International Journal of Cardiology 289 (2019) 119–124

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

An echocardiographic substrate for dyspnea identifies high risk patients with type 2 diabetes☆

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ARTICLE INFO

Article history:
Received 21 December 2018
Received in revised form 9 March 2019
Accepted 29 April 2019
Available online 1 May 2019

Keywords:
Echocardiography
Type 2 diabetes
Heart failure with preserved ejection fraction

ABSTRACT

Background: Dyspnea is a common clinical challenge in patients with type 2 diabetes and may be a sign of heart failure (HF). We sought to evaluate the predictive value dyspnea with and without an echocardiographic substrate in patients with type 2 diabetes without known heart disease.
Methods: A total of 724 patients with type 2 diabetes followed at specialized clinics participated in this prospective cohort study. Clinical evaluation, comprehensive echocardiography and follow-up through national registers were performed. An echocardiographic substrate was either left ventricular hypertrophy, increased left atrial size, E/e' > 15, or LV ejection fraction<50%. The end-points were cardiovascular (CVD) events and all-cause mortality.
Results: Median follow-up was 4.8 years [Interquartile range: 4.1, 5.3] for CVD event and 77 patients suffered a CVD event. Dyspnea was significantly associated with CVD event: Hazard ratio (HR): 1.58 (95% confidence interval: 1.01–2.48), $p = 0.04$. Stratifying by evidence of echocardiographic substrate revealed high risk individuals: CVD event: 0.71 (0.35–1.46), p = NS in patients with dyspnea and *no echocardiographic substrate* and 2.85 (1.74–4.67), $p < 0.001$ in patients with dyspnea *with echocardiographic substrate*). This pattern was similar in multivariable analyses. Also, C-statistics improved from 0.66 (0.60–0.72) to 0.69 (0.63–0.75), $p < 0.001$ and net reclassification index was 27.5%(5.0–50.0), $p = 0.01$ for CVD event. The results were similar for all-cause mortality except dyspnea was only a borderline significant predictor.
Conclusion: In patients with type 2 diabetes complaining of dyspnea, identifying an echocardiographic substrate - thus indicating patients with HF - accurately stratifies patients with increased risk of CV events and all-cause mortality.

1. Introduction

Dyspnea is a common complaint in patients with type 2 diabetes and represents an important clinical challenge because concomitant obesity and sedentary life-style in itself may be the cause of reduced functional capacity. However, dyspnea is also a cardinal symptom of heart failure (HF), that this patient group consistently has been shown to have a 2–4 fold increased risk of developing. [1,2] This is particularly evident in the elderly with type 2 diabetes, where HF is considered the most frequent late stage complication. [3] In distinguishing between dyspnea caused by HF and dyspnea from other causes, echocardiography is essential. [4] Echocardiography readily provides information on chamber volumes, structure and systolic and diastolic function. However, while HF with *reduced* ejection fraction (HF-REF) is a relatively rare finding in this patient group, HF with *preserved* ejection fraction (HF-PEF) is common. In accordance, diastolic dysfunction estimated by varying methods has been reported in approximately 40–70% of patients with type 2 diabetes, whereas systolic dysfunction with reduced left ventricular ejection fraction (LVEF) has been found in 1–10% of the patients depending on the used definitions ref [5–8]. The prognostic significance of having diastolic dysfunction has been established by previous studies, that have found that E/e' [9] and left atrial volume index [10] significantly predict adverse outcome in patients with type 2 diabetes. Also, awareness of heart failure in patients with type 2 diabetes has increased because of recent cardiovascular outcome trials have showed a reduced risk of HF associated with medical therapy [11,12]. Unfortunately, however, HF was poorly characterized at baseline and follow-up in these studies giving rise to the need of valid, prognostic important definitions of HF in patients with type 2 diabetes.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcard.2019.04.093
0167-5273/

The purpose of this study was to investigate whether echocardiography could stratify patients with type 2 diabetes without known heart disease complaining of dyspnea by identifying an echocardiographic substrate for dyspnea and thus, by doing so, indicating the presence of HF.

2. Methods

2.1. Study population

The Thousand&2 study is a prospective cohort study of patients with Type 2 diabetes characterized with baseline clinical information, biochemistry and comprehensive echocardiography. From 2011 to 2013, 2158 patients with type 2 diabetes followed at 2 specialized diabetes clinics in the Copenhagen, Denmark area were invited and 1030 patients participated in the Thousand&2 study. The details on the study inclusion is described elsewhere [13]. Before the study visit, all patients filled out a questionnaire with information on current medication, prior heart disease (myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, congestive heart failure and atrial fibrillation), prior stroke and peripheral artery disease, family history of coronary heart disease, smoking habits, prior diagnosis of chronic obstructive lung disease/asthma, height and weight. The questionnaire was reviewed with the patient at the study visit by PGJ. For the present study, we excluded patients with known heart disease defined as self-reported prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting ($n = 188$) and patients with previous heart valve surgery ($n = 6$). Also, we excluded patients with missing values of the parameters that defined the presence of echocardiographic substrate for dyspnea ($n = 111$). This included patients with atrial fibrillation at the time of the echocardiographic examination in which functional diastolic measures are unreliable. The study was conducted in accordance with the Helsinki Declaration, approved by The Danish National Committee on Biomedical Research Ethics, amendment to protocol no. H-3-2009-139 [14]. All participants gave written, informed consent.

Known chronic pulmonary disease was defined as either self-reported or use of inhaled bronchodilators/corticosteroids. Blood pressure was measured in the supine position after at least 15 min of rest. Body mass index (BMI) was calculated (weight (kg)/height (m)2) based on self-reported measurements. Lipid levels, haemoglobin A1c, albuminuria status and creatinine were obtained from routine blood tests performed.

2.2. Assessment dyspnea

At the study visit, the presence of dyspnea was evaluated with the patient by PGJ using categories equivalent to the *New York Heart Association (NYHA)* classification. Mild dyspnea was considered present when the patient had symptoms were equivalent to NYHA class II, moderate when equivalent to NYHA class III and severe when equivalent to NYHA class IV.

2.3. Echocardiography

Echocardiography was performed at the study visit by PGJ (>95%) using GE General Electrics, Vivid 7 and Vivid E9 (GE Vingmed Ultrasound, Horten, Norway). The offline analyses were performed using GE EchoPAC software, BT13. All analyses were performed as previously published at baseline by PGJ [13]. Chamber quantifications were done in accordance with recommendations of the European Association of Echocardiography and the American Society of Echocardiography [15] and valve disease was classified using an integrative approach as proposed by the European Association of Echocardiography [16,17].

An echocardiographic substrate, as previously published by our group [18], was defined as in the presence of at least one of the following: 1) an LVEF by *Simpson's biplane method* < 50, 2) Ratio of early diastolic mitral inflow velocity (E) to early diastolic septal annular velocity (e') (E/e'_{septal}) ≥15, 3) Increased left ventricular (LV) mass index (> 95 g/m^2 for women and > 115 g/m^2 for men), 4) Left atrial (LA) volume index >34 ml/m^2, or 5) presence of at least moderate heart valve disorder.

2.4. Follow-up

Follow-up was performed using *The Danish National Board of Health's National Patient Registry* and *The Register of Cause of Death*, that have previously been found to have high accuracy when comparing to medical journals [19]. The primary end-point was CVD event that was the composite of admission with CVD (including coronary revascularization, myocardial infarction (International classification of diseases (ICD)-10 codes I21-I25), heart failure (ICD-10 codes I11, I13, I42, I43 and I50), cardiac arrest (I46), cerebrovascular disease (I60-I69 and peripheral artery disease (I70-I79)) and CVD death. Because all death certificates are reviewed before entering the registers, follow-up for CVD death ended with 2015 and deaths after this period were considered as all-cause mortalities. All-cause mortality obtained from the same registry was considered as the secondary end-point. Follow-up was 99.9% because of 1 person with wrongly registered social security number.

2.5. Statistics

We used the Welsh's *t*-test for Gaussian and Mann-Whitney *U* test for non-Gaussian distributed continuous variables and Chi-square test for categorical variables. The Kaplan-Meier estimator was used to generate survival and event-free survival curves that were compared using the log-rank test. Cox proportional hazard regression was used to determine uni- and multivariable associations of dyspnea and dyspnea with and without echocardiographic substrate and risk of CVD event and all-cause mortality. Model discrimination was tested with C-statistics and net reclassification index. *P*-values <0.05 were considered statistically significant. All statistics were performed using R for Mac, version 3.4.3 (R Project for Statistical Computing, Vienna University of Economics and Business Administration, Wien, Austria).

3. Results

The study population consisted of 724 patients with type 2 diabetes without known heart disease. Median age of the total population was 64.5 [interquartile range: 57.0–69.8]. Median follow-up time was 4.8 years [interquartile range: 4.1–5.3] for CVD event and 5.0 years [interquartile range: 4.2–5.3] for all-cause mortality. In total, 248 patients complained of dyspnea. Of these, 19 (7.7%) had an LVEF <50%, 58 (23.3%) had an E/e' > 15, 44 (17.7%) had increased LV mass index, 31 (12.5%) had increased LA mass index and 9 (3.6%) had at least moderate heart valve disorder. Of patients not complaining about dyspnea, $n = 476$, 38 (8.0%) had an LVEF <50%, 64 (13.4%) had an E/e' > 15, 42 (8.8%) had increased LV mass index, 72 (15.1%) had increased LA mass index and 8 (9.8%) had at least moderate heart valve disorder. In total, 77 (10.6%) suffered from a CVD event (9 CVD deaths, 14 admissions with heart failure, 18 myocardial infarctions, 13 coronary interventions, 16 admissions with cerebrovascular disease and 7 admissions with peripheral vascular disease) and 65 (9.0%) died.

Baseline characteristics of patients *with* vs *without* dyspnea and patients with dyspnea *with* vs *without* an echocardiographic substrate are shown in Table 1. In general, 34% of the patients had some degree of dyspnea. While mild dyspnea was most common, moderate or severe dyspnea was present in 82 patients or 33% of the patients with dyspnea. Patients complaining of dyspnea were of similar age, less often men, had higher BMI but not more often prior CVD. They were also more likely to receive insulin or beta-blocker than patients not complaining of dyspnea. In patients with dyspnea, 44% had an echocardiographic substrate for dyspnea. Patients with an echocardiographic substrate more often complained of >moderate dyspnea but still, 59% had only mild dyspnea. Patients with dyspnea more often had known pulmonary disease. However, among patients with dyspnea, it was not more common to have an echocardiographic substrate in those *without* known pulmonary disease compared to those *with* pulmonary disease. Thus, having a concomitant echocardiographic substrate for dyspnea was the case in 28 of 54 (51.9%) patients with pulmonary disease complaining about dyspnea. The patients with an echocardiographic substrate were older, had higher systolic blood pressure and creatinine levels. They were less likely to be treated with metformin or glucagon-like peptide-1 receptor agonists, more likely to be treated with beta-blockers and diuretics. Also, the use of bronchodilators/corticosteroids was more common both in patients complaining about dyspnea and those with dyspnea *and* an echocardiographic substrate.

There was significant interaction between having dyspnea and having echocardiographic substrate for dyspnea for CVD event ($p = 0.03$ for univariate and $p = 0.02$ after adjusting for age, sex, diabetes duration, BMI, systolic blood pressure, known CVD and known pulmonary disease) but not for all-cause mortality though borderline significant in multivariable analyses ($p = 0.11$ for univariate and $p = 0.06$ after adjusting for age, sex, diabetes duration, BMI, systolic blood pressure, known CVD and known pulmonary disease). Event-free survival and proportion alive stratified by dyspnea and dyspnea *with or without* an echocardiographic substrate are shown in Fig. 1. Having dyspnea was associated with increased risk for CVD event but only borderline for all-cause mortality. For both end-points however, stratifying by echocardiographic substrate for dyspnea revealed high-risk groups for both

Table 1
Baseline characteristics.

	No dyspnea	Dyspnea	*P-value*	Dyspnea, no echocardiographic substrate	Dyspnea, echocardiographic substrate	*P-value*
	n = 476	n = 248		n = 139	n = 109	
Clinical characteristics						
Age (years)	64 [57, 69]	66 [57, 70]	0.10	64 [56, 69]	67 [60, 72]	0.001
Male sex, n (%)	315 (66.2)	129 (52.0)	<0.001	79 (56.8)	50 (45.9)	0.11
Diabetes duration (years)	10 [5, 16]	12 [6, 18]	0.05	12 [5, 17]	13 [7, 20]	0.05
Body mass index (kg/m^2)	28 [26, 32]	31 [27, 34]	<0.001	30 [26, 34]	32 [28, 35]	0.06
Systolic blood pressure (mmHg)	136 (16)	136 (18)	0.65	134 (17)	139 (18)	0.02
Diastolic blood pressure (mmHg)	81 (11)	80 (10)	0.31	80 (10)	80 (11)	0.84
Prior CVD, n (%)	27 (5.7)	19 (7.7)	0.38	8 (5.8)	11 (10.1)	0.30
Known pulmonary disease, n (%)	26 (5.5)	54 (21.8%)	<0.001	26 (18.7)	28 (25.7)	0.24
Smoking			0.28			0.87
Never, n (%)	214 (45.0)	100 (40.3)		54 (38.8)	46 (42.2)	
Prior, n (%)	195 (41.0)	103 (41.5)		59 (42.4)	44 (40.4)	
Active, n (%)	67 (14.1)	45 (18.1)		26 (18.7)	19 (17.4)	
Dyspnea						
Mild, n (%)		166 (66.9)		102 (73.4)	64 (58.7)	0.02
Moderate, n (%)		73 (29.4)		31 (22.3)	42 (38.5)	
Severe, n (%)		9 (3.6)		6 (4.3)	3 (2.8)	
Biochemistry						
Albuminuria, n (%)	106 (22.8)	59 (24.1)	0.78	28 (20.4)	31 (28.7)	0.18
Total cholesterol (mmol/L)	4.2 [3.6, 4.8]	4.1 [3.6, 4.9]	0.82	4.2 [3.5, 5.0]	4.1 [3.6, 4.8]	0.82
Low density lipoprotein cholesterol (mmol/L)	2.0 [1.6, 2.6]	2.0 [1.5, 2.6]	0.77	2.0 [1.5, 2.7]	2.0 [1.7, 2.4]	0.77
Creatinine (μmol/L)	78 [65, 93]	77 [63, 97]	0.84	72 [60, 87]	83 [69, 104]	<0.001
Estimated glomerular filtration rate (ml/min/ 1.73 m^2)	78.3 (21.0)	75.2 (22.0)	<0.001	81.6 (20.9)	67.0 (20.6)	<0.001
Haemoglobin A_{1c} (%)	7.4 (1.4)	7.5 (1.5)	0.65	7.5 (1.4)	7.5 (1.6)	0.79
Haemoglobin A_{1c} (mmol/L)	55 [48,65]	55 [48,65]	0.90	55 [48, 65]	54 [45, 66]	0.96
Glucose lowering medication						
Metformin, n (%)	357 (75.0)	176 (71.0)	0.28	109 (78.4)	67 (61.5)	0.005
Dipeptidyl peptidase-4 inhibitors, n (%)	51 (10.7)	20 (8.1)	0.31	12 (8.6)	8 (7.3)	0.89
Sulfonylurea, n (%)	84 (17.6)	35 (14.1)	0.27	21 (15.1)	14 (12.8)	0.75
Glucagon-like peptide-1 receptor agonists, n (%)	110 (23.1)	60 (24.2)	0.82	42 (30.2)	18 (16.5)	0.02
Insulin, n (%)	194 (40.8)	134 (54.0)	0.001	70 (50.4)	64 (58.7)	0.24
Other medication						
Beta blockers, n (%)	64 (13.4)	50 (20.2)	0.025	20 (14.4)	30 (27.5)	0.02
Angiotensin-converting enzyme inhibitors, n (%)	179 (37.6)	92 (37.1)	0.96	53 (38.1)	39 (35.8)	0.80
Angiotensin II receptor blockers, n (%)	173 (36.3)	100 (40.3)	0.33	54 (38.8)	46 (42.2)	0.69
Calcium antagonists, n (%)	142 (29.8)	82 (33.1)	0.42	39 (28.1)	43 (39.4)	0.08
Diuretics, n (%)	212 (44.5)	129 (52.0)	0.07	64 (46.0)	65 (59.6)	0.046
Statins, n (%)	359 (75.4)	195 (78.6)	0.38	112 (80.6)	83 (76.1)	0.49
Antiplatelets, n (%)	297 (62.4)	148 (59.7)	0.53	75 (54.0)	73 (67.0)	0.05
Bronchodilators/cortico-steroids, n (%)	13 (2.7)	35 (14.1)	<0.001	13 (9.4)	22 (20.2)	0.025

Continuous traits are reported as mean (standard deviation) or median [interquartile range] in case of non-normal distribution.

end-points ($p < 0.001$ for both). In the univariable, Fig. 2, and multivariable analyses, supplemental Fig. 1, this pattern was repeated: Having dyspnea was associated with only CVD event in the univariate analyses unless it was moderate-severe in which case it was associated with both end-points in both uni- and multivariable analyses. Also, having an echocardiographic substrate for dyspnea was associated with a 2–3-fold increased risk of both CVD event and all-cause mortality regardless of dyspnea severity. Finally, the prognosis of patients with dyspnea but *no* echocardiographic substrate for this had similar prognosis to patients without dyspnea for both uni- and multivariable analyses and for both end-points.

Model performance is shown in Table 2. In multivariable analyses the C-statistics and reclassification index increased significantly for both end-points. Thus, adding dyspnea with or without an echocardiographic substrate to the adjusted model, would correctly reclassify respectively 27.5% for CVD event and 35.0% for all-cause mortality when performing risk assessment.

4. Discussion

This study highlights the severity of the symptom *dyspnea* – especially when moderate-severe - in out-patients with type 2 diabetes without known heart disease and suggests a method to accurately identify dyspnea patients with high-risk and dyspnea patients with a risk similar to patients not complaining about dyspnea. We found, that dyspnea was a common complaint in these patients and that the future risk of CVD event was increased even when only mild dyspnea was reported. Also, all-cause mortality was increased in patients complaining about moderate-severe dyspnea. Identifying an echocardiographic substrate for dyspnea, and thus providing an indication of HF, significantly increased the risk of suffering from future CVD event and all-cause mortality – even in patients only complaining about mild dyspnea. On the contrary, complaining about moderate-severe dyspnea *without* an echocardiographic substrate did not increase future risk of CVD event or all-cause mortality. In addition, adding dyspnea with and without an echocardiographic substrate to a multivariable model significantly improved model performance estimated as C-statistics and net reclassification index regardless of which end-point considered.

4.1. Echocardiography and prognosis in type 2 diabetes

This study is, to our knowledge, the first to incorporate symptomatic status, i. e. *dyspnea,* in the evaluation of the prognostic significance of echocardiographically detected myocardial impairment in patients with type 2 diabetes. Previous studies have examined the prognostic significance of echocardiographic abnormalities in type 2 diabetes. From et al. found that E/e' and diastolic dysfunction expressed as an E/e' > 15 was a predictor of admission with heart failure in a retrospective cohort of 1760 patients with type 2 diabetes [9]. Blomstrand et al. also identified E/e' as the strongest predictor of CVD events after a

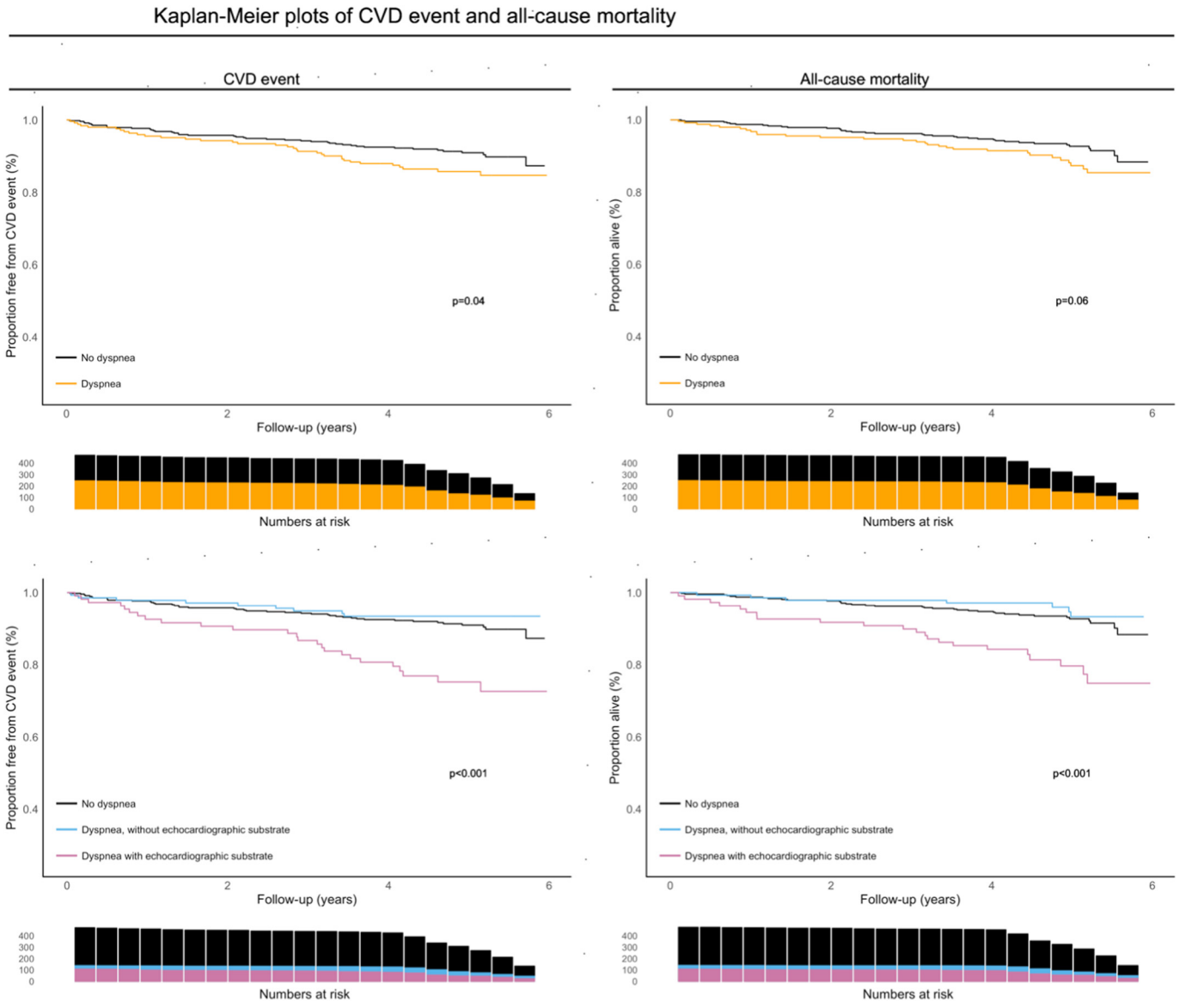
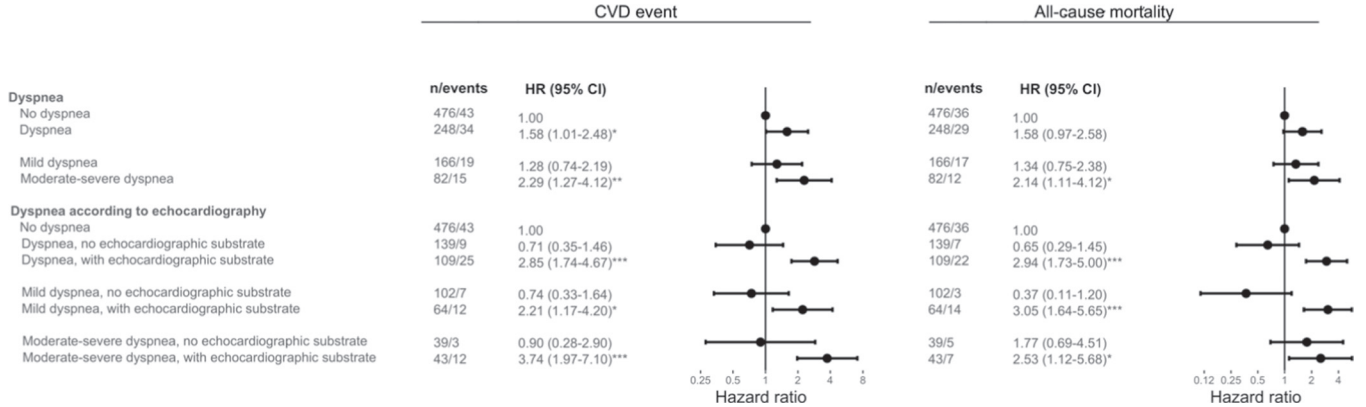


Fig. 1. Kaplan-Meier curves of risk of CVD and all-cause mortality in all patients according to presence of dyspnea with and without an echocardiographic substrate.

mean follow-up of 67 months in 512 patients with type 2 diabetes followed in primary care [20]. On the contrary, Poulsen et al. found that only LA volume index - and not E/e' - was an independent echocardiographic measurement to predict a combined end-point of major cardiac events or death in 305 patients without known heart disease [10]. Finally, we have in recently reported that E/e' and global



Levels of significance: * p<0·05, ** p<0·01, *** p<0·001.

Fig. 2. Univariable associations of dyspnea with and without echocardiographic substrate and risk of CV event or all-cause mortality. Levels of significance: * p < 0·05, ** p < 0·01, *** p < 0·001.

Table 2
Effect of adding the presence of dyspnea with and without an echocardiographic substrate on model performance.

	C-statistics		Net reclassification index of model *without* vs *with* dyspnea +/− an echocardiographic substrate	
All patients				
CVD event		P-value		P-value
Dyspnea +/− an echocardiographic substrate (univariable)	0.61 (0.55–0.67)			
Model without dyspnea +/− an echocardiographic substrate	0.66 (0.60–0.72)	<0.001	27.5% (5.0–50.0)	0.02
Model with dyspnea +/− an echocardiographic substrate	0.69 (0.63–0.75)			
All-cause mortality				
Dyspnea +/− an echocardiographic substrate (univariable)	0.62 (0.56–0.69)			
Model without dyspnea +/− an echocardiographic substrate	0.64 (0.57–0.71)	0.001	35.0% (9.8–60.2)	0.007
Model with dyspnea +/− an echocardiographic substrate	0.70 (0.62–0.77)			

Model includes age, sex, diabetes duration, body mass index, systolic blood pressure, known cardiovascular disease and known chronic pulmonary disease.
CVD: Cardiovascular disease.

longitudinal strain were strong predictors of CVD with a rather surprising gender interaction as E/e' was strongest in men and global longitudinal strain in women [21].

Type 2 diabetes is, however, closely associated with a range of cardiovascular risk factors including obesity, hypertension and hyperlipidemia that per se are associated with substantial cardiac remodeling affecting also the functional measures [22–24]. Accordingly, we have shown, that the cardiac impairment in type 2 diabetes is dependent of the burden of uncontrolled metabolic risk factors [25]. Thus, as type 2 diabetes and its associated cardiovascular risk factors may affect the myocardium through different pathways, we argue, that rather than regarding a single, unifying echocardiographic measurement, it is more clinically relevant to include a range of echocardiographic parameters in the evaluation of the patient with type 2 diabetes. Consequently, we have demonstrated that by including simple echocardiographic parameters in the evaluation of dyspnea, we were able to accurately stratify type 2 diabetes out-patients.

In the recent years, global longitudinal strain measured by 2D strain echocardiography has emerged as a sensitive marker of LV systolic function in patients with type 2 diabetes. In accordance we have found, that subtle impairment in LV function is associated with macroalbuminuria [26], cholesterol remnants/triglyceride [22] and burden of uncontrolled metabolic risk factors [25]. Also, global longitudinal strain has been shown to be predictors future adverse events in type 2 diabetes [20,27]. However, we chose not to include reduced global longitudinal strain in the definition of *echocardiographic substrate* in these analyses for 2 reasons: 1) because of the lack of consensus on standardization of the methodology and 2) because of vendor-specific differences in algorithms for calculating global longitudinal strain. This decision was made before the follow-up data was available because we felt that these limitations would impede any clinical implementation of our findings.

4.2. HFpEF and prognosis in patients with type 2 diabetes

Over the past decades there has been a decreasing incidence of coronary heart disease and stroke in patients with type 2 diabetes [28]. In consequence, HF and peripheral artery disease has emerged as the two most common complications to type 2 diabetes [29]. Despite this, major diabetes outcome trials continue to choose myocardial infarction and stroke as the primary outcomes [30]. However, the EMPA-REG OUTCOME [11] and the CANVAS [12] trials demonstrated decreased risk of HF in patients treated with either *empagliflozin* or *canagliflozin*. Yet, while HF is receiving increasing attention, clear characterization of HF in this population is lacking. In this study we have shown, that among out-patients with type 2 diabetes, a HF diagnosis based on presence of dyspnea with an echocardiographic substrate is very common and is associated with a particularly adverse prognosis even though HFrEF was only rarely present in this population.

4.3. Strengths and limitations

This study is strong in that it is a prospective cohort study with careful baseline characterization, comprehensive echocardiography and with a long follow-up time. Study weaknesses include lack of measurement of pulmonary function that may help differentiate between dyspnea with pulmonary and with cardiac aetiology. However, while dyspnea may also be caused by pulmonary disease it's difficult clinically to discern cardiac and pulmonary dyspnea and thus clinically exclude a component of cardiac dysfunction in dyspnea patients with known pulmonary disease. Additionally, while known pulmonary disease was more common in patients with dyspnea, having a concomitant echocardiographic substrate for dyspnea was common according to our results. Thus, from a clinical point of view, patients with pulmonary dysfunction should also be examined to determine possible concomitant cardiac substrate for dyspnea. We report a high prevalence of dyspnea in this cohort. This could in part be explained by the fact that the patients were directly confronted with questions on dyspnea and dyspnea was thus not the direct cause of the patient contact with a physician.

5. Conclusion

In this study, we have demonstrated that out-patients with type 2 diabetes without known heart disease complaining about dyspnea have a worse prognosis regarding future CVD event than patients without dyspnea. Also, patients complaining about moderate-severe dyspnea had increased risk of all-cause mortality. Patients with an echocardiographic substrate for dyspnea – regardless of dyspnea severity - had a greatly increased risk of both end-points and adding dyspnea *with* and *without* an echocardiographic substrate significantly improved risk prediction in this population. The study highlights the need for dyspnea assessment and further validates echocardiography as a pivotal examination in out-patients with type 2 diabetes.

Potential conflicts of interests

TBS, RM and TFH have no conflicts of interest. PGJ has received lecture fee from Novo Nordisk. PR reports grants from and shares in Novo Nordisk. Advisory boards in MSD, Astra Zeneca, Boehringer, Eli Lilly, Janssen, Novo Nordisk Astellas, Abbvie (all fees to institution). Lecture fee to institution from Bayer. TV has received lecture fees and/or unrestricted research grants from, participated in advisory boards of and/or consulted for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD/Merck, Novo Nordisk and Sanofi. MTJ has served as consultant, on advisory boards, or invited speaker for Astra Zeneca, Novo Nordisk, Novartis, and GE.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.093.

Funding

The study was carried out as part PGJ's appointment at department of cardiology, Gentofte and Herlev University Hospital.

Acknowledgements

The study group is greatly indebted to the initiator of the Thousand&2 study, professor Jan Skov Jensen, MD, PhD, DMSc, who tragically passed away July 2, 2018.

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