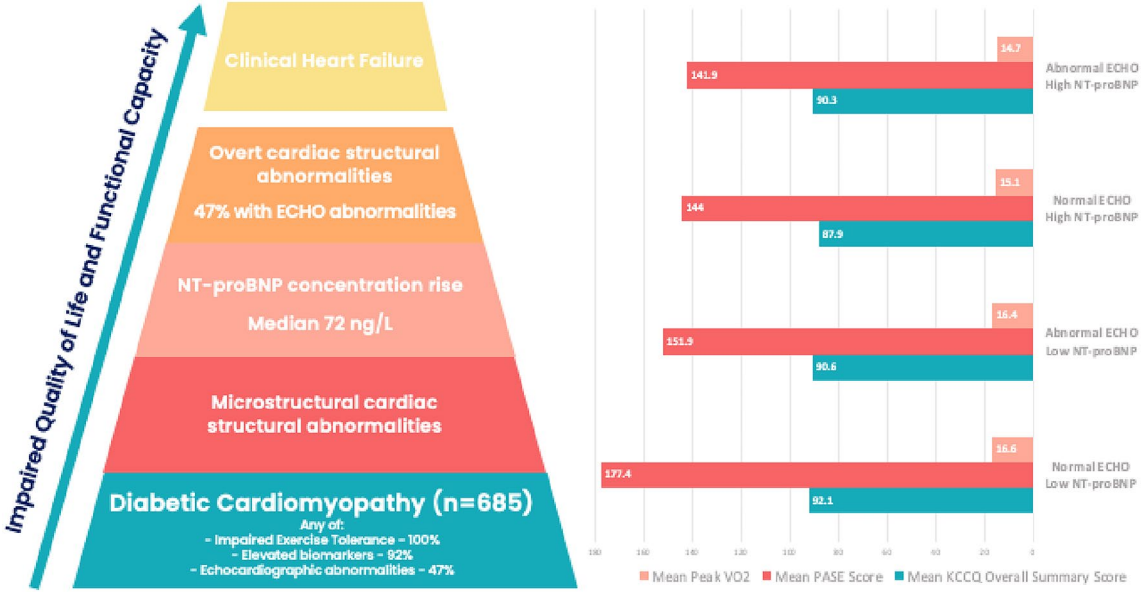
These findings suggest that regardless of cardiac structural abnormalities, biomarker concentrations reflect important deterioration in functional capacity in affected individuals.

Trial registration ARISE-HF, NCT 04083339 Date Registered August 23, 2019.

Graphical abstract Abnormal ECHO defined as Myocardial Global Longitudinal Strain < −16 or left ventricular mass index > 95 for females or > 115 for males or E/e' > 13 or left atrial volume index > 34. †Normal ECHO is defined as the absence of these abnormalities. Low NT-proBNP is defined as < 71 ng/L while high NT-proBNP is defined as ≥ 71 ng/L.



Introduction

Globally, diabetes mellitus affects more than 415 million people and is projected to continue to increase in the upcoming decades [1, 2]. Although diabetes mellitus is associated with a broad range of cardiovascular complications, the role of heart failure (HF) in persons with diabetes has gained increasing attention [3]. Presently, new onset HF occurs at a rate of 30 per 1000 patient-years in individuals, with diabetes mellitus representing a major source of cardiovascular morbidity and mortality in this population [4]. In this regard, greater emphasis has been given to earlier recognition of HF risk among individuals with diabetes mellitus, including the presence of HF in the absence of overt symptomatic stages of the diagnosis. Also known as Stage B HF [5], such a scenario is a risk factor for progression to more overt symptoms and worse prognosis, and represents an opportunity for intervention to reduce progression to symptomatic HF. To do so, a better understanding of the factors leading to HF risk may be necessary.

Stage B HF may be caused by several factors among individuals with diabetes mellitus, including hypertension, coronary artery disease, and valvular heart disease. However, even in the absence of these risk factors, development of heart muscle disease may occur. Diabetic cardiomyopathy (DbCM) is an increasingly recognized cause of HF among individuals with risk factors such as longstanding hyperglycemia, advanced age, or other complications of diabetes mellitus [6]. Numerous mechanisms have been identified that contribute to the development of DbCM including impaired calcium homeostasis, increased oxidative stress, altered substrate metabolism, mitochondrial dysfunction, and activation of the renin-angiotensin system [7].

Among individuals with DbCM without overt HF symptoms, a high prevalence of structural cardiac abnormalities has been reported, estimated to affect between 28 and 66% of this population [8, 9]; the risk for symptomatic HF is proportional to the number of structural heart abnormalities present [10]. The challenge is whether other tools might be used to evaluate the diagnosis of DbCM. For example, among individuals with type 2 diabetes (T2D) without advanced HF, concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) have repeatedly been demonstrated to be a strongly discriminatory variable for death and cardiovascular events

[11–14]. The role of NT-proBNP testing in patients with DbCM and its relationship with echocardiographic abnormalities and functional status remains unclear. In the general population, echocardiography and biomarkers may be of use to reclassify individuals to a higher risk of developing HF (Stage B), both independently and in conjunction with each other [15].

The Aldose Reductase Inhibition for Stabilization of Exercise Capacity in Heart Failure Trial (ARISE-HF) trial was a clinical trial evaluating the effects of a novel aldose-reductase inhibitor for DbCM [16]. In the trial, treatment with AT-001 did not result in improved exercise capacity compared to placebo [17]. Using baseline data from study participants in the trial, this study aimed to evaluate associations between NT-proBNP concentrations, clinical characteristics, echocardiographic findings, health status and activity, and outcomes from cardiopulmonary exercise testing.

Methods

Study design

The ARISE-HF trial (NCT 04083339; Date Registered August 23, 2019) is an ongoing phase 3 randomized, placebo-controlled, double-blinded clinical trial that aims to investigate the efficacy of AT-001, an aldose reductase inhibitor, in patients with DbCM, with any prior history of overt HF. All patients provided written, informed consent. All study procedures were approved by individual Institutional Review Boards and the study was conducted in accordance with the Declaration of Helsinki. The rationale and methods of the trial have been previously published [16]. Participants were included if they had a known diagnosis of T2D and age ≥ 60 (or ≥ 45 with a duration of diabetes of ≥ 10 years or eGFR ≤ 60 ml min/1.73 m^2). Participants were required to have evidence of one of: (1) structural cardiac abnormality, (2) elevated cardiac biomarkers, or (3) impaired exercise tolerance, defined as a peak oxygen uptake (VO_2) ≤ 75% of predicted based on age and gender with a respiratory exchange ratio of ≥ 1.05 on cardiopulmonary exercise testing. To be included, structural cardiac abnormalities could include abnormal global longitudinal strain (GLS) < −16%, left ventricular hypertrophy (left ventricular mass index [LVMI] ≥ 95 g/m^2 in women or ≥ 115 g/m^2 in men), left atrial enlargement (left atrial volume index [LAVI] > 34 ml/m^2), abnormal myocardial relaxation (ratio of early transmitral diastolic filling velocity/early mitral annular velocity (E/e') ≥ 13, elevated right ventricular systolic pressure (RVSP) > 35 mmHg. Elevated cardiac biomarkers were defined as an NT-proBNP ≥ 50 ng/L or high sensitivity cardiac troponin (hs-cTnT) T ≥ 6 ng/L.

Key exclusion criteria include a diagnosis of symptomatic HF, LV ejection fraction (LVEF) < 40% or use of loop diuretics, acute coronary syndrome or unrevascularized severe coronary artery disease, lower extremity complications of peripheral artery disease (critical limb ischemia, ulcers, gangrene, amputation), prior stroke, severe valvular heart disease, recent cardiac arrhythmia, uncontrolled hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90mmHg at screening regardless of concomitant treatment), any previous cardiomyopathy (congenital, infection, toxic, infiltrative, post-partum, hypertrophic, autoimmune myocarditis) hemoglobin A1C > 8.5%, hemoglobin < 10 g/dL, eGFR < 45 ml/min/1.73 m^2, body mass index ≥ 45 kg/m^2, recurrent kidney stones, or inability to exercise. Additionally, severe disease of any organ system, that would limit the implementation of the study protocol or interpretation of the study results was an exclusion. A complete inclusion and exclusion list can be found in Supplementary Table 1.

Echocardiographic assessment

A baseline echocardiographic assessment was undertaken for all patients, with data analyzed by a blinded echocardiography core lab as per the most appropriate American Society of Echocardiography guidelines [18]. The following variables were analyzed: GLS, LVMI, LAVI, LVEF, E/e' and RVSP, with abnormal cut-offs outline above. An abnormal echocardiogram was defined as the abnormalities in any of: GLS, LVMI, LAVI or E/e' using abnormal values outlined above. LVEF was not used since our study excluded patients with significant systolic dysfunction, and neither was RVSP due to the lack of sensitivity/specificity for DbCM.

Health status and functional capacity

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was administered to all participants at baseline and is reported using the physical limitation score, clinical summary score, and the overall summary score [19]. The Physical Activity Scale for the Elderly (PASE) is a 12-item questionnaire that assesses the frequency and duration of leisure activities, household activities, and work-related activities in the preceding seven days [20]. All participants underwent baseline cardiopulmonary exercise testing from which duration of exercise in minutes, peak VO_2, ratio of minute ventilation/carbon dioxide production (VE/VCO^2 slope), and peak respiratory exchange rate were recorded. CPET testing was primarily undertaken with cycle ergometry, but a treadmill protocol was devised so that both modalities would lead to a 15 W/min increase in workload.

Biomarkers

Concentrations of NT-proBNP and hs-cTnT (Roche Diagnostics, Mannheim GE) were measured in a core laboratory (Medpace, Inc).

Statistical analysis

Baseline characteristics, echocardiographic abnormalities, functional capacity, and cardiopulmonary exercise testing variables are described stratified by quartiles of NT-proBNP. A sensitivity analysis was undertaken comparing characteristics based on an NT-proBNP cut-off of 125 ng/L. Categorical variables were presented as frequencies with proportions, and they were compared across groups using chi-square or Fisher's exact tests. Continuous variables having normal distribution such as age were summarized as mean (SD; standard deviation) and compared with the ANOVA (Analysis of Variance) test across groups. Variables that are not normally distributed, are presented as median (IQR; interquartile range) and compared using the Kruskal Wallis tests. To explore correlations of NT-proBNP concentrations with clinical variables, univariate and multivariate linear regression models were used. Variables in the univariable model with a p-value of <0.05 were input into the multivariable model. Multiple imputations by chained equation were used to account for missing values. Correlations between NT-proBNP concentrations, echocardiographic, and functional variables were assessed using Spearman's and illustrated using scatter plots with a regression line and 95% confidence interval. Spearman's correlation was adjusted for confounders identified in our multivariable regression model and included age, sex, systolic blood pressure, diastolic blood pressure, heart rate, statin use, beta-blocker use, glucagon-like peptide-1 use, hemoglobin A1c, hemoglobin, estimated glomerular filtrations rate, urine albumin creatinine ratio, high-density lipoprotein and low-density lipoprotein.

Results

Baseline characteristics and NT-proBNP quartiles

Of 691 participants in the ARISE-HF trial, 685 (99.1%) had a documented baseline NT-proBNP and were included in this analysis. Overall, study participants had a mean age of 67 years and 50.1% were female. The median (Q1, Q3) NT-proBNP concentration was 71 (35, 135) ng/L, with 26.7% above a proposed prognostic NT-proBNP threshold of 125 ng/L [3, 21]. All participants met the impaired exercise tolerance criterion, 630 (92.0%) met the elevated biomarker criterion and 324 (47.2%) met the echocardiographic abnormality criterion. Of participants, 664 (96.9%) met two or more inclusion criteria and 2389 (42.2%) met all three criteria (Supplementary Fig. 1).

Table 1 details the baseline characteristics of study participants by NT-proBNP quartiles. Compared to patients in the highest quartile, those in the lowest quartile were younger (64.1 ± 7.3 vs. 69.8 ± 7.0 years), less often female (31.6% vs. 62.5%), had lower systolic blood pressures (127 ± 12 vs. 131 ± 11 mmHg), and had higher heart rates (73 ± 12 vs. 66 ± 11 beats per minute; Table 1). Patients in the lowest NT-proBNP quartile also demonstrated higher hemoglobin (14.2 ± 1.3 vs. 13.2 ± 1.3 g/dL) and estimated glomerular filtration rate (84.8 ± 15.7 vs. 74. ± 16.2 mL/min/1.73m^2), compared to those in the highest NT-proBNP quartile. No significant differences were observed in relation to the prevalence of dyslipidemia, duration of diabetes, HbA1c levels or lipid parameters. Of note, participants in the lowest NT-proBNP quartile demonstrated greater use of glucagon-like peptide 1 (GLP-1) receptor agonist, compared to other quartiles (35.1% vs. 17.4–22.6%; $p=0.002$).

Multivariable models identified that independent predictors of higher log-transformed NT-proBNP included age ($p=0.002$), systolic blood pressure ($p<0.001$), beta-blocker use ($p<0.001$), urine albumin creatine ratio ($p=0.02$), and VE/VCO2 slope ($p<0.001$), while heart rate ($p<0.001$), hemoglobin concentration ($p<0.001$), estimated glomerular filtration rate ($p=0.01$), and duration of CPET testing ($p=0.01$) predicted lower NT-proBNP concentrations (Supplementary Table 2).

Compared to participants with an NT-proBNP of ≤125 (73.3%), those with an NT-proBNP of >125 (26.7%) were older (69.7 ± 6.9 years vs. 66.6 ± 7.1 years; $p<0.001$), more frequently female (62.3% vs. 45.6%; $p<0.001$), had a lower heart rate (66 ± 10 bpm vs. 70 ± 11 bpm; $p<0.001$), had lower hemoglobin (13.2 ± 1.3 g/dL vs. 13.8 ± 1.4; $p<0.001$), and had a lower estimated glomerular filtration rate (75.2 ± 16.1 ml/min/1.73m^2 vs. 82.3 ± 16.0 ml/min/1.73 m^2; $p<0.001$; Supplementary Table 3).

Echocardiographic parameters

Across the echocardiographic parameters examined, there were no differences in mean measurements of these variables across NT-proBNP quartiles (Table 2). The proportion of participants with a marker of increased left atrial pressure (E/e' ≥ 13) ranged from 16.1% in the lowest NT-proBNP quartile to 18.5% in the highest quartile. A greater proportion of participants in the lowest NT-proBNP quartile demonstrated a normal value for GLS (≤ − 16%) compared to other quartiles (34.5% vs. 21.5–22.8%). While an EF of <40% was an exclusion criterion, no differences in the mean LVEF between NT-proBNP quartiles were observed. Additionally, no significant differences between NT-proBNP quartiles were associated with the proportion of patients with LA enlargement (9.8–15.2%), LV hypertrophy (10.3–14.9%), or RVSP>35 mmHg (2.9–6.0%). Examining the population as a whole, no correlation was observed between NT-proBNP concentrations and adverse echocardiographic features as continuous variables (Fig. 1). However, after adjusting for

Table 1 Baseline characteristics by NT-proBNP quartiles

	Quartile 1 (*n* = 174)	Quartile 2 (*n* = 171)	Quartile 3 (*n* = 172)	Quartile 4 (*n* = 168)	*p*-value
NT-proBNP range, ng/L	5–35	36–71	72–135	136–4284	
Age, years, mean ± SD	64.1 (7.3)	67.8 (6.8)	67.9 (6.5)	69.8 (7.0)	< 0.001
Female (%)	55 (31.6)	87 (50.9)	96 (55.8)	105 (62.5)	< 0.001
Race (%)					0.009
White	98 (56.3)	108 (63.2)	113 (65.7)	112 (66.7)	
Hispanic	34 (19.5)	34 (19.9)	39 (22.7)	41 (24.4)	
Black	13 (7.5)	9 (5.3)	9 (5.2)	9 (5.4)	
Asian	22 (12.6)	18 (10.5)	11 (6.4)	5 (3.0)	
American Indian or Alaska Native	2 (1.1)	2 (1.2)	0 (0.0)	0 (0.0)	
Other	5 (2.9)	0 (0.0)	0 (0.0)	1 (0.6)	
Body-mass index, Kg/m^2, mean ± SD	30.7 (4.27)	31.0 (4.65)	30.4 (4.69)	30.3 (4.68)	0.48
Medical history, N, %					
Hypertension	129 (74.1)	128 (74.9)	133 (77.3)	129 (76.8)	0.89
Dyslipidemia	28 (16.1)	31 (18.1)	28 (16.3)	28 (16.7)	0.96
Duration of T2D, years, mean ± SD	14.9 (9.1)	14.2 (12.0)	13.1 (9.0)	15.2 (10.5)	0.86
Smoking status, N, %					0.51
Current smoker	22 (12.6)	11 (6.4)	18 (10.5)	13 (7.7)	
Previous smoker	61 (35.1)	62 (36.3)	60 (34.9)	56 (33.3)	
Never smoker	91 (52.3)	98 (57.3)	94 (54.7)	99 (58.9)	
Vital signs at screening					
Systolic blood pressure, mmHg, mean ± SD	127 (12)	129 (10)	130 (11)	131 (11)	0.018
Diastolic blood pressure, mmHg, mean ± SD	77 (8.0)	76 (8.3)	76 (7.8)	75 (9.0)	0.17
Heart rate, beats/minute, mean ± SD	73 (12)	68 (10.0)	67 (10)	66 (11)	< 0.001
Concomitant medications, N, %					
Statins	145 (83.3)	149 (87.1)	130 (75.6)	130 (77.4)	0.024
ACE inhibitor or ARB	140 (80.5)	120 (70.2)	129 (75.0)	127 (75.6)	0.18
Beta blocker	17 (9.8)	29 (17.0)	51 (29.7)	63 (37.5)	< 0.001
MRA	3 (1.7)	9 (5.3)	6 (3.5)	3 (1.8)	0.18
Hydrochlorothiazide	32 (18.4)	28 (16.4)	34 (19.8)	37 (22.0)	0.60
SGLT2 inhibitor	65 (37.4)	54 (31.6)	49 (28.5)	51 (30.4)	0.32
GLP-1 receptor agonist	61 (35.1)	43 (25.1)	30 (17.4)	38 (22.6)	0.002
Metformin	130 (74.7)	121 (70.8)	134 (77.9)	123 (73.2)	0.49
Insulin	52 (29.9)	50 (29.2)	39 (22.7)	46 (27.4)	0.43
Sulfonylurea	39 (22.4)	34 (19.9)	44 (25.6)	42 (25.0)	0.58
DPP4 inhibitor	19 (10.9)	20 (11.7)	23 (13.4)	23 (13.7)	0.84
Laboratory tests					
NT-proBNP, ng/L, median (Q1, Q3)	18 [10, 27]	54 [46, 63]	97 [83, 113]	206 [158, 292]	< 0.001
Hs-cTnT, ng/L, median (Q1, Q3)	9 [6, 12]	8 [6, 12]	9 [6, 12]	9 [6, 13]	0.59
HbA1c, %, mean (SD)	7.1 (0.77)	7.0 (0.83)	6.9 (0.75)	6.9 (0.81)	0.13
Hemoglobin, g/dL, mean (SD)	14.2 (1.3)	13.8 (1.4)	13. 5(1.3)	13.2 (1.3)	< 0.001
eGFR, mL/min/1.73m2, mean (SD)	84.8 (15.7)	82.6 (14.9)	79.4 (16.6)	74.7 (16.2)	< 0.001
UACR, mg/g, median (Q1, Q3)	13 [8, 31]	17 [90, 62]	14 [8, 33]	16 [9, 37]	0.14
Total cholesterol, mg/dL, median (Q1, Q3)	152 [130, 174]	153 [134, 180]	155 [132, 185]	156 [136, 187]	0.31
HDL cholesterol, mg/dL, median (Q1, Q3)	44 [36, 55]	48 [40, 60]	48 [39, 57]	49 [40, 59]	0.10
LDL cholesterol, mg/dL, median (Q1, Q3)	70 [51, 90]	70 [52, 94]	72 [59, 95]	74 [57, 103]	0.16

SD, standard deviation; T2D, type two diabetes; ACE, angiotensin converting enzyme; ARB angiotensin two receptor blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium glucose cotransporter-2 inhibitor; GLP-1; glucagon-like peptide 1; DPP4, dipeptidyl peptidase 4 inhibitor; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hs-cTnT, high sensitivity cardiac troponin T; HbA1C, hemoglobin A1c; eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio; HDL, high density lipoprotein; LDL, low density lipoprotein

Table 2 Echocardiographic features by NT-proBNP quartiles

	Quartile 1 (*n* = 174)	Quartile 2 (*n* = 171)	Quartile 3 (*n* = 172)	Quartile 4 (*n* = 168)	*p*-value
NT-proBNP range, ng/L	5–35	36–71	72–135	136–4284	
E/e', median (Q1, Q3)	9.7 [8.0, 11.7]	9.7 [7.9, 11.7]	9.4 [7.8, 11.7]	9.2 [7.5, 12.3]	0.79
E/e' ≥ 13	28 (16.1)	30 (17.5)	32 (18.6)	31 (18.5)	0.93
GLS, %, median (Q1, Q3)	− 16.8 [− 18.9, − 15.0]	− 18.1 [− 19.5, − 15.5]	− 17.8 [− 19.8, − 15.5]	− 17.9 [− 19.7, − 15.1]	0.23
GLS < − 16%	60 (34.5)	39 (22.8)	37 (21.5)	37 (22.0)	0.01
LAVI, mL/m^2, median (Q1, Q3)	23.7 [19.8, 28.8]	24.0 [19.8, 29.0]	23.6 [19.1, 29.2]	22.7 [17.7, 28.8]	0.65
LAVI > 34 mL/m^2	17 (9.8)	26 (15.2)	21 (12.2)	17 (10.1)	0.38
LVEF, %, median (Q1, Q3)	63 [59, 66]	63 [60, 66]	62 [58, 65]	62 [59, 66]	0.12
LVMI, g/m^2, median (Q1, Q3)	75.0 [65.0, 88.2]	73.5 [63.5, 86.0]	73.0 [63.5, 87.0]	72.0 [61.5, 88.5]	0.61
Elevated LVMI*	18 (10.3)	19 (11.1)	20 (11.6)	25 (14.9)	0.59
RVSP, mmHg, median (Q1, Q3)	23 [19, 27]	23 [19, 27]	23 [19, 27]	25 [20, 30]	0.18
RVSP > 35 mmHg	6 (3.4)	5 (2.9)	5 (2.9)	10 (6.0)	0.40

NT-proBNP, N-terminal pro-B-type natriuretic peptide; E/e', Ratio between early mitral inflow velocity and mitral annular early diastolic velocity; GLS, global longitudinal strain; LAVI, Left atrial volume indexed; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass indexed; RVSP, right ventricular systolic pressure; *≥ 115 g/m2 in men and ≥ 95 g/m2 in women

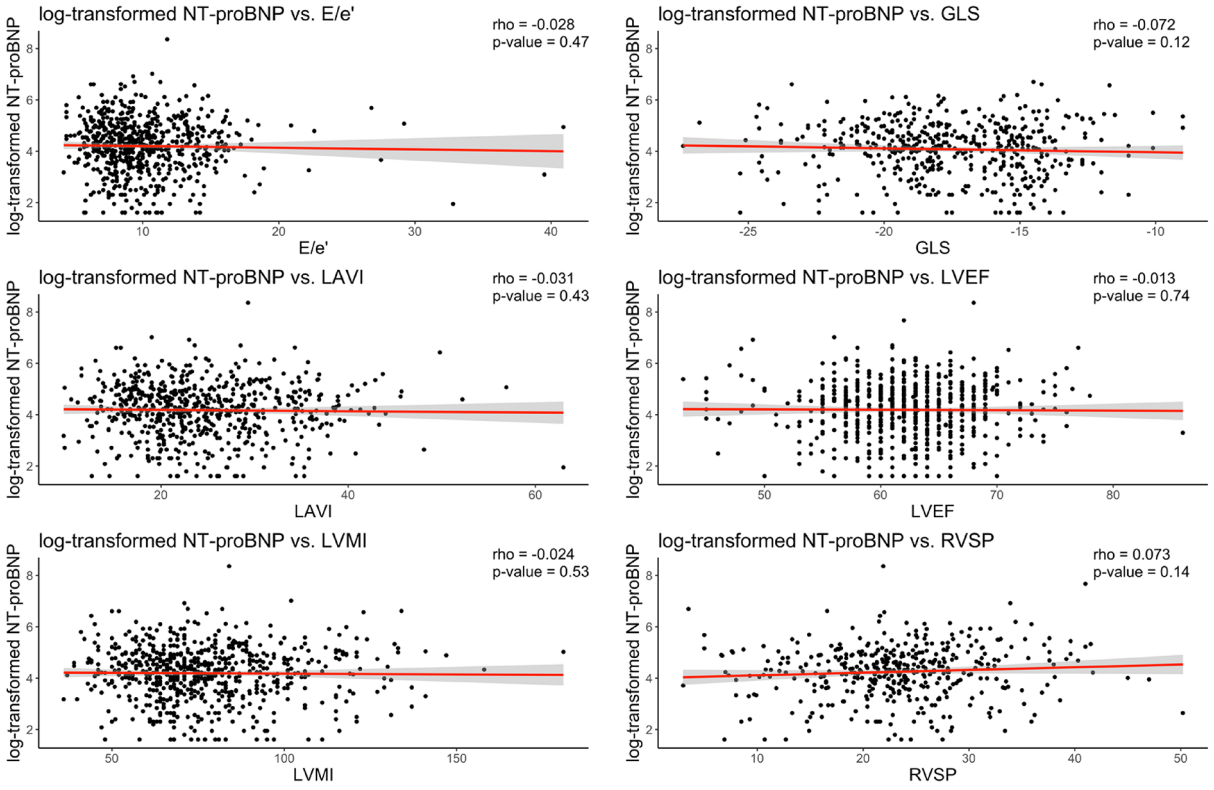


Fig. 1 Correlation of NT-proBNP levels and adverse echocardiographic features. *Abbreviations* NT-proBNP, N-terminal pro-B-type natriuretic peptide; E/e', Ratio between early mitral inflow velocity and mitral annular early diastolic velocity; GLS, global longitudinal strain; LAVI, Left atrial volume indexed; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass indexed; RVSP, right ventricular systolic pressure

known confounders NT-proBNP was mildly correlated with LVEF (rho = − 0.10; p = 0.02; Supplementary Table 4).

The proportion of participants with echocardiographic abnormalities was not statistically different between participants who had an NT-proBNP of ≥125 ng/L compared to those < 125 ng/L (Supplementary Table 3).

Health status and functional capacity

Study participants in the lowest NT-proBNP quartile reported better health status with more favorable KCCQ physical limitations scores, higher KCCQ clinical summary scores, and higher KCCQ overall summary scores (Table 3). Study participants in the lower two NT-proBNP quartiles also reported greater physical activity levels. Considering the PASE Score results, individuals in

Table 3 Health Status and activity by NT-proBNP quartiles

	Quartile 1 (*n* = 174)	Quartile 2 (*n* = 171)	Quartile 3 (*n* = 172)	Quartile 4 (*n* = 168)	*p*-value
NT-proBNP range, ng/L	5–35	36–71	72–135	136–4284	
KCCQ physical limitation score, mean ± SD	92 (15)	89 (16)	89 (16)	86 (19)	0.016
KCCQ clinical summary score, mean ± SD	93 (11)	90 (15)	90 (15)	88 (15)	0.014
KCCQ overall summary score, mean ± SD	92 (12)	90 (15)	90 (15)	88 (16)	0.10
PASE score, mean ± SD	163 (95)	169 (100)	152 (79)	135 (82)	0.008

NT-proBNP, N-terminal pro-B-type natriuretic peptide; E/e', Ratio between early mitral inflow velocity and mitral annular early diastolic velocity; GLS, global longitudinal strain; LAVI, Left atrial volume indexed; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass indexed; RVSP, right ventricular systolic pressure; *≥ 115 g/m^2 in men and ≥95 g/m^2 in women.

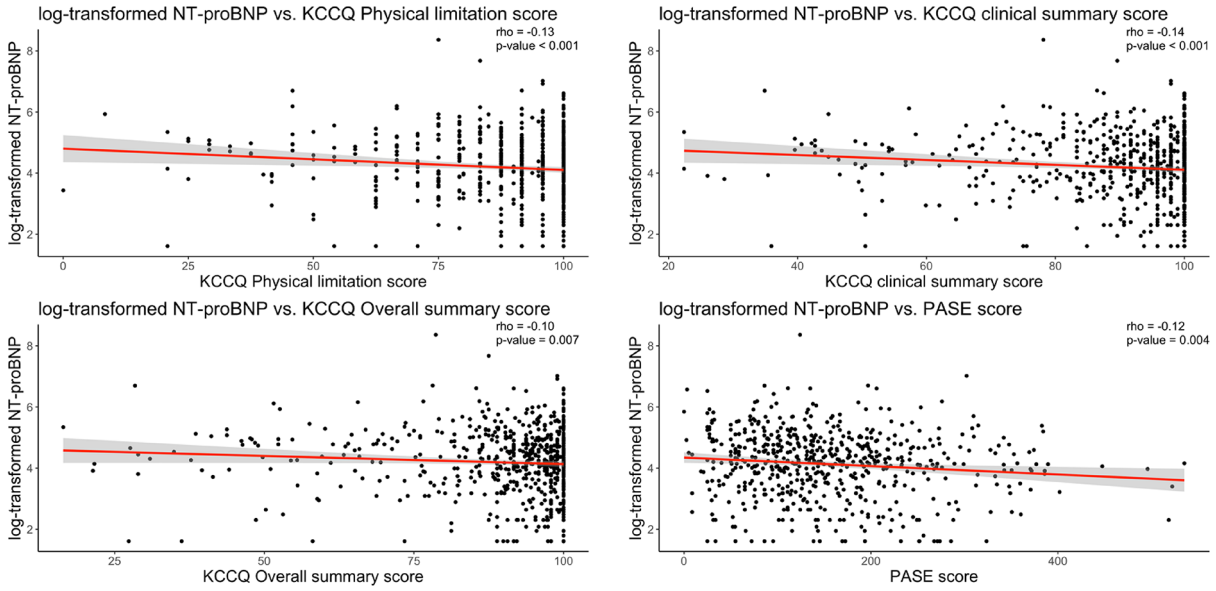


Fig. 2 Correlation of NT-proBNP levels, Health Status and Activity. *Abbreviations* NT-proBNP, N-terminal pro-B-type natriuretic peptide; KCCQ, Kansas City Cardiomyopathy Questionnaire; PASE, physical activity scale for the elderly.

the lowest NT-proBNP quartile demonstrated the highest scores (163), whereas those with more elevated NT-proBNP concentrations were more sedentary, with significantly lower PASE Scores (135; $P=0.008$ for difference). NT-proBNP concentrations were significantly correlated with KCCQ and PASE Scores (Fig. 2). However, after adjusting for known confounders of NT-proBNP the correlations were weaker and for the KCCQ overall summary score and PASE score, no longer significant (Supplementary Table 4).

Participants with an NT-proBNP of ≥125 ng/L demonstrated lower KCCQ physical limitations scores, lower KCCQ clinical summary scores (Fig. 3), lower KCCQ overall summary scores, and lower physical activity scores compared to participants with an NT-proBNP of <125 ng/L (Supplementary Table 3).

Lastly, on cardiopulmonary exercise testing, study participants in the lowest NT-proBNP quartile exercised longer, achieved a higher peak VO_2, and had lower minute ventilation to carbon dioxide production ratio (Table 4). NT-proBNP concentrations were significantly correlated with these examined parameters (Fig. 2). After adjusting for known confounders of NT-proBNP, the correlations were weaker but still significant (Supplementary Table 4).

Participants with an NT-proBNP of ≥125 ng/L exercised for shorter durations, a chieved a lower peak VO_2, and had a higher minute ventilation to carbon dioxide production ratio (Supplementary Table 3).

Concomitant effects of elevated NT-proBNP and echocardiographic abnormalities

Of 283 (41.3%) participants with an abnormal echocardiogram, 150 (53.0%) had an NT-proBNP concentration<71 ng/L (median) and 133 (47.0%) had an NT-proBNP of ≥71 ng/L. Of 402 (58.7%) participants without an echocardiographic abnormality, 191 (47.5%) had an NT-proBNP of <71 ng/L and 211 (52.5%) had an NT-proBNP of ≥71 ng/L.

Participants with an NT-proBNP concentration below the median of 71 ng/L without echocardiographic abnormalities had the highest peak VO2 (16.61 ± 3.79), followed by those with an abnormal echocardiogram and NT-proBNP<71 ng/L (16.40 ± 3.77), then those without

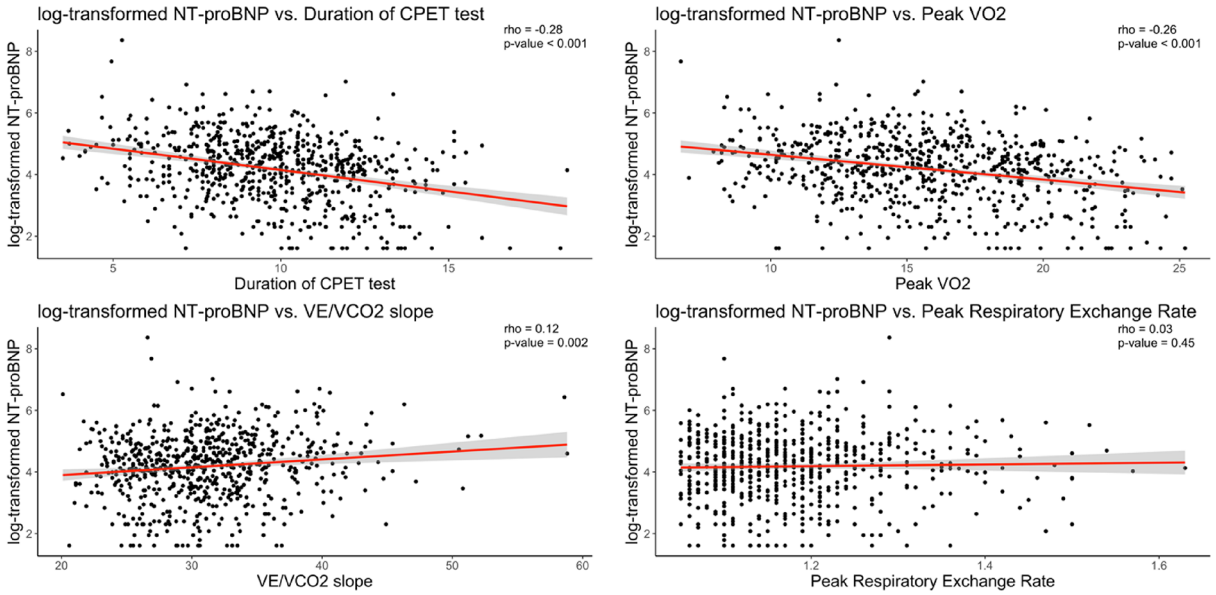


Fig. 3 Correlation of NT-proBNP levels and cardiopulmonary exercise testing. *Abbreviations* NT-proBNP, N-terminal pro-B-type natriuretic peptide; CPET, cardiopulmonary exercise testing; VO_2, maximal oxygen consumption; VE/VCO2, ventilatory efficiency

Table 4 Cardiopulmonary exercise testing results by NT-proBNP quartiles

	Quartile 1 (*n* = 174)	Quartile 2 (*n* = 171)	Quartile 3 (*n* = 172)	Quartile 4 (*n* = 168)	*p*-value
NT-proBNP range, ng/L	5–35	36–71	72–135	136–4284	
Duration of CPET test, min, mean ± SD	10.55 (2.31)	9.92 (2.41)	9.70 (2.31)	8.80 (2.25)	< 0.001
Peak VO_2, mL/Kg/min, mean ± SD	17.18 (3.81)	15.79 (3.63)	15.34 (3.93)	14.55 (3.34)	< 0.001
VE/VCO2 slope, mean ± SD	30.58 (4.70)	30.70 (5.13)	31.53 (5.55)	32.08 (6.05)	0.031
Peak respiratory exchange rate, mean ± SD	1.17 (0.09)	1.18 (0.11)	1.18 (0.09)	1.18 (0.09)	0.81
Predicted % peak VO_2, mean (SD)	54.87 (10.57)	53.74 (11.20)	52.72 (12.25)	50.74 (10.68)	0.006
Peak heart rate, beats per min, mean (SD)	138.49 (17.24)	131.63 (19.36)	128.03 (18.74)	124.83 (18.74)	< 0.001
Peak systolic blood pressure, mmHg, mean (SD)	186.57 (26.45)	181.16 (28.73)	175.94 (23.27)	171.61 (25.98)	< 0.001
Peak diastolic blood pressure, mmHg, mean (SD)	87.43 (15.37)	85.11 (16.87)	85.05 (14.83)	83.87 (12.48)	0.18
Oxygen pulse (VO_2/heart rate), ml/beat, mean (SD)	0.12 (0.03)	0.12 (0.03)	0.12 (0.03)	0.12 (0.03)	0.12

NT-proBNP, N-terminal pro-B-type natriuretic peptide; CPET, cardiopulmonary exercise testing; VO2, maximal oxygen consumption; VE/VCO2, ventilatory efficiency; SD, standard deviation.

echocardiographic abnormalities and NT-proBNP ≥ 71 ng/L (15.07 ± 3.62),and finally, participants with an abnormal echocardiogram and NT-proBNP ≥ 71 ng/L had the lowest peak VO2(14.74 ± 3.75; $p < 0.001$). Similar trends were observed for other metrics of functional status and exercise capacity (Table 5).

Discussion

In a large cohort of patients with well-controlled T2D, Stage B HF, and DbCM, we demonstrated that structural cardiac abnormalities as evaluated by echocardiography were common, however, NT-proBNP concentrations did not correlate with the severity or frequency of these abnormalities. In contrast, NT-proBNP concentrations correlated with quality of life, reported physical activities, and objective measurements of exercise capacity. These findings have previously been reported in other patient populations, with the present study supporting these relationships in the setting of Stage B DbCM. The combination of NT-proBNP concentrations and echocardiographic parameters identified graded abnormalities in health status and CPET performance (Graphical Abstract). However, the temporal relationship between NT-proBNP, cardiac structural abnormalities and functional capacity remains unclear.

Prior analyses have demonstrated that echocardiographic abnormalities are common in patients with DbCM, including diastolic dysfunction [10, 22], atrial enlargement [23], ventricular hypertrophy [24], and impaired systolic function [24]. In contrast to patients with symptomatic HF where NT-proBNP concentrations are directly correlated with the magnitude of cardiovascular dysfunction, in this population, NT-proBNP does not appear to be correlated with more subclinical echocardiographic abnormalities. This should be taken in the context of an asymptomatic population with overall low

Table 5 Concomitant effect of NT-proBNP and Echocardiographic Abnormalities on Health Status, Physical Activity and Cardiopulmonary Exercise Testing

	Grouping				*p*-value
	Normal Echo† Low NT-proBNP	Abnormal Echo* Low NT-proBNP	Normal Echo† High NT-proBNP	Abnormal Echo * High NT-proBNP	
n	191	150	211	133	
KCCQ physical limitation score, mean (SD)	91.61 (13.83)	89.42 (16.66)	86.80 (18.62)	88.27 (15.74)	0.03
KCCQ clinical summary score, mean (SD)	92.54 (12.89)	91.17 (13.50)	88.42 (16.17)	90.38 (12.91)	0.03
KCCQ overall summary score, mean (SD)	92.07 (13.24)	90.56 (14.15)	87.89 (17.45)	90.26 (12.63)	0.04
PASE score. mean (SD)	177.43 (101.71)	151.88 (89.78)	144.04 (82.65)	141.94 (78.61)	0.001
Duration of CPET test, min, mean (SD)	10.23 (2.35)	10.27 (2.42)	9.26 (2.19)	9.26 (2.53)	< 0.001
Peak VO2, mL/Kg/min, mean (SD)	16.61 (3.79)	16.40 (3.77)	15.07 (3.62)	14.74 (3.75)	< 0.001
VE/VCO2 slope, mean (SD)	30.43 (4.88)	31.01 (4.94)	31.75 (6.00)	31.73 (5.50)	0.06
Peak respiratory exchange rate, mean (SD)	1.18 (0.10)	1.18 (0.10)	1.18 (0.10)	1.17 (0.09)	0.86

*Abnormal ECHO defined as Myocardial Global Longitudinal Strain < −16 or left ventricular mass index > 95 for females or > 115 for males or E/e' >13 or left atrial volume index > 34. † Normal ECHO is defined as the absence of these abnormalities. Low NT-proBNP is defined as < 71 ng/L while high NT-proBNP is defined as ≥ 71 ng/L

NT-proBNP, N-terminal pro-B-type natriuretic peptide; KCCQ, Kansas City Cardiomyopathy Questionnaire; PASE, physical activity scale for the elderly; SD, standard deviation; CPET, cardiopulmonary exercise testing; VO2, maximal oxygen consumption; VE/VCO2, ventilatory efficiency

concentration of NT-proBNP (median 71 ng/L), which is significantly below the diagnostic threshold in HF (125 ng/L). Additionally, subclinical echocardiographic abnormalities may not result in significant changes in left ventricular filling and subsequent NT-proBNP concentration elevation, a phenomenon observed in other cohorts of patients with diabetes [22, 25]. For this reason, DbCM is not diagnosed based on the basis of NT-proBNP alone, but in conjunction with imaging and functional assessments. The role of novel metabolic biomarkers (cardiotrophin-1, insulin-like growth factor binding protein 7, activin A and long-non coding RNAs) that would aid earlier detection of DbCM, remains to be seen [25–28]. While the relationship between echocardiographic abnormalities and NT-proBNP in DbCM is unclear, it is likely that both imaging variable and biomarkers provide synergistic prognostic information [29]. This effect was seen in our study and other populations such as mitral regurgitation [30], aortic stenosis [31] and heart failure [29]. This highlights the importance of multimodality assessments (biochemical, functional, imaging), with abnormalities in multiple domains suggestive of increased risk of adverse events.

Previous hypothesis-generating studies have estimated that 6% of HF patients may have a relative natriuretic peptide deficiency [32], which may be increased in DbCM cohorts due to the effects of insulin resistance [33] or concomitant medication use (GLP-1 receptor agonists) that have been shown to reduce NT-proBNP concentrations [34]. Other factors that have been identified to be associated with unexpectedly low natriuretic peptide concentrations include higher BMI, higher EF, older age, higher kidney function and race/ethnicity (lower levels observed among black individuals) ([32, 33, 35, 36]. Further hypothesis generating data to identify individuals with impaired natriuretic peptide metabolism or "non-responders", can be gleaned from examining HF trials with serial natriuretic peptide measurements. Natriuretic peptide "non-responders" (failing to decrease NT-proBNP ≤ 1000 pg/ml) despite implementation of HF therapies is common (57–69%) and has been associated higher baseline NT-proBNP levels, ischemic etiology, lower systolic blood pressure, higher heart rates, black race, higher New York Heart Association (NYHA) symptom classification and the presence of chronic obstructive pulmonary disease and atrial fibrillation [37, 38]. Taken together these provide clues in understanding individual variation in natriuretic peptide metabolism and regulation.

Overall, elevated natriuretic peptide concentrations are associated with long-term cardiovascular events in DbCM but less discriminatory for subclinical echocardiographic findings [39]. In the present study, no cardiac structural abnormalities were identified in many participants with an elevated NT-proBNP. In this subgroup, one explanation is that cardiac structural abnormalities are indeed present leading to NT-proBNP release but are not able to be identified with routinely used echocardiographic variables. In contrast, many patients with cardiac structural abnormalities did not demonstrate elevated concentrations of NT-proBNP.

There is a paucity of studies that have evaluated health status and functional capacity in patients with subclinical DbCM. In this trial, a striking finding was the presence of markedly impaired activity levels and reduced functional capacity despite including individuals without overt HF. Importantly, reduction in functional capacity was an inclusion criterion for the study, but the impairment is nonetheless impressive. NT-proBNP concentrations were able to delineate individuals with impaired functional

capacity, decreased physical activity, and worse health status. This inverse relationship between natriuretic peptides and VO_2 has been described in other populations including healthy participants [40], pulmonary disorders [41] and chronic heart failure [42]. However, the NT-proBNP threshold at which this occurs is less clear, with patients in even the lowest NT-proBNP quartiles demonstrating reduced functional capacity. This is relevant as a threshold value of 125 ng/L has been supported for risk assessment in the literature [3]. While this concentration was not able to discriminate for cardiac structure/function, it strongly identified impaired functionality. As such, our data suggest the optimal NT-proBNP concentration for such an indication may be lower than 125 ng/L, however, more work is necessary to identify an NT-proBNP threshold that identifies eligibility for treatment to reduce risk for overt HF progression.

Several limitations exist that should be taken into consideration when interpreting our data. The echocardiographic analysis undertaken utilized echocardiographic parameters that are routinely used in clinical practice. Novel echocardiographic variables such as assessments of myocardial reserve using stress echocardiography, three-dimensional strain and left atrial strain may be able to detect structural cardiac abnormalities with greater sensitivity and specificity. Additionally, the population that was studied lacked overt symptoms and did not demonstrate significant systolic dysfunction, as such our results cannot be generalized to those populations. Similarly, the included population did not have any history or symptoms suggestive of significant atherosclerosis in any vascular territory, however without universal screening we are unable to determine the impact of undiagnosed atherosclerotic disease on the observed echocardiographic findings and functional capacity. One of the inclusion criteria for entry into the study was impaired functional capacity as evaluated by CPET. While all participants met this criterion, only 20 (2.9%) did so without any evidence of structural cardiac abnormalities or an elevated concentration of NT-proBNP. This has led to the purposeful enrollment of a DbCM population with a higher degree of functional impairment and our results should be considered in this context. CPET testing was undertaken using both cycle ergometry and treadmill, which may introduce bias into the interpretation of VO_2 and exercise duration. While 89% of participants underwent CPET cycle ergometry testing, the devised exercise protocol appears to have achieved its desired effect with similar VO_2 results (cycle ergometry – 15.8 ml/kg/min; treadmill – 15.3 ml/kg/min) and average durations (cycle ergometry – 9 min 39 s; treadmill – 9 min 37s) observed.

In conclusion, this study has demonstrated that among individuals with subclinical DbCM, there remains significant heterogeneity within the population with regards to the extent of echocardiographic abnormalities, biomarker concentrations and functional capacity. While NT-proBNP is correlated with functional status, physical activity, and health status, it is not associated with structural cardiac abnormalities. This highlights that currently used biomarkers may not be adequate to identify early cardiac abnormalities in Stage B DbCM, which may require multimodality assessments.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02378-w.

Supplementary Material 1.

Author contributions

All authors have made substantial contributions to the design of the analysis, interpretation of the data, substantively revised the manuscript, accepted the submitted version and have agreed to be accountable for the work presented. YL contributed to the analysis. PG/JE/JJ were responsible for drafting the first draft of the manuscript.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Competing interests

Javed Butler: Consultant—Abbott, American Regent, Amgen, Applied Therapeutic, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimension, Cardior, CVRx, Cytokinetics, Edwards, Element Science, Innolife, Impulse Dynamics, Imbria, Inventiva, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Prolaio, Roche, Sequana, SQ Innovation, Tenex, and ViforWilson Tang: Dr. Tang served as consultant for Sequana Medical, Cardiol Therapeutics, Genomics plc, Zehna Therapeutics, Renovacor, WhiteSwell, Kiniksa, Boston Scientific, CardiaTec Biosciences, Intellia Therapeutics, and has received honorarium from Springer, Belvoir Media Group, and American Board of Internal Medicine. Carolyn S.P. Lam: Carolyn SP Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has Received research support from NovoNordisk and Roche Diagnostics; has Served as consultant or on the Advisory Board/ Steering Committee/ Executive Committee for Alleviant Medical, Allysta Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, Cytokinetics, Darma Inc., EchoNous Inc, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Quidel Corporation, Radcliffe Group Ltd., Recardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as co-founder & non-executive director of Us2.ai.Stefano Del Prato reports serving as president of EASD/EFSD (2020-2022) and has received research grants to the institution from AstraZeneca and Boehringer Ingelheim; has served as advisor for Abbott, Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., EvaPharma, Jiangsu Hengrui Pharmaceuticals Co., Menarini International, Merck Sharpe & Dohme, Novartis Pharmaceutical Co., Novo Nordisk, Sanofi, Sun Pharmaceuticals; has received fees for speaking from Abbott, AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Eli Lilly & Co., Laboratori Guidotti, Menarini International, Merck Sharpe & Dohme, Novo Nordisk, Sanofi. All other authors declare no conflicts of interest.

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