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PREVALENCE OF ECG ABNORMALITIES IN PEOPLE WITH TYPE 2 DIABETES: PROSPECTIVE STUDY AT TERTIARY CARE HOSPITAL FROM NORTH INDIA

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ABSTRACT

Cardiovascular disease (CVD) accounts for the majority of deaths for people with type 2 diabetes mellitus. CVD is a broad term which includes any condition causing pathological changes in blood vessels, cardiac muscle or valves and cardiac rhythm. The electrocardiogram (ECG) offers a quick, non-invasive clinical and research screen for the early detection of CVD. Resting Electrocardiogram (ECG) is recommended in all Type2- Diabetes Mellitus(Type2-DM) with hypertension or suspected cardiovascular disease (CVD). However, knowledge on the prevalence of ECG abnormalities is incomplete. In this study, we have tried to analyse the prevalence of ECG abnormalities and their cross-sectional associations with cardiovascular risk factors in people with type2 diabetes reporting in Medical OPD(MOPD) and Medical IPD(MIPD) of Dr RML Institute of Medical Sciences, Lucknow The prevalence was calculated for the total study population (n = 4034) and the subgroup of people without a history of CVD (n = 3247). Logistic regression models were used to assess cross-sectional associations. Approximately one-third of the total population had minor (16.0%) or major (13.1%) ECG abnormalities. Of the participants without a CVD history, approximately one-quarter had minor (14.9%) or major (9.1%) ECG abnormalities and for those with hypertension or very high CVD risk, the prevalence was 27.5% and 39.6%, respectively. ECG abnormalities were significantly and consistently associated with established CVD risk factors. Resting ECG abnormalities are common in all people with type 2 diabetes (29.1%) including those without a history of CVD (24.0%) and their prevalence is related to traditional cardiovascular risk factors such as older age, male sex, hypertension, lower HDL cholesterol, higher LDL cholesterol ,higher Triglyceride,higher BMI and smoking behaviour.

KEYWORDS: ECG Abnormality, Type2-Diabetes Mellitus, Cardiovascular System.

INTRODUCTION

Cardiovascular disease (CVD) accounts for the majority of deaths for people with type[2] diabetes mellitus. CVD is a broad term which includes any condition causing pathological changes in blood vessels, cardiac muscle or valves and cardiac rhythm. The electrocardiogram (ECG) offers a quick, non-invasive clinical and research screen for the early detection of CVD. Electrocardiographic changes in raw and corrected QT intervals and R wave amplitudes are early indicators of evolving CVD and increased cardiovascular risk. Prolonged QT and QTc intervals are considered reliable predictors of heart disease and fatal ventricular arrhythmias[3,4,5] A positive linear relationship exists between QTc interval prolongation and diabetic cardiac autonomic neuropathy (DAN) severity in diabetic population.[4,5,6] Heart rate variability (HRV), one indicator of DAN, decreases with diabetes which indicates increased mortality risk.[6,7,8] QT and QTc interval abnormalities reflect changes in cardiac architecture. A positive correlation between QT or QTc interval prolongation and left ventricular (LV) mass has been reported.[6,7,8] LV hypertrophy presents as exaggerated R wave amplitudes on ECG recordings. Elevated R wave amplitudes are an independent risk factor for cardiovascular events.[8,9,10] LV hypertrophy and QT interval alterations coupled with decreased cardiac function are commonly observed with diabetes related CVD.[11,12,13] Non pharmacological interventions for CVD focus primarily on lifestyle changes with physical activity as the primary focus and a risk reduction strategy. Physical activity reduces QTc interval prolongation and cardiac dysfunction in healthy subjects.[11,12] Exercise lowers heart rate and increases HRV in healthy and diseased population.[11,12,15,16] Physical activity can serve as potent prescription in the delay and attenuation of the CVD complications for persons with type 2 diabetes but additional comparative

studies are needed regarding the cardiac response to exercise under diabetic conditions at various time points of the disease.The Zucker Diabetic Fatty (ZDF) rat is a model of type 2 diabetes. The ZDF rat develops hyperglycemia and hyperlipidemia by week 8 and overt diabetes by week 12. The progression mimics the obesity-related insulin resistance and inflammation seen in humans.[15,16,17,21] The ZDF rat is commonly used to investigate prevention of diabetes; however, research related to the diabetic heart disease including ECG studies with this animal model is limited. We hypothesized that ECG changes occur in ZDF rats early in the disease process and aerobic exercise training is able to alleviate the changes. We detected changes in ECG parameters that were partially corrected by exercise training. Our findings add to the characterization of the ZDF model for studying type 2 diabetes effects on the heart and explore the benefits of an early exercise intervention in the presentation and progression of diabetes related CVD People with type 2 diabetes have a two-fold higher risk of cardiovascular disease (CVD) compared to the general population[1,2] In the general population, resting electrocardiogram (ECG) abnormalities, such as pathological Q-waves, bundle branch block, tall R wave, left ventricular hypertrophy, abnormal QRSaxis and ST/T segment abnormalities are associated with excess risk of CVD morbidity or mortality, indepen dently of known cardiovascular risk factors and the reported prevalence is normally around a few percent.[3,4] Despite its intuitive appeal, the benefit of cardiac screening using ECG has long been questioned.[5,6,11,12] Screening with an ECG must not only reliably identify unrecognized CVD or determine the risk for a future CVD event but findings must also be prevalent enough. Moreover, they must lead to clinical actions resulting in improvements in clinical outcomes that are superior to those resulting from existing preventative strategies.[7,8,9,10,19,20] Both the American Diabetes Association (ADA) and the recent joint European Society of Cardiology and European Association for the Study of Diabetes (ESC/EASD) guidelines recommend to regularly perform a resting ECG in people with type 2 diabetes and hypertension or suspected CVD without mentioning a time interval.[7,8,9,21,22] To date, several studies have reported the prevalence of ECG abnormalities in people with type 2 diabetes. However, these studies present an incomplete picture because they focused on solitary Elecrocardiographic ECG abnormality[23,24,25,26,27,28,29,30] were conducted in relatively small samples (<500 participants)[11,12,13,14,15,21,22,30] or included only people withECG Native South Asian India[32,33,34,35] Furthermore, the reported prevalence of ECG abnormalities varied greatly among these studies, ranging from a few percent up to about 40%, depending on the type of ECG abnormal ties specified and study population.

MATERIAL AND METHOD

The study included 4034 participants (93%) with an ECG were used to calculate the prevalence of ECG abnormalities and the prevalence strat ified by sex and age groups as well as to study the associations of minor and major ECG abnormalities with traditional cardiovascular risk factors. In a subgroup analysis, the 3247 study participants (80%) without a history of CVD were used to calculate the prevalence of ECG abnormal ities and the prevalence stratified by hypertension and estimated ten year fatal CVD risk categories.During the examination a standard 10 s, resting 12‑lead ECG was digitally recorded. The ECGs were subsequently evaluated and coded following the Minnesota Classification (MC) coding system by one single trained examiner out of one senior resident of Medicine under supervision of one of faculty researchers The exact criteria for Minnesota Classification codes have been elaborately described in the Minnesota code manual for electrocardiographic findings.[36] In a random sample of 60 ECGs, our ECG scoring was compared with the coding of two independent Physician This revealed a specific agreement of the different codes between 0.78 (95% CI: 0.71 to 0.84) and 0.97 (95% CI: 0.95 to 0.99). MC codes concerning a specific section or type of ECG abnormality were pooled into categories (Supplementary Table S2). Concisely, the QS pattern abnormalities category comprised all abnormal Q-waves. The QRS-axis deviation category contained leftward shift of the QRS-axis (−30° through −90°). The R-waves category encompassed exceedingly tall amplitude R-waves (i.e., Sokolow-Lyon-criterion or any of the following criteria: >26 mm in V5 or V6; >20 mm in II, III or AVF; >15 mm in I; >12 mm in aVL;). The ST-segment abnormalities category included all downward sloping or depressed ST-segments, and/or T-waves that were flat, negative, or biphasic (negative-positive type only). The atrioventricular conduction defects category encompassed prolonged PR (PQ) intervals in the limb leads (≥0.22 s). The ventricular conduction defects category comprised incomplete right bundle branch block (BBB), intraventricular conduction delay, complete right BBB and complete left BBB. The arrhythmias category consisted of atrial fibrilltaion, atrial flutter and premature atrial or ventricular contractions. Next, MC codes were classified as minor or major abnormalities in accordance with consensus between previous studies who categorised abnormalities according to perceived importance and/or severity (Supplementary Table S2). Succinctly, the minor abnormalities category included minor QS pattern abnormalities, minor ST-segment abnormalities, complete right bundle branch block, or premature atrial or ventricular contractions. The major abnormalities category included major QS pattern abnormalities, major ST-segment abnor malities, complete left bundle branch block or intraventricular block, or atrial fibrillation or flutter. When minor and major abnormalities were present simultaneously, participants were classified into the major abnormalities category.Sex, date of birth and the date of type 2 diabetes diagnosis were re corded at entry into the DCS cohort,

and age or the duration of type 2 diabetes was calculated in years since birth or diagnosis. Anthropometric variables measurements included height, weight from which Body Mass Index (BMI) was calculated. Height and weight were measured with participants bare footed and in light clothing. BMI was calculated by dividing body weight in kg by height in meters squared. Systolic and diastolic blood pressures were measured twice (3 min apart) at the upper right arm after 5 min of rest with participants in a seated position, using an automatic oscillometric digital blood pressure device . The mean of the two values was used as the result of the blood pressure reading.Overnight fasting blood and first-voided urine samples were collected following standard operating procedures. Glycated haemoglobin (HbA1c) was established using the turbidimetric inhibition immunoassay for whole haemolysed EDTA-blood and was expressed in both mmol/mol and %. Fasting blood glucose level was determined in fluorinated plasma with the UV test using hexokinase. Total cholesterol, HDL cholesterol, and triglycerides levels were measured using standard enzymatic methods. LDL cholesterol was subsequently calculated using the Friedewald formula.[37] Cholesterol ratio was determined by dividing the total cholesterol by HDL cholesterol. The creatinine concentration was de- termined enzymatically in both urine and heparinized blood. The urinary albumin concentration was measured immunoturbidimetricly. All labora- tory measurements were performed on a Cobas c501, Roche Diagnostics, Mannheim, Germany. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collabora- tion (CKD-EPI) creatinine equation.[38] The urinary albumin creatinine ratio (UACR) was calculated by dividing albumin in mg/l by creatinine in mmol/Hypertension was defined as elevated blood pressure (systolic >140 mmHg or diastolic >90 mmHg) and/or antihypertensive medication use. Dyslipidaemia included elevated LDL-cholesterol (>2.4 mmol/l) and/or lipid lowering medication use. The eGFR was categorised as: nor- mal or high (eGFR >90 ml/min), mildly decreased (eGFR 60–90 ml/min), moderately decreased (eGFR 30–60 ml/min) or severely de- creased (eGFR <30 ml/min). Albuminuria was categorised as: normal to mild (UACR <3 mg/mmol), moderate (UACR 3–30 mg/mmol) Severe (UACR >30 mg/mmol) according to KDIGO 2012 Workgroup guidelines.[39] For the subgroup of people without a history of CVD, the ten-year risk of fatal CVD was calculated and considered low to moderate (<5%), high (5–10%), or very high (>10%) according to the European Society of Cardiology's Systematic Coronary Risk Evaluation (SCORE) model from 2003 which is based on sex, age, systolic blood pressure, total cholesterol and smoking status.[40] We used the SCORE model from 2003 because there is evidence that the later Dutch recalibrated version underestimates the actual risk in the general population.[41]

For the SCORE calculation of people with hyperten- sion or dyslipidaemia, we used in-treatment levels of systolic blood pressure and total cholesterol.Medication use, educational level, smoking behaviour, and CVD events were obtained through self-report. Information on medication use was obtained by inspecting dispensing labels and included the name of the drug, prescribed quantity, dosage and the Anatomical Therapeutic Chemical classification code. The use of glucose-lowering medication was classified as: no medication, only oral medication, only insulin use, and oral and insulin use. Highest achieved education was classified as either low, middle, or high. Smoking behaviour was classified into three categories: never, a former smoker, and a current smoker. History of CVD was defined as self-reported myocardial infarc tion, angina pectoris, heart failure, stroke, cardiac arrest, or (ventricular) heart rhythm disorder. An analysis in 453 participants, verifying the self-reported CVD events against regional hospital and GP records, showed the sensitivity of self-report was 86%, and the specificity was 90%, while the positive and negative predictive values were 90% and 87%, respectively.[35]

Statistical Analyses

Differences between people with or without a recorded ECG, and be- tween people with or without ECG abnormalities were compared for demographic and clinical characteristics, using unpaired Student's t- tests, Mann-Whitney U tests or a Chi-square tests as appropriate. Be- cause the proportion of missing values for covariates did not exceed the a priority chosen limit of 5% (<0.3% for all covariates, except educa- tional level (2.2%), fasting glucose (2.4%), and urinary albumin (5.0%)), no multiple imputation was performed and instead missing values were excluded pairwise.The prevalence of minor and major ECG abnormalities, and spe- cific types of ECG abnormalities (i.e., QS pattern, QRS-axis, R-waves, ST-segment, atrioventricular conduction, ventricular conduction, and arrhythmias) was determined for the total study population and the subgroup of people without a history of CVD. Furthermore, for the total study population, the prevalence was stratified by sex and five-year age strata. In the subgroup of people without a history of CVD, the prevalence was stratified by hypertension and estimated ten-year fatal CVD risk strata. The prevalence was computed with a 95% confidence interval (CI) and was checked for trends with in- creasing age or estimated CVD risk, using linear-by-linear chi- square test.Univariable and multivariable binary logistic regression models were used to explore the association of cardiovascular risk factors with minor, major, and both minor and major ECG abnormalities, computing odds ratios (ORs) with 95% CIs. The following variables were entered into the models: age, sex, type 2 diabetes duration, educational level, smoking behaviour, BMI, HbA1c, fasting glucose, HDL cholesterol, glucose-lowering medication use, hypertension, dyslipidaemia, and categorised eGFR. The multivariable models in- cluded all variables simultaneously. The assumptions of

binary logisitic regression were checked. To compare participants with minor or major ECG abnormalities, respectively, solely to participants without any ECG abnormalities, participants with major ECG abnormalities were excluded from the control group in the minor ECG abnormalities model and vice versa.For all statistical tests significance was set at the $p < 0.05$ level (two- tailed). All statistical analyses were performed with SPSS version 24 (IBM corporation) for Windows.

RESULT

Table 1 shows the characteristics of the participants. Compared to those without ECG abnormalities, participants with ECG abnormalities were older, more often men, had longer T2D duration and a generally more unfavourable clinical profile.Approximately one-third of the study population had minor (16.0%) or major (13.1%) ECG abnormalities (Fig. 1a). Ventricular conduction defects (13.9%) and arrhythmias (11.0%) were the most common spe- cific types of ECG abnormalities in all groups (total, women and men). The prevalence was significantly higher in men compared to women for minor or major abnormalities, QS pattern, QRS-axis, atrioventricular conduction, and ventricular conduction abnormalities.Stratified by age groupsAll ECG abnormalities were more prevalent in older people (Fig. 1b). Between the groups aged below 60 and above 80, the prevalence of minor and major ECG abnormalities increased 15.6%-points and 21.3%-points, respectively. Of the specific types of ECG abnormalities, increase was most marked in the atrioventricular conduction, ventricu- lar conduction and arrhythmia categories. For all abnormalities, clear linear trends for age were detected (ptrend-values < 0.01).Prevalence for subgroup without CVDTotal subgroup, and those with or without hypertension Of the participants without a CVD history, approximately one- quarter had minor (14.9%) or major (9.1%) ECG abnormalities (Fig. 2a). Of the specific types of abnormalities, ventricular conduction de- fects and arrhythmias were the most prevalent. The prevalence was sig- nificantly higher in people with hypertension compared to people without hypertension for minor or major abnormalities, QS pattern, R- waves, ST-segment, atrioventricular or ventricular conduction abnor- malities, and arrhythmias.Stratified by estimated CVD risk groupsAll ECG abnormalities were more prevalent in people with a higher estimated risk of CVD (Fig. 2b). Between the low to moderate and very high CVD risk groups, the prevalence of minor and major ECG ab- normalities increased 13.7%-points and 9.8%-points, respectively. Of the specific types of ECG abnormalities increase was most marked in the atrioventricular conduction, ventricular conduction and arrhythmia categories, respectively. For all abnormalities, clear linear trends for CVD risk were detected (ptrend-values < 0.01).Cross-sectional associationsIn the total population, older age, male sex, smoking behaviour, higher BMI, higher HbA1c, lower fasting glucose, lower HDL cholesterol, hypertension, and moderately decreased eGFR were significantly asso- ciated with minor and/or major ECG abnormalities in the multivariable analyses (Table 2). Moreover, older age, male sex, higher BMI, lower HDL cholesterol and hypertension were consistently associated with minor and major ECG abnormalities in all multivariable analyses, inde- pendently of other traditional cardiovascular risk factors.

Table 1: Characteristics of the study population stratified by no, minor, or major ECG abnormalities.

Characteristic	Total	No ECG abnormalities	Minor ECG abnormalities	Major ECG abnormalities	No vs minor p-value	No vs major p-value
	N = 4034	N = 2862	N = 646	N = 527		
Age (years)	67.7 ± 11.0	65.8 ± 11.0	71.4 ± 9.6	73.4 ± 9.4	<0.01	<0.01
Men (%)	55.6%	52.6%	60.1%	66.4%	<0.01	<0.01
T2D duration (years)	8.7 (9.7)	8.3 (9.3)	9.7 (9.9)	9.7 (10.0)	<0.01	<0.01
T2D duration >10 years (%)	42.4%	39.8%	48.8%	48.9%	<0.01	<0.01
Educational level (%)					0.23	0.09
Low	39.6%	38.9%	40.4%	42.4%		
Middle	43.4%	44.3%	41.7%	41.0%		
High	16.9%	16.8%	17.9%	16.6%		
Smoking behaviour (%)					<0.01	<0.01
Never	31.8%	33.8%	27.2%	27.1%		
Former	53.5%	51.0%	58.2%	61.3%		
Current	14.7%	15.2%	14.6%	11.6%		
BMI (kg/m^2)	30.0 ± 5.4	30.0 ± 5.4	30.0 ± 5.4	29.7 ± 5.4	0.97	0.1
SBP (mmHg)	140.6 ± 20.9	139.1 ± 20.2	144.8 ± 22.0	143.1 ± 21.8	<0.01	<0.01
DBP (mmHg)	78.3 ± 8.5	78.6 ± 8.1	77.6 ± 9.0	77.4 ± 9.8	<0.01	<0.01
HbA1c (mmol/mol)	51.0 (14.0)	50.0 (14.0)	51.0 (15.0)	51.0 (14.0)	0.07	0.31
HbA1c (%)	6.8 (1.3)	6.8 (1.3)	6.8 (1.3)	6.8 (1.3)	0.07	0.31
Fasting glucose (mmol/l)	8.1 (2.3)	8.1 (2.3)	8.2 (2.5)	8.1 (2.2)	0.30	0.74
Total cholesterol (mmol/l)	4.3 ± 1.1	4.4 ± 1.1	4.3 ± 1.1	4.1 ± 1.0	<0.01	<0.01

LDL cholesterol (mmol/l)	2.3 ± 0.9	2.3 ± 0.9	2.2 ± 0.9	2.1 ± 0.9	<0.01	<0.01
HDL cholesterol(mmol/l)	1.3 ± 0.4	1.3 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	<0.01	<0.01
TC/HDL ratio	3.4 (1.5)	3.4 (1.5)	3.4 (1.5)	3.4 (1.6)	0.84	0.34
Triglycerides (mmol/L)	1.6 (1.0)	1.6 (1.0)	1.6 (1.0)	1.5 (1.0)	0.02	0.15
eGFR (ml/min)	74.0 ± 19.7	76.5 ± 19.3	69.7 ± 19.4	65.3 ± 19.1	<0.01	<0.01
UACR (mg/mmol)	0.7 (1.4)	0.6 (1.0)	0.9 (2.4)	1.1 (3.1)	<0.01	<0.01
Glucose-lowering medication use (%)					0.04	<0.01
No medication	22.0%	22.8%	19.7%	20.0%		
Oral only	55.7%	55.9%	56.2%	53.8%		
Insulin only	4.9%	4.6%	5.5%	5.8%		
Oral & insulin	17.5%	16.7%	18.6%	20.4%		
Antihypertensive medication (%)	70.2%	65.0%	78.5%	88.5%	<0.01	<0.01
Lipid-lowering medication (%)	66.4%	64.2%	72.7%	70.4%	<0.01	<0.01
Hypertension (%)	80.1%	75.7%	87.8%	94.2%	<0.01	<0.01
Dyslipidaemia (%)	90.1%	89.7%	91.1%	90.8%	0.14	0.30
eGFR categories (%)					<0.01	<0.01
Normal or high (>90)	21.4%	25.2%	14.7%	9.0%		
Mildly decreased (60–90)	54.8%	55.2%	55.6%	51.7%		
Moderately decreased (30–60)	22.1%	18.4%	26.7%	36.6%		
Severely decreased (<30)	1.6%	1.1%	3.0%	2.7%		
Albuminuria (%)					<0.01	<0.01
Normal to mild (UACR <3)	81.6%	85.1%	75.1%	71.0%		
Moderate (UACR 3–30)	15.4%	12.8%	20.7%	23.3%		
Severe (UACR >30)	2.9%	2.1%	4.2%	5.8%		
History of CVD (%)	19.5%	13.8%	25.2%	43.7%	<0.01	<0.01

Data are presented as mean ± SD, median (IQR), or proportion (%).

T2D, type 2 diabetes; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, haemoglobin A1c; LDL, low density lipoprotein; HDL, high density lipo- protein; TC, total cholesterol; eGFR, estimated glomerular filtration rate; UACR, urinary albumin creatinine ratio; CVD, Cardiovascular disease.

In 354 participants, minor and major abnormalities were present simultaneously, these participants were classified into the major category.

DISCUSSION

The scarce previous studies in people with type 2 diabetes reported a prevalence of minor or major ECG abnormalities ranging from 12.5% to 37.0%, and from 7.5% to 23%, respectively.32,34 However, these results were observed in populations of people with Native American or Afro- American ancestry that may not be applicable to our study population of people with South Asian Indian. In a sample (n = 100) from a perhaps more comparable population of Indian people with type 2 diabe- tes without symptomatic CVD, 26.0% had any ECG abnormality.29 In an- other small sample (n = 221) of Spanish people with type 2 diabetes without known CVD, 24.9% had any ECG abnormality based on the MC.16 These percentages are equivalent to the 24.0% of minor and major ECG abnormalities we observed in people with type 2 diabetes without a CVD history.Moreover, a small study from Sub-Sahara Africa compared vari- ous specific types of ECG abnormalities in people with type 2 diabe- tes and also found conduction defects (11.9%) and arrhythmias (16.2%) to be among the most common.31 The higher prevalence ofventricular conduction defects and arrhythmias in people with type 2 diabetes might be related to unrecognized ischemic heart disease and/or contractile dysfunction as a result of impaired Ca2+ handling induced by type 2 diabetes, a proposed mechanism of diabetic cardiomyopathy42,43 The higher prevalence of ECG abnormalities in men and with higher age was previously also shown in the general population.4 In addition to age and sex, we found that unfavourable HbA1c, BMI or HDL cholesterol, smoking behaviour, and hypertension were also associated with com- bined minor and major ECG abnormalities in multivariable-adjusted analyses. Furthermore, in those without a history of CVD, hypertension and (very) high estimated CVD risk was associated with a higher prev- alence of all ECG abnormalities.A potential limitation of this study is that a sole examiner did the coding of ECGs. Nonetheless, the coding is validated by the excellent specific agreement with the judgements of two independent cardiolo- gists, which we reported in paragraph 2.3: ‘ECG abnormalities’. Therefore, we do not expect this to influence the results of this study. A second limitation is the exclusion of people without a recorded ECG.

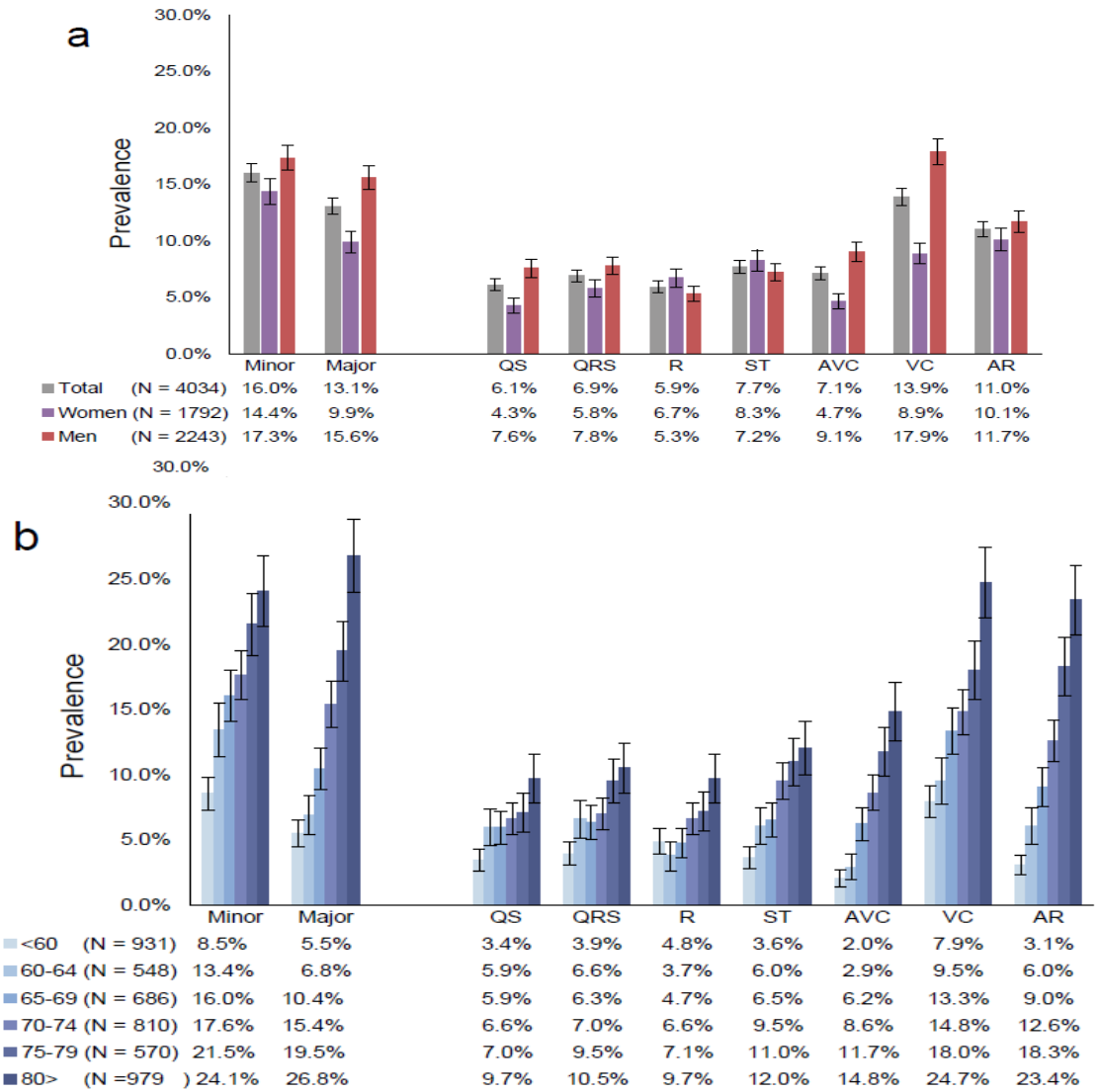

Fig. 1: Prevalence with 95% CI of ECG abnormalities in 2018 for total study population. Panel a: total, women, and men; Panel b: stratified by five-year age groups. QS, QS pattern; QRS, QRS- axis; R, R-waves; ST, ST-segment; AVC, Atrioventricular conduction; VC, Ventricular conduction; AR, Arrhythmias.

Still, comparison of the characteristics with the included people re- vealed that these people had a more unfavourable clinical profile. Therefore, we expect analyses without this selection bias would have observed even higher prevalence percentages and ORs. A third potential limitation is the SCORE from 2003, since it has been suggested this model underestimates CVD risk in people with type 2 diabetes because diabetes status is not included as a parameter. However, evidence sug- gests the Dutch re-calibrated SCORE version would exacerbate this un- derestimation of CVD risk.41 Additionally, the generalisability to other populations is better for the SCORE from 2003. Therefore, we feel that the SCORE model from 2003 was probably the best option. A fourth po- tential limitation is the application of the SCORE model to people older than 65 years, and the use of in-treatment levels of systolic blood pres- sure and total cholesterol in the SCORE calculation of people with hy- pertension or dyslipidaemia. Nevertheless, in clinical practice and research this is often done to assess the (potential) CVD risk reduction due to treatment effects (pre-post comparison) or to estimate the actual risk of people in treatment. A fifth limitation is the mainly European an- cestry of the study population, which limits the applicability of our re- sults to people with different ancestry. A fifth limitation is the cross-sectional study design which prohibits any inference on causal or tem- poral relationships of ECG abnormalities with CVD. Our study has several strengths. First, to our knowledge, it provides the most thorough description of the prevalence of ECG abnormalities in people with type 2 diabetes because it reports on various ECG abnor- malities in an unselected and large population with comprehensive mea- surements. Second, it studies the subgroup of people with type2 diabetes without a CVD history that is the usual target group for CVD screening with ECG. Third, it considers diverse aspects of ECG abnormality preva- lence such as differences across sex, age, hypertension or estimated CVD risk groups, and cross-sectional associations with established cardiovas-

cular risk factors.Because minor and major ECG abnormalities are relatively common in people with type 2 diabetes, they can potentially be useful in CVD risk screening in people with type 2 diabetes. However, this is only the case if ECG abnormalities are associated with incident CVD events indepen- dently of traditional cardiovascular risk factors. If so, ECG abnormalities should also prove to have added prognostic value for CVD morbidity or mortality beyond traditional cardiovascular risk predictors. Future stud- ies should investigate the association of ECG abnormalities with CVD.

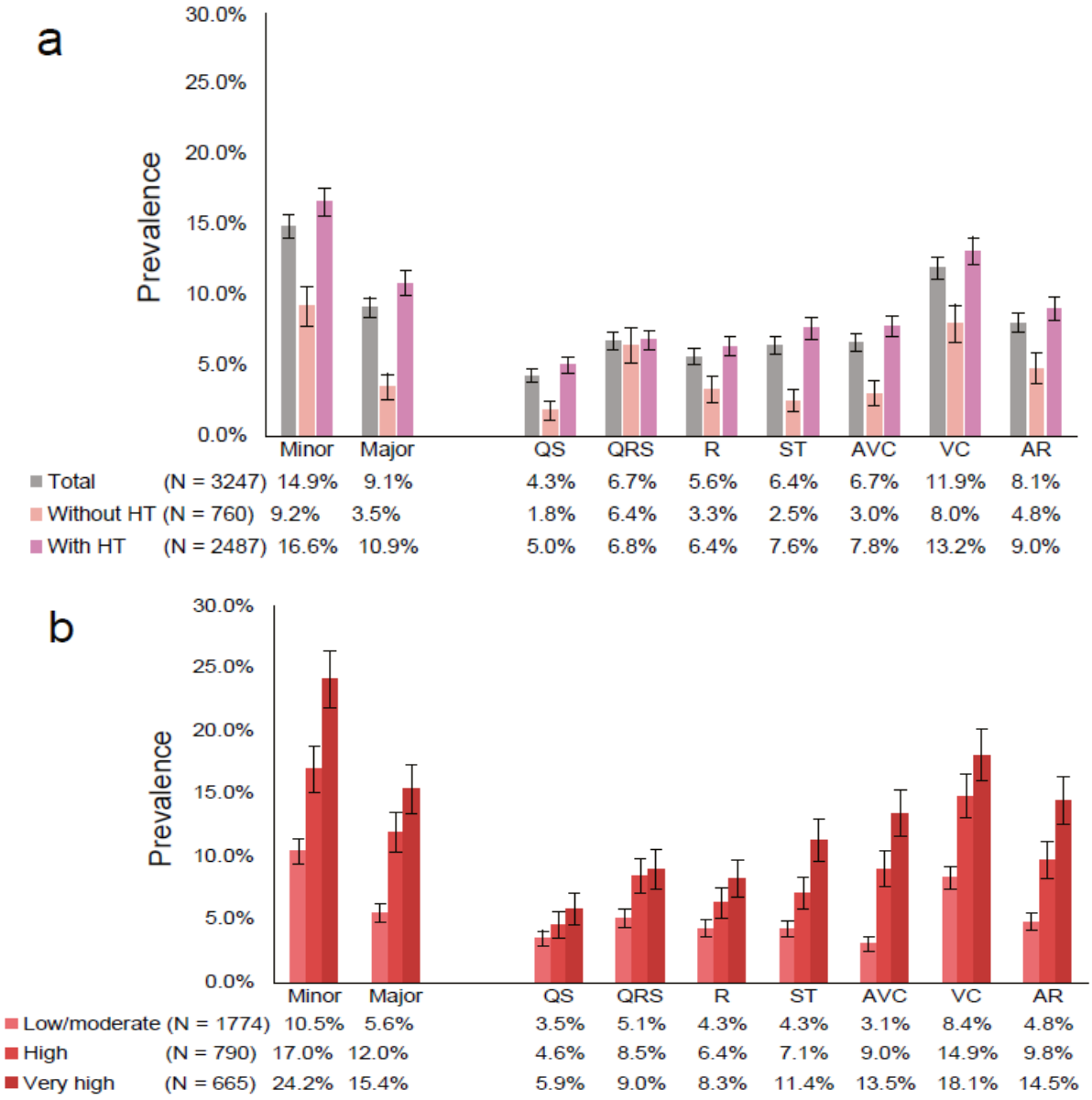

Fig. 2: Prevalence with 95% CI of ECG abnormalities in 2018 for subgroup without a history of CVD. Panel a: total, people without hypertension (HT), and people with hypertension (HT); Panel b: stratified by ten-year fatal CVD risk estimated with the SCORE modela (low/moderate: <5%, high: 5–10%, very high: >10%). QS, QS pattern; QRS, QRS-axis; R, R-waves; ST, ST- segment; AVC, Atrioventricular conduction; VC, Ventricular conduction; AR, Arrhythmias. a Note that for the SCORE calculation of people with hypertension or dyslipidaemia in- treatment levels of systolic blood pressure and total cholesterol were used.

morbidity or mortality in people with type 2 diabetes, and to what ex- tent they can improve existing CVD prediction models for people with type 2 diabetes. Because the findings presented in this study do not an- swer these questions, they do not support or disprove the recommenda- tions in the ADA, and the new ESC/EASD diabetes guidelines to screen people with type 2 diabetes and hypertension or suspected CVD using resting ECG. The ADA and ESC/EASD diabetes guidelines are only based on by expert opinion level evidence. Therefore, they need to be further substantiated, preferably with evidence from extensive longitu- dinal studies in people

with type 2 diabetes representative of type 2 di- abetes healthcare populations. Interestingly, the prevalence of minor or major ECG abnormalities in people with type 2 diabetes is similar to other populations with an elevated risk of CVD for which added value of ECG abnormalities in screening has been reported: people with hypertension,44,45 and older people.[17]

Table 2: The cross-sectional associations of CVD risk factors with minor, major and both combined ECG abnormalities in people with type 2 diabetes.

Risk factor abnormality	OR of minor abnormality		OR of major abnormality		OR of minor or major	
	N = 3508		N = 3388		N = 4034	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Age (year)	1.05 (1.05–1.06)□ □	1.06 (1.05–1.07)□ □	1.08 (1.07–1.09)□ □	1.07 (1.06–1.08)□ □	1.06 (1.06–1.07)□ □	1.06 (1.06–1.07)□ □
Men	1.36 (1.20–1.54)□ □	1.38 (1.19–1.60)□ □	1.78 (1.55–2.04)□ □	2.01 (1.70–2.38)□ □	1.53 (1.39–1.69)□ □	1.62 (1.44–1.83)□ □
T2D duration (years)	1.03 (1.02–1.04)□ □	1.00 (0.99–1.01)	1.03 (1.02–1.04)□ □	0.99 (0.98–1.01)	1.03 (1.02–1.04)□ □	1.00 (0.99–1.01)
Educational level						
Low	Reference	Reference	Reference	Reference	Reference	Reference
Middle	0.91 (0.79–1.04)	1.06 (0.92–1.22)	0.85 (0.73–0.98)□	1.00 (0.85–1.17)	0.88 (0.79–0.98)□	1.04 (0.92–1.17)
High	1.03 (0.87–1.23)	1.21 (1.00–1.46)	0.91 (0.75–1.10)	1.08 (0.87–1.34)	0.97 (0.85–1.12)	1.15 (0.98–1.34)
Smoking behaviour						
Never	Reference	Reference	Reference	Reference	Reference	Reference
Former	1.42 (1.23–1.63)□ □	1.21 (1.04–1.41)□	1.50 (1.29–1.74)□ □	1.13 (0.95–1.33)	1.45 (1.30–1.62)□ □	1.17 (1.04–1.33)□ □
Current	1.19 (0.98–1.45)	1.48 (1.19–1.83)□ □	0.95 (0.76–1.19)	1.22 (0.94–1.57)	1.08 (0.93–1.27)	1.35 (1.13–1.62)□ □
BMI (kg/m^2)	1.00 (1.00–1.01)	1.02 (1.01–1.04)□ □	0.97 (0.98–1.00)	1.02 (1.01–1.04)□	1.00 (0.99–1.00)	1.02 (1.01–1.03)□ □
HbA1c (mmol/mol)[a]	1.00 (1.00–1.01)	1.01 (1.00–1.01)	1.00 (1.00–1.01)	1.01 (1.00–1.02)□	1.00 (1.00–1.01)	1.01 (1.00–1.01)□
HbA1c (%)[a]	1.03 (0.98–1.08)	1.07 (0.99–1.17)	1.02 (0.96–1.07)	1.10 (1.01–1.21)□	1.02 (0.98–1.07)	1.09 (1.02–1.16)□
Fasting glucose (mmol/l)	1.01 (0.99–1.04)	0.99 (0.96–1.03)	0.97 (0.95–1.01)	0.95 (0.91–1.00)□	1.00 (0.98–1.02)	0.98 (0.95–1.01)
HDL cholesterol(mmol/l)	0.79 (0.67–0.93)□ □	0.80 (0.66–0.98)□	0.67 (0.56–0.81)□ □	0.76 (0.61–0.94)□	0.74 (0.65–0.84)□ □	0.79 (0.67–0.92)□ □
Glucose-lowering medication use						
No medication	Reference	Reference	Reference	Reference	Reference	Reference
Oral only	1.16 (0.99–1.36)	1.13 (0.95–1.34)	1.09 (0.92–1.30)	1.10 (0.91–1.34)	1.13 (1.00–1.28)	1.12 (0.97–1.30)
Insulin only	1.38 (1.03–1.86)□	1.00 (0.70–1.42)	1.44 (1.05–1.96)□	1.19 (0.81–1.76)	1.41 (1.11–1.78)□ □	1.09 (0.82–1.46)
Oral & insulin	1.29 (1.06–1.57)□	1.11 (0.86–1.42)	1.40 (1.13–1.72)□ □	1.24 (0.94–1.64)	1.34 (1.15–1.56)□ □	1.17 (0.95–1.43)
Hypertension (yes)	2.32 (1.94–2.77)□ □	1.58 (1.30–1.93)□ □	5.22 (4.00–6.80)□ □	2.92 (2.20–3.89)□ □	3.13 (2.69–3.64)□ □	1.99 (1.68–2.36)□ □
Dyslipidaemia (yes)	1.17 (0.95–1.44)	0.96 (0.76–1.20)	1.13 (0.90–1.41)	0.89 (0.69–1.15)	1.15 (0.98–1.36)	0.94 (0.78–1.13)
eGFR categories						
Normal or high (>90)	Reference	Reference	Reference	Reference	Reference	Reference
Mildly decreased (60–90)	1.73 (1.45–2.05)□ □	0.95 (0.78–1.17)	2.61 (2.08–3.28)□ □	1.18 (0.91–1.53)	2.02 (1.75–2.33)□ □	1.02 (0.86–1.21)
Moderately decreased (30–60)	2.49 (2.05–3.02)□ □	0.94 (0.74–1.20)	5.53 (4.36–7.02)□ □	1.56 (1.16–2.09)□ □	3.51 (2.99–4.11)□ □	1.16 (0.95–1.42)
Severely decreased (<30)	4.57 (2.99–6.99)□ □	1.46 (0.90–2.35)	6.53 (4.00–10.64)□ □	1.45 (0.84–2.52)	5.22 (3.63–7.52)□ □	1.45 (0.96–2.18)

Data are presented as odds ratios (OR) (95%CI). The multivariable models included all variables simultaneously.
T2D, type 2 diabetes; BMI, body mass index; HbA1c, haemoglobin A1c; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate.
a Note that HbA1c is shown in both mmol/mol and % for convenience and HbA1c was not doubly entered into the multivariable models.
□ Significant at the $p < 0.05$ level.
□ □ Significant at the $p < 0.01$ level.

Abbreviations: ADA, American Diabetes Association; BBB, bundle branch block; BMI, Body Mass Index; CVD, cardiovascular disease; DCS, Diabetes Care System; EASD, European Association for the Study of Diabetes; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; GP, general practitioner; GCP, Good Clinical Practice; MC, Minnesota Classification; SCORE, Systematic Coronary Risk Evaluation; T2D, type 2 diabetes; UACR, urinary albumin creatinine ratio.

CONCLUSION

Resting ECG abnormalities are common in all people with type 2 di abetes (29.1%), including those without a history of CVD (24.0%), and their prevalence is related to traditional cardiovascular risk factors such as older age, male sex, hypertension, lower HDL cholesterol, higher BMI, and smoking behaviour. In line with the ADA and ESC/EASD guide- lines resting ECG abnormalities might be a useful tool for CVD screening people with type 2 diabetes.

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