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Diagnostic and prognostic value of the electrocardiogram in stable outpatients with type 2 diabetes

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ABSTRACT

Aims. The European Society of Cardiology guidelines on diabetes and cardiovascular disease (CVD) recommend an electrocardiogram (ECG) in patients with diabetes and hypertension or with suspected CVD. We investigated whether ECG abnormalities can be used as a diagnostic and prognostic marker of heart failure (HF) in patients with type-2 diabetes (T2D) in secondary care diabetes-clinics. **Methods**. We included 722 patients with T2D in sinus rhythm. HF with preserved ejection fraction (HFpEF) was defined according to the European Society of Cardiology guidelines. Heart failure with mid-range ejection fraction (HFmrEF) was patients with dyspnoea and an LVEF 41–49%. Heart failure with reduced ejection fraction (HFrEF) or asymptomatic left ventricular systolic dysfunction (ALVSD) was defined as a LVEF ≤40%. **Results**. Overall, 24% patients had ECG abnormalities. A total of 15% had HF whereof 48% had ECG abnormalities. A normal ECG had a 99.3% negative predictive value (NPV) of ruling out HFrEF/ALVSD. In a sub-group with 0–1 simple clinical risk markers, the ECG ruled out both HFrEF/ALVSD, HFmrEF, and HFpEF with an NPV of 96.6%. The hazard-ratio (HR) of incident CVD or death in patients with HF and a normal ECG compared with patients without HF was 1.85 [95%CI 1.01–3.39], $p = .05$, while an abnormal ECG increased the HR to 3.84 [2.33–6.33], $p < .001$. **Conclusion**. HFrEF/ALVSD and HFmrEF were rare and HFpEF was frequent in this T2D population. A normal ECG ruled out HFrEF/ALVSD and in a sub-population with 0–1 simple clinical risk markers also both HFrEF/ALVSD, HFmrEF, and HFpEF.

KEY MESSAGES

What is already known about this subject?
In early studies of unselected patients from primary care with suspected chronic heart failure, the presence of a normal ECG was found be useful to rule out heart failure with reduced ejection fraction.
What does this study add?
This study confirms that a standard electrocardiogram when normal in 722 stable outpatients with type 2 diabetes can be used to rule out HFrEF/ALVSD. Further, it adds knowledge about the risk of incident cardiovascular disease or death as a pathologic electrocardiogram increases the hazard ratio.
How might this implicate clinical practice?
With this study clinicians in secondary diabetes care clinics can use an electrocardiogram to select patients to undergo echocardiography when suspecting heart failure with reduced ejection fraction, as a normal electrocardiogram will rule out this diagnosis with a negative predictive value of >99%.

Abbreviations: ALVSD: Asymptomatic left ventricular systolic dysfunction; BMI: Body mass index; CV: Cardiovascular disease; ECG: Electrocardiographic; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mid-range ejection fraction; LVH: Left ventricular hypertrophy; NPV: Negative predictive value; NT-proBNP: NT-pro natriuretic peptide; PPV: Positive predictive value; T2D: Type 2 diabetes

Introduction

Type 2 diabetes (T2D) is the ninth major cause of death worldwide [1] and the number of patients living with T2D is expected to increase dramatically in the coming decades [2]. Heart failure (HF) in patients with T2D is receiving increasingly attention due to recent cardiovascular (CV)

outcome trials and was found to be the second most common initial manifestation of cardiovascular disease (CVD) in T2D in a cohort of 1.9 million people [3]. HF, however, can be difficult to recognise as the symptoms are non-specific [4]. This is illustrated by the fact that the presence of HF with reduced ejection fraction (HFrEF) or asymptomatic left ventricular systolic dysfunction (ALVSD), mid-range ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF) in patients with T2D is often unrecognised; though 4-28% of the patients suffer from HFrEF or HFpEF [5,6]. Early diagnosis and treatment of HF is of paramount importance; especially HFrEF/ALVSD for which there are evidence-based therapies to improve the quantity and quality of life.

Echocardiography, the gold standard in diagnosing HF is, however, expensive and time-consuming and not widely available in the diabetes clinics. On the contrary, the electrocardiogram (ECG) is an inexpensive and easily available tool, that can assist in identifying individuals with T2D at high CV risk [7]. Further, the European Society of Cardiology (ESC) recommends a resting ECG in patients with diabetes and diagnosed hypertension or with suspected CVD [8].

In early studies of unselected patients from primary care with suspected chronic HF, the presence of a normal ECG was found be useful to rule out HFrEF [9]. However, the diagnostic accuracy of HF – HFrEF/ALVSD and HFmrEF as well as HFpEF – in a contemporary T2D population is unknown. Also, the prognostic importance of HF in the absence of ECG abnormalities in patients with T2D is unknown. Thus, the aim of this study was to determine whether the ECG can be used as a diagnostic and prognostic marker for CVD events or CV death in T2D. Further, as T2D and incident CVD is closely related to the burden of prevailing other risk markers [10], we aimed to test whether including an evaluation of easy-accessible, already routinely used and simple clinical risk markers (albuminuria, hypertension, body mass index (BMI)<30, active smoking and haemoglobin A1c <48 mmol/mol) could identify subgroups of patients with increased diagnostic precision of the ECG.

Methods

All participants were recruited from the Thousand&2 Study with T2D patients followed at two secondary diabetes clinics in The Capital Region of Denmark: Steno Diabetes Center Copenhagen and the Diabetes Clinic at Herlev and Gentofte Hospital, University of Copenhagen. The study has previously been described in detail [11]. In brief, a total of 2.158 T2D patients were invited to participate whereof 1.030 accepted. At study enrolment, patients were asked to fill out a standardised questionnaire with self-reported medical history including current medication, coronary heart disease (myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting), congestive HF, atrial fibrillation, self-reported dyspnoea, and cardiovascular risk markers (prior stroke, peripheral artery disease, family history of coronary artery disease, and smoking status).

Laboratory values (cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, haemoglobin A1c, and creatinine) were obtained from the electronic health records. NT-pro brain-natriuretic peptide (NT-proBNP) was measured by use of MAGLUMI^{TM} 800 Chemiluminescence Immunoassay by Snibe Diagnostics, Shenzhen, China. Albuminuria was defined as urine albumin/creatinine ratio above 30 mg or urine albumin above 30 mg/day on at least 2 consecutive measurements. BMI was calculated from height- and weight measurements. Blood pressure was measured in supine position after 15 min rest with a validated device. Hypertension was defined as either a systolic blood pressure >140 mmHg or the ingestion of antihypertensive medication (e.g. beta blockers, calcium antagonists, angiotensin II receptor blocker, or angiotensin-converting enzyme inhibitor). These variables (haemoglobin A1c, systolic blood pressure, BMI, albuminuria, and cholesterols) are all simple clinical risk markers for the development and progression of cardiac function in patients with T2D, measured as part of routine follow-up [12].

Clinical examination

A 12-lead ECG (Cardiosoft version 6.61, GE Healthcare) was recorded at the visit and interpreted by two independent investigators (MCG and PGJ), any disagreements were resolved with discussion. A normal ECG was defined as the absence of all the following: (1) left or right bundle branch block defined as QRS-complex duration >120 ms; (2) abnormal Q-waves defined as a Q-wave duration of ≥0.02 s in V2-3 and a duration and depth of ≥0.03 s and ≥1 mm respectively in any other leads; (3) left ventricular hypertrophy (LVH) according to the Sokolow-Lyon criteria; (4) ST deviations defined as ST-depression ≥0.5 mm or inverted T-waves ≥1 mm. Echocardiographic recordings were performed and analysed by a single investigator (PGJ) in accordance with recommendations of the European Association of Echocardiography and the American Association of Echocardiography. Further details with respect to the echocardiographic recordings are published elsewhere [13]. Hence, both the ECG and echocardiography were performed on the same day. HFpEF was defined as: Patients with dyspnoea, with a NT-pro-BNP >125 pg/mL *and* either one of the following four echocardiographic criteria fulfilled: (1) increased left ventricular mass index; (2) Septal E/é >15; (3) left atrial size >34 ml/m^2; or (4) left ventricular ejection fraction ≥50%. HFrEF/ALVSD was defined as a left ventricular ejection fraction ≤40% while HFmrEF was defined as patients with dyspnoea and left ventricular ejection fraction between 41-49%. In the present study, 308 patients were excluded (more than moderate heart valve disease or previous heart valve replacement $n = 34$, missing NT-proBNP measurement $n = 74$, missing ECGs $n = 68$, missing echocardiographic measurement $n = 69$, atrial fibrillation $n = 62$, or missing follow-up data $n = 1$). Patients with atrial fibrillation (on first baseline ECG obtained in the secondary clinic) were excluded as they usually get a routine echocardiographic examination in

Denmark. Further, E/é is unusable in patients with ongoing atrial fibrillation and their NT-proBNP is usually elevated making the HF and especially the diagnosis of HFpEF difficult.

Follow-up

Follow-up was performed through national registers (National Patient Register and Cause of Death Register) and the end-point was the composite of incident CV events (defined as coronary revascularization, myocardial infarction (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)) or CV death.

Statistics

Parametric and non-parametric analyses were used to compare groups were applicable. Sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) for the diagnostic value of ECG were all calculated in different subgroups of patients with HF (either HFrEF/ALVSD alone or range of heart failure [both HFrEF/ALVSD, HFmrEF, and HFpEF]). Receiver Operating Characteristic curves were applied to determine the ability of an ECG to diagnose HF when added to a multivariable logistic regression model adjusted for age, sex, albuminuria, haemoglobin A1c, BMI, active smoking, and systolic blood pressure. Cumulative incidence curves were used to examine

the association with the composite endpoint with non-cardiovascular death as competing risk. Association with prognosis was examined using uni- and multivariable Cox proportionate hazard regression models including the before-ementioned covariates. When examining association of sub-types of heart failure with the composite endpoint, we did not perform multivariable adjustments due to the low number of patients in each group. All statistics were calculated using R for Mac, version 2.15.3 (R Project for Statistical Computing, Vienna University of Economics and Business Administration, Wien, Austria).

Approval

The study was conducted in accordance with the Helsinki Declaration and 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 to participate in the study.

Patient and public involvement

No patients were involved in the design, recruitment, or interpretation of the results in this study.

Results

We included a total of 722 patients with T2D followed at secondary care clinics. Patient characteristics and baseline values are presented in Table 1. We identified 175 patients

Table 1. Population demographics.

	Normal ECG $n = 547$	Abnormal ECG $n = 175$	p Value (normal vs abnormal ECG)
Clinical information			
Age (years)	64 [56, 69]	67 [61, 74]	**<.001**
Male sex (%)	349 (63.8)	123 (70.3)	.139
Diabetes duration (years)	12 [6, 17]	12 [5, 19]	.879
Body mass index (kg/m2)	29.1 [26.1, 33.0]	29.3 [26.7, 33.2]	.353
Systolic blood pressure (mmHg)	135 (16)	137 (18)	.100
Diastolic blood pressure (mmHg)	80 (10)	78 (11)	.065
Coronary heart disease (%)	63 (11.5)	70 (40.0)	**<.001**
Hypertension, yes (%)	480 (87.8)	165 (94.3)	**.022**
Active smoking, yes, (%)	76 (13.9)	29 (16.6)	.45
Laboratory values			
LDL-cholesterol (mmol/l)	2.0 [1.5, 2.6]	1.9 [1.6, 2.3]	.272
HDL-cholesterol (mmol/l)	1.2 [0.9, 1.5]	1.1 [0.9, 1.3]	**<.001**
Total Cholesterol (mmol/l)	4.1 [3.5, 4.8]	3.9 [3.4, 4.6]	**.038**
Albuminuria (%)	129 (24)	44 (25)	.826
Hemoglobin A_{1c} (%)	55 [48, 65]	54 [47, 67]	.515
Hemoglobin A_{1c} (mmol/mol)	7.5 (1.43)	7.4 (1.44)	.689
Creatinine (μmol/l)	77 [65, 94]	83 [67, 103]	**.02**
NT-proBNP (median [IQR])	130.2 [73.2, 305.2]	270.1 [130.7, 623.1]	**<.001**
Medications			
Metformin (%)	395 (72)	120 (69)	.406
DPP4 inhibitors (%)	56 (10)	19 (11)	.927
Sulfonylurea (%)	88 (16)	26 (15)	.788
Glucagon-like peptide 1-receptor agonist (%)	134 (25)	42 (24)	.974
Insulin (%)	267 (49)	82 (47)	.716
Beta blockers (%)	109 (20)	63 (36)	**<.001**
Angiotensin-converting enzyme inhibitors (%)	207 (38)	69 (39)	.775
Angiotensin ‖ receptor blockers (%)	210 (38)	72 (41)	.575
Calcium antagonists (%)	172 (31)	60 (34)	.543
Diuretics (%)	242 (44)	105 (60)	**.001**
Statins (%)	428 (78)	144 (82)	.298

(24%) with abnormal ECG findings (left $n = 12$ or right $n = 38$ bundle branch block, abnormal Q-waves $n = 52$, LVH $n = 7$, and ST-deviations or inverted T-waves $n = 66$). Overall, patients with abnormal ECG findings were significantly older, were more likely to have coronary heart disease and hypertension, had higher HDL-cholesterol and total cholesterol, a higher creatinine, a higher NT-proBNP, and were more often prescribed beta blockers and diuretics. Further, 18 patients (2.5%) were diagnosed with HFrEF/ALVSD, 30 (4.2%) patients were diagnosed with HFmrEF, and 57 patients (7.9%) were diagnosed with HFpEF.

Association of ECG abnormalities and heart failure in all included patients

The sensitivity, specificity, NPV and PPV of ECG abnormalities for diagnosing HF in all patients and when stratified for either dyspnoea or presence of 0-1 or ≥ 2 simple clinical risk markers is presented in Tables 2 and 3.

Of 722 included patients, 105 (15%) had either HFrEF/ALVSD, HFmrEF, or HFpEF according to the applied definitions. Of these, 50 (48% of patients with HF) had an abnormal ECG. We found that the ability of the ECG to identify HF (HFrEF/ALVSD, HFmrEF, and HFpEF combined) was only moderate with an NPV of 89.9% and a low sensitivity. For identification of HFrEF/ALVSD patients, however, the ECG could rule out this diagnosis when

normal with an NPV of 99.3%. Overall, the specificity of the ECG's ability to diagnose HF was around 80% with a low positive predictive value (PPV).

Adding ECG to a multivariate logistic regression model, in order to identify patients with HFrEF/ALVSD and HFpEF in the total population, increased the area under the curve from 0.71 to 0.75 ($p = .03$) (Figure 1).

Association of ECG abnormalities and HF in subgroups

In a subgroup of patients reporting dyspnoea ($n = 265$) the ECG had poor diagnostic value with respect to identifying HF patients (HFrEF/ALVSD, HFmrEF, and HFpEF combined). However, when a normal ECG was recorded, HFrEF/ALVSD could be ruled out with high precision (NPV and sensitivity ~100%). All the data are summarised in Table 2. In patients with 0–1 simple clinical risk markers (albuminuria, hypertension, BMI > 30, active smoking and haemoglobin A1c >48 mmol/mol) ($n = 305$) the diagnostic value of the ECG for HF (HFrEF/ALVSD, HFmrEF, and HFpEF) had an NPV of 96.6%. In these patients, with few simple clinical risk markers, a normal ECG could rule out HFrEF/ALVSD with an NPV of 99.5% and a modest sensitivity. When dealing with both HFpEF, HFmrEF, and HFrEF/ALVSD combined in patients with ≥ 2 clinical risk markers, the ECG did not prove useful to diagnose HF (see Table 3). Overall, the specificity of the ECG's ability to

Table 2. ECG as diagnostic tool for heart failure in all patients and in the subgroup of patients reporting dyspnoea.

	Heart failure		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Yes	No				
All patients (HFrEF/ALVSD alone)	$n = 18$	$n = 704$				
Normal ECG	4	543	77.8	77.1	8.0	99.3
Abnormal ECG	14	161				
All patients (Range of HF*)	$n = 105$	$n = 617$				
Normal ECG	55	492	47.6	79.7	28.6	89.9
Abnormal ECG	50	125				
Patients reporting dyspnea (HFrEF/ALVSD alone)	$n = 7$	$n = 258$				
Normal ECG	0	179	100.0	69.4	8.1	100.0
Abnormal ECG	7	79				
Patients reporting dyspnea (Range of HF*)	$n = 94$	$n = 180$				
Normal ECG	51	128	45.7	74.9	50.0	71.5
Abnormal ECG	43	43				

ECG: Electrocardiogram; HR: Hazard Ratio; HFrEF: Heart failure with reduced ejection fraction; ALVSD: asymptomatic left ventricular systolic dysfunction.
*Range of heart failure (HFrEF/ALVSD, HFmrEF, and HFpEF).

Table 3. ECG as diagnostic tool for heart failure in the subgroups of patients with 0–1 and ≥ 2 simple clinical risk markers.

	Heart failure		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Yes	No				
Patients with 0-1 simple clinical risk markers (HFrEF or ALVSD alone)	$n = 7$	$n = 264$				
Normal ECG	1	203	85.7	76.9	9.0	99.5
Abnormal ECG	6	61				
Patients with 0-1 simple clinical risk markers (Range of HF*)	$n = 25$	$n = 246$				
Normal ECG	7	197	72.0	80.1	26.9	96.6
Abnormal ECG	18	49				
Patients with ≥ 2 simple clinical risk markers (HFrEF/ALVSD alone)	$n = 11$	$n = 403$				
Normal ECG	3	312	72.7	77.4	8.1	99.0
Abnormal ECG	8	91				
Patients with ≥ 2 simple clinical risk markers (Range of HF*)	$n = 77$	$n = 337$				
Normal ECG	45	270	41.6	80.1	32.3	85.7
Abnormal ECG	32	67				

ECG: Electrocardiogram; HR: Hazard Ratio; HFrEF: Heart failure with reduced ejection fraction; ALVSD: asymptomatic left ventricular systolic dysfunction.
*Range of heart failure (HFrEF/ALVSD, HFmrEF, and HFpEF).

diagnose HF was around 80% with a low PPV. Of note, for patients with 0-1 simple clinical risk markers, the ECG increased the area under the curve from 0.70 to 0.83 ($p = .01$) (Figure 2(a)) and for patients with ≥ 2 clinical risk markers the ECG did not increase the area under the curve ($p = .23$) (Figure 2(b)).

Prognosis of patients with ECG abnormalities

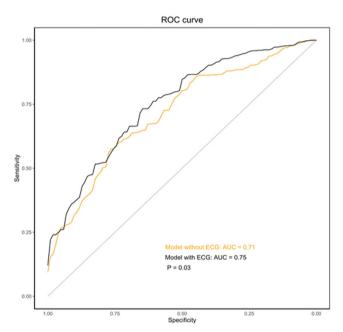During a median follow-up of 4.8 years [interquartile range: 4.1–5.3] a total of 110 (15.2%) reached the composite end-

Figure 1. Receiver operating characteristic curve comparing abnormal to normal electrocardiogram in all included patients. Area under the curve (AUC). Electrocardiogram (ECG).

point of incident CVD event or CV death. In a multivariable Cox Proportional Hazard Model, the hazard ratio (HR) of the composite end-point in patients with HF (HFrEF/ALVSD, HFmrEF or HFpEF) and a normal ECG compared to patients without HF was associated with an increased HR of 1.85 [95%CI 1.01-3.39] ($p = 0.05$). In patients with HF and an abnormal ECG the HR increased to 3.84 [2.33-6.33] ($p < 0.001$) in the multivariable analysis compared to patients without HF. When examining the association of subgroups of HF with prognosis, both patients with HFrEF/ALVSD and patients with HFmrEF had increased risk of the reaching the end-point especially when the ECG was abnormal. In patients with HFpEF, only patients with an abnormal ECG had increased risk (Table 4 and Figure 3).

Discussion

In this study, we examined the ability of the ECG to rule out HF in a contemporary cohort of patients with T2D. We found that, HFrEF/ALVSD and HFmrEF was rare and HFpEF was more common in this population. Overall, ECG abnormalities were common and a normal ECG in general could be used to rule out HFrEF/ALVSD with a fair sensitivity and a high NPV, especially in patients reporting dyspnoea. However, in a subgroup of patients with only 0–1 prevailing simple clinical risk markers, a normal ECG ruled out either HFrEF/ALVSD, HFmrEF, and HFpEF with an NPV of 96.6% (though with a low sensitivity). Overall, the specificity of the ECG in diagnosing HF was around 80% with a low PPV. Adding ECG to clinical risk markers resulted in improved diagnostic accuracy assessed by improved area under the curve. Lastly, we affirmed that patients with HF had a worse prognosis compared to
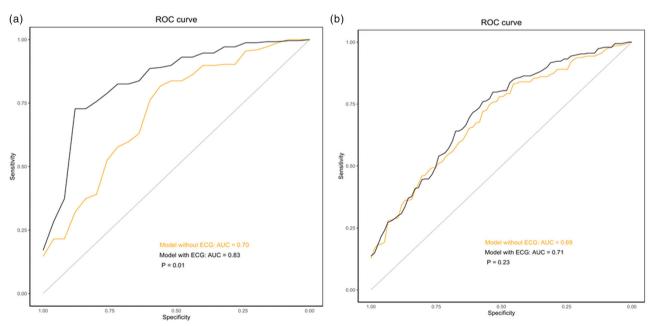

Figure 2. (a) Receiver operating characteristic curve comparing abnormal to normal electrocardiogram in patients with 0-1 simple clinical risk markers. Area under the curve (AUC). Electrocardiogram (ECG). *Adjusted for age, sex, systolic blood pressure, albuminuria, BMI, and HbA1c.* (b) Receiver operating characteristic curve comparing abnormal to normal electrocardiogram in patients with ≥ 2 simple clinical risk markers. Area under the curve (AUC). Electrocardiogram (ECG). *Adjusted for age, sex, systolic blood pressure, albuminuria, BMI, and HbA1c.*

Table 4. Cox Proportional Hazard Model for HF admission or death in patients with HF (HFrEF/ALVSD, HFmrEF, and HFpEF) and HFpEF alone according to ECG findings.

All patients with heart failure (HFrEF/ALVSD, HFmrEF, and HFpEF)	n/ no of events	Univariable		Multivariable*	
		HR (95% CI)	P-value	HR (95% CI)	P-value
No heart failure	617/73	1		1	
HF with a normal ECG	55/14	2.30 (1.30–4.08)	.004	1.85 (1.01–3.39)	05
HF with an abnormal ECG	50/23	5.18 (3.24–8.28)	<.001	3.84 (2.33–6.33)	<.001
Stratified for type of HF					
No heart failure	617/73	1		1	
HFrEF/ALVSD with a normal ECG	4/2	5.54 (1.36–22.6)	.02	–	–
HFrEF/ALVSD with an abnormal ECG	14/7	5.81 (2.67–12.6)	<.001	–	–
HFmrEF with a normal ECG	15/5	3.12 (1.26–7.72)	.01	–	–
HFmrEF with an abnormal ECG	15/10	9.79 (5.04–19.0)	<.001	–	–
HFpEF with a normal ECG	36/7	1.70 (0.78–3.69)	.18	–	–
HFpEF with an abnormal ECG	21/6	2.71 (1.18–6.24)	.02	–	–

*Adjusted for age, sex, albuminuria, haemoglobin A1c, BMI, active smoking, and systolic blood pressure. ECG: Electrocardiogram; HR: Hazard Ratio; HFrEF: Heart failure with reduced ejection fraction; ALVSD: asymptomatic left ventricular systolic dysfunction. Heart failure with preserved ejection fraction (HFpEF). Not adjusted when stratified for type of heart failure because of small number of groups and events within the groups.
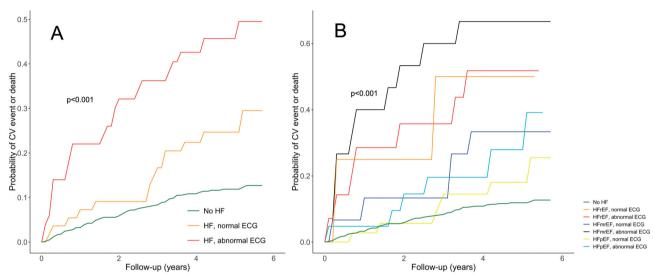

Figure 3. Cumulative incidence curves. A: Range of heart failure with and without normal ECG, B: Stratified by type of heart failure with and without a normal ECG. Cardiovascular (CV). Electrocardiogram (ECG). Heart failure (HF). Heart failure with preserved ejection fraction (HFpEF). Heart failure with mid-range ejection fraction (HFmrEF).

patients with T2D without HF – especially in the presence of an abnormal ECG.

Our findings in relation to previous studies

Our findings support a study of 534 non-diabetic patients referred by their general practitioner to echocardiography on suspicion of HF [9]. In this study, a normal ECG (defined as the absence of atrial fibrillation, signs of previous myocardial infarction, LVH, bundle branch block, or left axis deviation) was found to rule out HFrEF, as none of the 96 patients (out of the total group of 534 patients) with impaired left ventricular function had a normal ECG. Another study found that the combination of a normal ECG and no previous history of myocardial infarction was an accurate predictor for normal left ventricular function in 320 non-diabetic patients referred with suspected HFrEF [15]. Our study confirms and expands these findings regarding HFrEF/ALVSD to patients with T2D. A study from Boonman-de-Winther *et. al.* [16] concluded that a

diagnostic screening model including medical history, physical examination, ECG, and NT-proBNP were useful to preselect T2D patients for echocardiography which is in support of our findings.

We also examined the prognostic value of the ECG in both HFrEF/ALVSD and HFpEF. Not surprisingly, all patients with HF (both HFrEF/ALVSD, HFmrEF and HFpEF) had a significantly increased risk of incident CVD event or CV death compared to patients with T2D without HF. In patients with HF, the ECG was able to identify HF patients with a very high risk of future events as patients with HF *and* an abnormal ECG had an approximately 3.5-fold increased risk compared to patients without HF. The prognostic value of the ECG in patients with HF has previously been established, primarily in patients with HFrEF. Ramirez et al, identified an association of sudden cardiac death with certain types of ECG abnormalities in 650 HFrEF patients [17]. The same group also found an improvement of a prediction model for sudden cardiac death when combining ECG with standard clinical variables

in 597 HFrEF patients [18]. In the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial, which randomised 7.599 patients with symptomatic HF to receive candesartan or placebo, both bundle branch block and LVH were associated with a worse clinical outcome in patients with HFrEF [19,20]. However, in HFpEF, an ECG with bundle branch block had a more modest predictive effect while LVH in HFpEF patients was associated with CV death [19,20]. Another study with 3.425 HFpEF patients found that an ECG with QRS-duration of ≥120 ms identified subjects with a higher clinical risk of adverse outcomes [21]. A prolonged QRS-duration of ≥120 ms has been shown to be predictive of long-term-mortality in hospitalised HFpEF patients [22].

Strengths and limitations

A major strength of this study is the careful characterisation of all included patients with respect to risk markers, complete echocardiography, ECG, medical history, medical prescription list, and laboratory values. A single investigator did all echocardiographic examinations thereby limiting interobserver variation. The study is limited in that all patients were recruited from secondary care diabetes units, making the results difficult to generalise to a primary care setting. The lack of physical examination is a limitation to the study because we might potentially miss HFpEF and HfmrEF patients with signs of HF without symptoms. We believe, however, that in this population of stable outpatients, this would be a rare occurrence. Also, due to the observational nature of the study, there is an inherent risk of unmeasured confounding. Further, in our definition of an abnormal ECG, we included only the subset of abnormalities mostly associated with HF. Other abnormalities, such as prolonged PR interval or QTc prolongation were not included, which may represent a limitation in interpretation of the data. We excluded 308 patients for various reasons (dominantly missing data). It is reasonable to assume that some patients with HF were excluded thus limiting the power of our study. Lastly, only 18 of 722 patients had HfrEF/ALSVD in this population confirming that HfrEF/ALVSD is a rare complication in a general T2D outpatient setting. In general, the study findings need to be confirmed in larger cohorts of outpatients with T2D with an expected larger number of patients with HfrEF/ALVSD.

Clinical perspectives

Our data suggest that the ECG may be used routinely as a screening tool for HfrEF/ALVSD in patients with T2D in secondary care. HfrEF/ALVSD was a rare complication in this population. This high-lights a screening-based – i.e. ECG – rather than a diagnostic – i.e. referring to echocardiography – strategy to identify type 2 diabetes patients with HfrEF/ALVSD. Further, hazard ratios for the composite endpoint of HfpEF and HfmrEF was still significantly elevated why recognition of HF symptoms and/or abnormal ECG in a secondary diabetic clinic is important. Further

collaboration between cardiologist and diabetologist is vital for these patients. However, if there is suspicion of HfpEF or HfmrEF, the patient should be referred for echocardiography – especially in patients with other prevailing risk markers.

Conclusion

In conclusion, HfrEF/ALVSD and HfmrEF was uncommon and HfpEF was frequent among patients with T2D followed in a secondary care diabetes clinic. A normal ECG could safely rule out the presence of HfrEF/ALVSD in this population. In follow-up analyses, the presence of an abnormal ECG in HF increased the risk of the composite endpoint of incident CVD event and CV death.

Ethics approval and consent to participate

The study was conducted in accordance with the Helsinki Declaration and 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 to participate in the study.

Disclosure statement

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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