International Journal of Cardiology 295 (2019) 36–41

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Incidental abnormal ECG findings and long-term cardiovascular morbidity and all-cause mortality: A population based prospective study

Adam Goldman [a,1], Hanoch Hod [b,1], Angela Chetrit [c,1], Rachel Dankner [a,c,*,1]

[a] Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler School of Medicine, Tel Aviv University, Israel
[b] Leviev Heart Center, Sheba Medical Center, Ramat Gan, Israel
[c] Unit for Cardiovascular Epidemiology, the Gertner Institute for Epidemiology and Health Policy Research, Ramat Gan, Israel

ARTICLE INFO

Article history:
Received 4 May 2019
Received in revised form 31 July 2019
Accepted 5 August 2019
Available online 7 August 2019

Keywords:
Electrocardiogram (ECG)
Cardiovascular diseases
Cumulative incidence
Risk prediction
Survival analysis
Screening test

ABSTRACT

Background: The additional prognostic value of resting electrocardiogram (ECG) in long-term cardiovascular disease (CVD)-risk-assessment is unclear. We evaluated the association of incidental abnormal ECG findings with long-term CVD-risk and all-cause mortality, and assessed the additional prognostic value of ECG as a screening tool in adults without known CVD.

Methods: A cohort of 2601 Israeli men and women without known CVD were actively followed from 1976 to 1982 for 23-year cumulative CVD-incidence, and until May 2017 for all-cause mortality. At baseline and follow-up, participants underwent interviews, physical examinations, blood tests and ECG.

Results: At baseline, 1199 (46.1%) had incidental abnormal ECG findings (exposed-group). CVD cumulative incidence reached 31.6% among the 930 survivors who participated in the active follow-up (294/930). During a 31-year median follow-up, 1719 (66.1%) of the total cohort died. Incidental abnormal ECG findings were associated with 46% greater CVD-risk (odds ratio = 1.46, 95%CI = 1.09–1.97). The net reclassification improvement (NRI) of CVD-risk was 7.4% (95%CI_{NRI} = 1.5%–13.3%, $p = 0.01$) following the addition of ECG findings, but the C-index improvement was not statistically significant [C-index = 0.656 (0.619–0.694) vs. C-index = 0.666 (0.629–0.703), $p = 0.14$]. Multivariable Cox regression demonstrated an all-cause mortality hazard ratio (HR) of 1.18 (95%CI = 1.07–1.30) for exposed vs. unexposed individuals. Non-specific T-wave changes and left-axis deviation are the incidental ECG abnormalities that were associated with all-cause mortality [HR = 1.18 (95%CI = 1.05–1.33) and HR = 1.19 (95%CI = 1.00–1.42), respectively].

Conclusion: Incidental abnormal ECG findings, mainly non-specific T-wave changes and left-axis deviation, were associated with increased long-term CVD-risk and all-cause mortality among individuals without known CVD, and demonstrated net reclassification improvement for CVD-risk.

1. Background

Cardiovascular disease (CVD) is the leading cause of death globally, accounting for 23.4% of all deaths in the US in 2015 [1]. In Europe, it is the leading cause of death among older adults [2]. Annual costs of CVD in the US and the European-Union were estimated at $316.6 and $210 billion, respectively, which is more than every other group of diseases [3].

The Framingham study (1998) introduced the primary coronary heart disease risk calculator in the US, based on CVD risk factors: age, gender, total and HDL cholesterol, systolic blood pressure, diabetes mellitus and current smoking [4]. Several CVD risk prediction calculators have since been proposed, among them the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, which have been the recommended risk score in the US since 2013 [5], and SCORE CVD risk calculator, which is recommended by the European Society of Cardiology [6].

Data are limited regarding the additional value, beyond the traditional CVD risk factors, of the resting electrocardiogram (ECG) in the risk stratification of healthy individuals. The U.S Preventive Services Task Forces (USPSTF) does not recommend routine resting or exercise ECG tests in healthy individuals [7]. The ACC foundation/AHA guideline states that resting ECG "may be considered" in asymptomatic adults (class 2b) and is "reasonable" in asymptomatic adults with hypertension or diabetes (class 2a) [5]. However, ECG tests are often used in varied medical surveys, such as executives' surveys and athletes' physical examinations [8]. Furthermore, several studies have shown associations of ECG abnormalities, such as nonspecific ST-segment and T-wave

* Corresponding author at: Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.
E-mail address: racheld@gertner.health.gov.il (R. Dankner).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2019.08.015
0167-5273/

changes and ischemic findings, with increased risk for CVD morbidity and mortality [9,10]. T-wave inversion, increased duration of QRS complex, and QRS/T angle, in resting ECGs were also found to be predictors of sudden cardiac death in a large cohort of men [11,12].

In a previous study, we examined the value of specific ECG abnormalities (intraventricular conduction delay) in the prediction of all-cause mortality [13]. In the current study, we aimed to assess whether an incidental abnormal ECG finding of any kind in an adult population without known CVD is associated with a long-term increased risk of CVD and all-cause mortality, and to evaluate the additional prognostic value of ECG as a screening test.

2. Materials and methods

2.1. Study design and population

A subsample of 2769 men and women (Supplementary Fig. 1– study flowchart) from the Israel Study of Glucose Intolerance, Obesity and Hypertension (GOH) were included in the current follow-up study. The subsample was representative of the original cohort, which was randomly selected during 1967 from the Israel population registry, stratified according to sex, birth decade and ethnic origin (Supplementary 1- study methods) [14]. During 1976–1982 ("Phase-2"), participants underwent medical interviews, physical examinations, weight and height measurements, blood pressure measurements, blood testing for fasting glucose, lipid profile and creatinine, and resting ECG recording, at regional medical centers. For the current analysis, 166 individuals were excluded due to known CVD at baseline, defined as self-reported past myocardial infarction (MI), cerebrovascular accident or "other cardiovascular disease"; or phase-2 ECG findings of past MI or an implanted pacemaker. Two additional individuals were excluded due to missing vital state information. During 1999–2008, 930 survivors of the final study cohort underwent repeated interviews, and repeated measurements and testing as in phase-2, and were included in the current CVD outcome study ([15], Table 1- participants Baseline characteristics). The exposure variable of interest was incidental abnormal ECG findings at baseline, as defined in Supplementary 1, followed by sub-analysis of specific ECG abnormalities. All ECGs were interpreted and manually coded by a single cardiologist according to the Minnesota coding system [16], baseline ECG findings frequencies are detailed in ([15], Table 2). Further details about the GOH study methodology are described elsewhere [14].

Informed consent was obtained from each participant and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Sheba Medical Center's human research committee.

2.2. Endpoints and covariates

The two study outcomes were CVD cumulative incidence and all-cause mortality. CVD incidence was determined according to self-reported past myocardial infarction (MI), cerebrovascular accident, PAD or "other cardiovascular disease" or phase 3 ECG findings of "past MI" or "evidence of myocardial ischemia" (Supplementary 1). All-cause mortality and date of death were recorded by linkage of the study data-file with the Israeli population registry through May 2017.

2.3. Statistical methods

Student *t*-test and the chi-square test, with two-sided *p*-values (p) set at 0.05 level of significance were used for univariate analyses.

A multivariable analysis for cumulative CVD incidence was conducted by a logistic regression model; the duration of the follow-up period was from the baseline examination (1976–1982) to the follow-up examinations (1999–2008). The analysis was adjusted for age, sex, ethnicity, smoking habits, BMI, blood pressure, plasma lipids and creatinine, and diabetes co-morbidity (Supplementary 1), according to the Framingham Risk Score Calculator [4] and the Euro SCORE [6].

Sex specific survival curves according to the exposure were compared by the log-rank test. A multivariable Cox proportional hazard model analysis evaluated the association between the exposure and all-cause mortality. The examination date was the starting point of the follow-up period, and the endpoint was the date of death or censoring in May 2017. Furthermore, we assessed the specific ECG pathologies that were significantly associated with all-cause mortality, by a multivariable analysis that adjusted for the same covariates. The assumption of proportional hazards and the presence of effect modifiers were tested in each Cox model.

Evaluation of 23- year CVD risk and 31-year all-cause mortality was conducted by the multivariable logistic regression and Cox proportional hazard models, respectively, adjusted for the traditional CVD risk factors (age, sex, ethnicity, smoking habits, BMI, blood pressure and diabetes). To assess the performance of the prediction models, we evaluated the improvement in C-index and net reclassification following the addition of incidental ECG findings ([15], statistical methods). The discrimination measure, C-index, was calculated by the area under the receiver operating characteristic curve (AUC) for CVD incidence and by Harrel's C-index adaption for all-cause mortality [17]. Net reclassification improvement (NRI) was calculated as described by Pencina et al. [18]. For this purpose, we defined cutoffs for the likelihood to reach the outcome of interest, by adjusting the ACC/AHA risk calculator [5] categories (low, intermediate and high risk) thresholds to the increased duration of follow-up, from 10% and 20% to 20% and 30%, similar to the Framingham study extension method [19]. We estimated improvement in reclassification also by continuous NRI measure and by the integrated discrimination index (IDI), which are not affected by the chosen cutoff values.

Statistical analysis was performed with SPSS version 25.0 and R version 3.5.0.

3. Results

3.1. Baseline characteristics

The mean baseline age was 54.5 ± 8.0 years, 52% were women, and 1199 (46.1%) were found to have incidental abnormal ECG findings ([15], Table 3). Sex and ethnic origin distributions, smoking habits, diabetes frequencies, and serum creatinine mean values were similar between individuals with incidental abnormal ECG findings and those with completely normal ECG results (Table 1). Mean age, blood pressure, total cholesterol and BMI were significantly lower in individuals with normal ECG results.

3.2. All-cause mortality

During a median follow-up of 31.0 years, 71,885 person-years were accrued, and 1719 (66.1%) of the cohort members died. Kaplan-Meier survival curves based on the log-rank test revealed shorter time to death for the incidental abnormal ECG findings group ($p < 0.001$), and stratification by sex retained this finding (Fig. 1). The all-cause mortality rate in the unexposed group, i.e. with normal ECG results at baseline, was 19.4 per 1000 person-years, compared to 30.1 per 1000 person-years among those with an incidental abnormal ECG finding.

Univariable analysis (Table 2) showed increased risk for all-cause mortality, HR = 1.70 (95%CI, 1.55–1.87), among individuals with ECG abnormalities at baseline. Multivariable analysis, adjusted for the CVD risk factors: age, sex, origin, BMI, blood pressure (systolic and diastolic), smoking status, diabetes, creatinine and total cholesterol, revealed HR = 1.22 (95%CI, 1.06–1.44) for individuals with incidental abnormal ECG findings vs. individuals with completely normal ECGs (Table 2- model 1). A model that was not adjusted for serum creatinine and total cholesterol (Table 2, model 2) showed an 18% greater risk for earlier death: HR = 1.18 (95%CI, 1.07–1.30). After excluding the presence of diabetes, due to lack of statistical significance ($p > 0.05$), the final model showed similar results (Table 2, model 3). No interactions (effect modifications) were found between ECG test results and sex on associations with both outcomes.

Based on the final multivariable model (model 3), we assessed the specific ECG abnormalities that were associated with all-cause mortality. This was done by replacing the exposure variable, i.e. any ECG abnormality, with each of the most common specific pathologies in the cohort (Fig. 2). Non-specific T-wave changes (NST) were found to be significantly associated with the risk of mortality, HR = 1.18 (95%CI, 1.05–1.33, $p = 0.01$), as well as the association of left-axis deviation with mortality, HR = 1.19 (95%CI, 1.00–1.42, $p = 0.05$).

3.3. Cardiovascular disease

Of the 930 survivors who participated in the active follow-up, 294 (31.6%) developed CVD during a median follow-up of 23.0 years. Baseline incidental abnormal ECG findings were also found to be associated with the risk of CVD, after adjustment for CVD risk factors (detailed under Table 2). The multivariable models of CVD outcome revealed an odds ratio (OR) =1.47 (95%CI, 1.09–1.97) for individuals with any incidental abnormal ECG finding (Table 2 - model 3).

3.4. Prediction of cardiovascular disease and all-cause mortality

The addition of ECG findings to a 23-year CVD risk prediction model with traditional CVD risk factors (model 2) correctly reclassified 7.4% of

Table 1
Baseline (Phase 2) characteristics of 2601 Israeli individuals according to incidental ECG findings.

	Abnormal ECG N (%)	Normal ECG N (%)	P-value
Sex			
Male	598 (49.9)	669 (47.7)	0.3
Female	601 (50.1)	733 (52.3)	
Age (years)			
Mean (±SD)	54.6 ± 7.9	50.8 ± 7.8	<0.001
Origin			
Yemen	302 (25.2)	346 (24.7)	0.8
Middle-East/Asia	303 (25.3)	349 (24.9)	
North Africa	249 (20.8)	279 (19.9)	
Europe/America	345 (28.8)	428 (30.5)	
Blood pressure (mmHg			
Systolic (mean ± SD)	137.6 ± 23.6	128.7 ± 19.6	< 0.001
Diastolic (mean ± SD)	85.9 ± 12.3	83.2 ± 10.6	< 0.001
Normal	268 (22.7)	460 (33.2)	
Pre-hypertension	378 (32.0)	502 (36.3)	0.01
Hypertension	535 (45.3)	422 (30.5)	< 0.001
BMI (Kg/M^2)			
Mean (±SD)	26.5 ± 4.4	25.9 ± 4.1	< 0.001
Normal	605 (51.1)	482 (34.8)	
Overweight	432 (36.5)	628 (45.3)	< 0.001
Obese	146 (12.3)	275 (19.9)	< 0.001
Total cholesterol (mg/dL)			
Mean (±SD)	223.1 ± 54.3	216.7 ± 53.6	0.01
Normal	315 (37.0)	382 (41.6)	
Borderline	230 (27.0)	216 (23.5)	0.04
High risk	307 (36.0)	320 (34.9)	0.2
Creatinine (mg/dL)			
Men (Mean ± SD)	0.97 ± 0.3	0.97 ± 0.2	0.9
Women (Mean ± SD)	0.95 ± 0.2	0.97 ± 0.4	0.5
Smoking			
Never	404 (33.8)	456 (32.5)	0.5
Former smoker	70 (5.8)	96 (6.8)	
Current smoker	723 (60.4)	850 (60.6)	
Diabetes			
Normoglycemia	453 (37.8)	480 (34.2)	0.3
Pre-diabetes	580 (48.4)	714 (50.9)	
Diabetes	159 (13.3)	202 (14.4)	

Blood pressure classification: Normal- systolic BP ≤ 120 or diastolic BP ≤ 80; Prehypertension- 140 > systolic BP ≥ 120 or 90 > diastolic BP ≥ 80; Hypertension – systolic BP ≥ 140 or diastolic BP ≥ 90.
Total cholesterol classification: Normal- Total cholesterol < 200; Borderline- 200 ≤ Total cholesterol < 240; High risk ≥ 240
BMI classification: Normal- BMI < 25; Overweight- 25 ≤ BMI < 30; Obese- BMI ≥ 30.
Categorical variables were examined for differences between overall categories by the Chi-square test, with further testing for differences in each category only for statistically significantly different variables.

individuals (NRI 95%CI, 1.5–13.3%, $p = 0.01$), according to the chosen cutoff values (NRI table is provided in ([15], Table 5)). The prediction of CVD probability was correctly revised for 25.8% of the individuals by the extended model (Continuous NRI 95%CI, 12.0–39.5%, $p < 0.001$), and the IDI was 0.63% (95%CI, 0.08%- 1.17%, $p = 0.02$). The addition of ECG findings to the 31-year all-cause mortality prediction model did not result in a significant improvement of reclassification ($p = 0.52$), while continuous NRI and IDI values were significant – 41.0% (95%CI, 33.1%- 48.9%) and 0.21% (95%CI, 0.04%- 0.39%), respectively. CVD prediction model, including the traditional risk factors, demonstrated C-index of 0.656 (95%CI, 0.619–0.694) which was not improved significantly by the addition of ECG incidental findings (C-index = 0.666 (95%CI 0.629–0.703), $p = 0.14$); ROC curves are provided in [15], Fig. 1. Likewise, all-cause mortality prediction model C-index was not improved significantly following the addition of ECG incidental findings (0.752 (95% CI, 0.751–0.753) vs. 0.753 (95%CI, 0.752–0.754)). The CVD risk prediction model was well calibrated, as measured by the Hosmer-Lemeshow test ($p = 0.51$), as was the all-cause mortality prediction model, as shown by the calibration curve ([15], Fig. 2).

4. Discussion

Our results demonstrate that incidental abnormal ECG findings, in adults randomly selected from a population without known preexisting CVD, are associated with an increased risk of CVD, during a median follow-up of 23-years, and overall mortality during a median of 31-years. Moreover, incidental abnormal ECG findings conferred increased risk of CVD and all-cause mortality beyond any other CVD risk factor. We found ECG incidental abnormal findings at baseline to be associated with an 18% increased hazard for all-cause mortality and a 46% increased risk for CVD, after adjustment for traditional CVD risk factors. Similar results were reported by the Health ABC study, which found that major and minor ECG abnormalities were associated with an increased risk of coronary heart disease [9]. Other studies have shown ECG ischemic findings or non-specific ST-T abnormalities to increase the risk for CVD, CV mortality and all-cause mortality [10,20]. The current results also support previous reports [5,7,21] of the significant contribution of the conventional CVD risk factors: age, sex, blood pressure, BMI and current smoking, to predictions of CVD and overall mortality. Of the risk factors examined, current smoking had the strongest association with all-cause mortality and CVD, followed by female sex (Table 2). Diabetes and creatinine did not show significant associations with the outcomes examined herein, while total cholesterol showed a modest association in the univariable analysis, which waned after adjustment. A possible explanation for these findings is that an elevated creatinine level may have limited ability in estimating renal function. Further calculation of estimated glomerular renal function (eGFR) by the Cockcroft-Gault equation revealed that 79.4% of the participants had normal or mildly decreased GFR (GFR > 60), a range of values that did not show significant association with CVD or all-cause mortality also in other studies [22]. It should be mentioned that baseline ECG incidental abnormal findings frequencies were 47.2% in men and 45.0% in women, similar to other studies [9,23].

4.1. Specific ECG abnormalities

Multivariable analysis of specific ECG incidental changes revealed that NST changes and left-axis deviation were independently associated with increased risk for all-cause mortality. NST changes and left axis deviation might be benign findings but are also associated with a variety of pathological processes. NST changes can be caused by drugs, cardiac diseases, such as myocardial ischemia or cardiomyopathies, and other disorders (e.g. anemia, fever, acidosis etc.). Left axis deviation may be associated with coronary artery disease, left ventricular hypertrophy, hypertrophic cardiomyopathies and electrical conduction abnormalities, such as left bundle branch block or left-anterior hemi-block. NST changes and left axis deviation on a routine ECG screening test might reveal early myocardial ischemia or electrical conduction abnormalities. These results are in line with previous studies that found significant associations of NST changes and left axis deviation with increased risk for future cardiac events, coronary heart disease, cardiovascular mortality and all-cause mortality [9,20,24]. The findings help elucidate the abnormalities that are associated with future mortality, i.e. NST changes and left axis deviation, but further studies are needed.

4.2. The prognostic value of the resting ECG test

We investigated the additional prognostic value of ECG-testing in CVD and overall prediction of mortality risk, beyond conventional CVD risk factors, in order to assess the potential role of resting ECG as an early screening test.

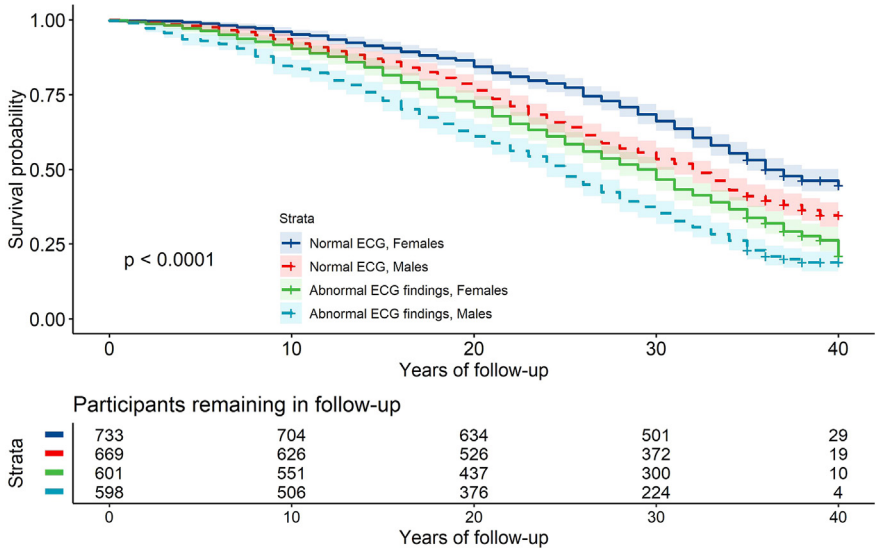

Fig. 1. Kaplan-Meier survival curves of 1267 men and 1334 women according to baseline ECG findings. Mean survival times: abnormal ECG group- 25.8 (95%CI, 25.1–26.4) years, normal ECG group- 30.7 (95%CI, 30.2–31.3) years, Log-rank test- $p < 0.001$.

We calculated reclassification-based measures for both outcomes of interest, which have been demonstrated to be more sensitive than discrimination C index [18,25]. The addition of the baseline ECG findings to a CVD risk prediction model correctly reclassified 7.4% of the individuals into CVD risk categories (low, intermediate and high). Most of the correctly reclassified persons (6.7%, Table 5 in [15]) had not experienced a CVD event and were reclassified to the lower risk category (i.e. non-event NRI). These results suggest a possible benefit of ECG-testing in stratifying asymptomatic individuals into CVD risk categories, particularly in reducing the false positive stratification of individuals into a higher risk category, i.e. increasing the specificity of the model. Likewise, continuous NRI and IDI, which are independent of the chosen categories, showed significant results ([15], Table 4). The NRI in our study is similar to findings of previous studies. Bauer et al. found an NRI improvement of 7.4% following the addition of ECG abnormalities to the prediction of cardiac heart disease risk in an elderly population [9]. Another study had demonstrated a 4.3% improvement in NRI following The addition of normal ECG and echocardiogram to Framingham risk score for heart failure [23]. Sudden cardiac death (SCD) risk NRI was also improved by 4.5% following the addition of the QRS duration [11]. Likewise, T-Wave inversion and QRS/T angle yielded a modest C–index improvement in SCD risk prediction, when were added to the

Table 2
Unadjusted and adjusted logistic regression models for 23-year (median) cumulative CVD-risk and unadjusted and adjusted Cox-models for 31-year (median) all-cause mortality.

	Logistic regression for CVD-risk		Cox PH regression for all-cause mortality	
	Univariate (unadjusted) OR (95% C·I)	Multivariate (adjusted) OR (95% C·I)	Univariate (unadjusted) HR (95% C·I)	Multivariate (adjusted) HR (95% C·I)
Age (years)	1.05 (1.03–1.07)	1.05 (1.02–1.07)	1.11 (1.10–1.12)	1.10 (1.09–1.11)
Sex (female)	0.69 (0.53–0.89)	0.77 (0.56–1.04)	0.73 (0.67–0.80)	0.75 (0.67–0.83)
Origin				
Yemen	Reference	Reference	Reference	Reference
Asia	1.03 (0.69–1.55)	0.96 (0.63–1.48)	0.97 (0.85–1.10)	0.85 (0.74–0.80)
North-Africa	1.20 (0.76–1.88)	1.06 (0.65–1.72)	1.05 (0.91–1.20)	0.96 (0.83–1.11)
Europe/America	1.19 (0.81–1.74)	1.10 (0.73–1.65)	0.90 (0.72–1.03)	0.79 (0.69–0.90)
Smoking				
Former	1.05 (0.59–1.87)	0.95 (0.51–174)	1.20 (0.99–1.45)	1.07 (0.88–1.31)
Current	1.65 (1.23–2.22)	1.74 (1.26–2.41)	1.19 (1.08–1.32)	1.30 (1.16–1.44)
Blood pressure [a] (mmHg)				
Systolic	1.02 (1.01–1.02)	1.01 (0.99–1.02)	1.02 (1.02–1.03)	1.02 (1.02–1.02)
Diastolic	1.02 (1.01–1.04)	1.01 (0.98–1.03)	1.03 (1.02–1.04)	0.99 (0.98–1.00)
BMI (Kg/M^2)	1.07 (1.03–1.11)	1.05 (1.00–1.09)	1.05 (1.04–1.06)	1.02 (1.01–1.03)
Diabetes				
Pre-diabetes	0.94 (0.69–1.28)	0.90 (0.65–1.24)	0.94 (0.85–1.04)	0.94 (0.85–1.05)
Diabetes	0.90 (0.59–1.36)	0.82 (0.53–1.27)	0.91 (0.78–1.05)	0.90 (0.77–1.05)
Creatinine (mg/dL)	0.67 (0.33–1.34)	–	0.98 (0.83–1.17)	–
Total cholesterol (mg/dL)	1.01 (1.00–1.01)	–	1.00 (1.00–1.00)	–
Incidental ECG findings	1.68 (1.27–2.23)		1.70 (1.55–1.87)	
Model 1[b]		1.37 (0.92–2.06)		1.22 (1.06–1.44)
Model 2[c]		1.46 (1.08–1.96)		1.18 (1.07–1.30)
Model 3[d]		1.47 (1.09–1.97)		1.18 (1.07–1.31)

[a] Blood pressure- systolic and diastolic values are the average of 4–6 consecutive days measurements, 3 at each arm.
[b] Model 1 (1152 subjects for Cox regression and 547 subjects for logistic regression) adjusted for the variables: sex, age, origin, smoking, blood pressure (systolic and diastolic), BMI, diabetes, serum creatinine and total cholesterol.
[c] Model 2 (2520 subjects for Cox regression and 916 subjects for logistic regression) adjusted for the variables: sex, age, origin, smoking, blood pressure (systolic and diastolic), BMI and diabetes.
[d] Model 3 (2533 subjects for Cox regression and 917 subjects for logistic regression) for the association between incidental ECG findings and all-cause mortality and for CVD cumulative incidence, respectively, adjusted for sex, age, ethnic-origin, smoking status, blood pressure (systolic and diastolic), and BMI.

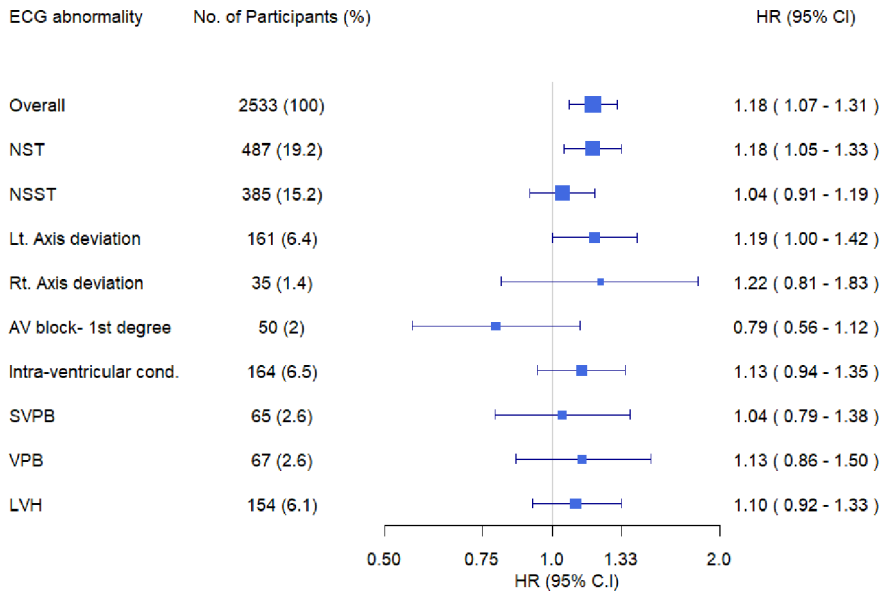

Fig. 2. Multivariable analysis of the association between specific ECG pathologies and all-cause mortality. NST- Nonspecific T wave changes; NSST- Nonspecific ST Segment changes; Intra-ventricular cond. (conduction) category includes complete and incomplete LBBB or RBBB; SVPB- Supra-ventricular premature beats (either single or multiple); VPB- Ventricular premature beats (either single or multiple); LVH- left ventricle hypertrophy.

traditional risk factors (from 0.779 to 0.784 and 0.783 respectively) [12]. Biomarkers, such as C-reactive protein and fibrinogen demonstrated less improvement in reclassification, regarding the prediction of CVD risk: 1.52% and 0.83%, respectively [26]. This demonstrates how improved reclassification can affect individual risk stratification in clinical practice and subsequently impact clinical decision making.

4.3. Strengths and limitations

A few limitations of our study should be acknowledged. First, although two specific ECG abnormalities (NST-changes and left-axis deviation) were found to be associated with overall mortality, other pathologies may have an important role in individual risk assessment, despite their lack of statistical significance in the current study. The latter may be due to under powering of subgroup analysis. Second, due to the absence of a CVD diagnosis date, the cumulative incidence and the odds ratios, but not hazard ratios, were calculated for the CVD outcome. Third, the lack of repeated measurements of ECG or other covariates may have subjected our associations to bias due to regression-to-the-mean. Finally, since CVD incidence determination included self-report of history of CVD, it may affect the sensitivity of this outcome.

Several strengths of the study should also be acknowledged: the long follow-up period, with 71,885 person-years accumulated; the high external validity of the cohort; the interpretation of all ECG tests by a single senior cardiologist, which eliminated intra-observer-variability; and the precision and high validity of the exposure definition and of the CVD outcome. These were objectively defined by ECG-testing in addition to self-report, to reduce underreporting bias.

Reclassification analysis was not performed in previous studies, except by Auer et al. [9] who conducted NRI analysis in an elderly population. Such analysis can provide further insights about the potential benefit of ECG screening in individual CVD risk stratification.

4.4. Current recommendations versus practice

Recommendations against routine ECG screening (such as by the USPSTF, the American Academy of Family Physicians and the AHA) [7,8,27] stem from the potential harms of false-positive results, leading to unnecessary invasive procedures, overtreatment, and economic burden. Nonetheless, ECG screening tests are not infrequently performed in clinical practice; According to the Consumer's Report Survey, as many as 39% of asymptomatic adults without hypertension or elevated blood cholesterol level reported undergoing resting ECG-testing in the preceding 5 years [28]. Since the publication of these data, devices for ECG personal use have emerged, which may increase considerably the use of routine home ECG tests in upcoming years. Therefore, it is likely that clinicians will more often encounter incidental abnormal ECG findings, having to cope with the decision whether further workup is necessary, stressing the relevancy of our study.

5. Conclusion

Our findings demonstrate that incidental ECG abnormal findings in asymptomatic adults significantly increase the long-term risk of CVD and all-cause mortality. NST changes and left-axis deviation were the changes found to have the most significant association with the outcomes of interest. ECG abnormalities are linked to various pathological processes and may be the first sign of an underlying cardiac morbidity. Therefore, resting ECG screening tests can contribute to the identification of patients for further investigation with additional modalities, and thus may promote early CVD detection. Furthermore, our findings support the additional prognostic value of abnormal resting ECG findings in CVD risk reclassification. In light of our findings, based on a high quality and long-term follow-up, albeit from a single prospective cohort, we suggest that screening ECG should be considered in asymptomatic low risk healthy adult men and women for the long-term prevention of CVD incidence.

Acknowledgement

\This study is part of the Master's thesis of Mr. Adam Goldman in fulfillment of his M.D. M.P.H. studies at the School of Public Health at the Sackler School for Medicine, the Tel Aviv University, Israel.

Declaration of competing interest

None to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.08.015.

References

[1] Heron M. Deaths, Leading causes for 2015, Natl Vital Stat Rep 66 (5) (2017) 1–76.
[2] E. Wilkins, L. Wilson, Wickramasinghe K, et al, European Cardiovascular Disease Statistics 2017 Edition, 2017http://www.ehnheart.org/cvd-statistics.html.
[3] D. Mozaffarian, E.J. Benjamin, A.S. Go, et al., Heart disease and stroke statistics-2016 update a report from the, American Heart Association. 133 (2016)https://doi.org/10.1161/CIR.0000000000000350.
[4] P.W.F.D. Wilson, R.B. Agostino, D. Levy, et al., Prediction of coronary heart disease using risk factor categories, Circulation. 97 (18) (1998) 1837–1847.
[5] D.C. Goff, D.M. Lloyd-Jones, G. Bennett, et al., ACC/AHA guideline on the assessment of cardiovascular risk. *Circulation*, 2014;129(25 suppl 2):S49 LP-S73, 2013http://circ.ahajournals.org/content/129/25_suppl_2/S49.abstract.
[6] Piepoli MF, Hoes AW, Agewall S, et al; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016 Aug 1;37(29):2315–2381. doi: https://doi.org/10.1093/eurheartj/ehw106.
[7] U.S. Preventive Services Task Force, Screening for cardiovascular disease risk with electrocardiography: us preventive services task force recommendation statement, JAMA. 319 (22) (2018) 2308–2314.
[8] R. Chou, A. Qaseem, J. Biebelhausen, et al., Cardiac screening with electrocardiography, stress echocardiography, or myocardial perfusion imaging: advice for high-value care from the American college of physicians, Ann. Intern. Med. 162 (6) (2015) 438–447.
[9] D.C. Bauer, L.J. Min, J. Cornuz, S. Satterfield, A.B. Newman, Association of Major and Minor ECG abnormalities with coronary heart disease events, JAMA. 307 (14) (2012) 1497–1505.
[10] D. De Bacquer, G. De Backer, M. Kornitzer, K. Myny, Z. Doyen, H. Blackburn, Prognostic value of ischemic electrocardiographic findings for cardiovascular mortality in men and women, J. Am. Coll. Cardiol. 32 (3) (1998) 680–685.
[11] S. Kurl, T.H. Ma, Duration of QRS complex in resting electrocardiogram is a predictor of sudden cardiac death in men, Circulation. 125 (21) (2012) 2588–2594.
[12] J.A. Laukkanen, Angelantonio E. Di, H. Khan, T-wave inversion , QRS duration , and QRS / T angle as electrocardiographic predictors of the risk for sudden cardiac death, Am. J. Cardiol. 113 (7) (2014) 1178–1183.
[13] S. Tiosano, H. Hod, B. Oberman, A. Chetrit, R. Dankner, A three-decade survival analysis of intraventricular conduction delay in adults without ischemic heart disease, Am. J. Med. 129 (11) (2016) 1219.e11–1219.e16.
[14] R. Dankner, M.A. Abdul-Ghani, Y. Gerber, A. Chetrit, J. Wainstein, I. Raz, Predicting the 20-year diabetes incidence rate, Diabetes Metab. Res. Rev. 23 (7) (2007) 551–558.
[15] Goldman A, Hod H, Chetrit A, Dankner R. Data for a population based cohort study on abnormal findings of electrocardiograms (ECG), recorded during follow-up periodic examinations, and their association with long-term cardiovascular morbidity and all-cause mortality. Data in Brief. (in press).
[16] R.J. Prineas, Richard S. Crow, Zhu-Ming Zhang, The Minnesota Code Manual of Electrocardiographic Findings, Springer London, 1982https://doi.org/10.1007/978-1-84882-778-3.
[17] F.E. Harrell, K.L. Lee, D.B. Mark, Prognostic/clinical prediction models: multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors, Tutorials Biostat Stat Methods Clin Stud. 1 (2005) 223–249.
[18] Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS, Pencina, Michael J., D' Agostino, Ralph B., Vasan, Ramachandran S., Michael J. Pencina, Ralph B. D' Agostino RSV. *Evaluating the Added Predictive Ability of a New Marker: From Area under the ROC Curve to Reclassification and Beyond*. Stat. Med.; 2008. doi:https://doi.org/10.1002/sim.2929.
[19] M.J. Pencina, R.B. D'Agostino, M.G. Larson, J.M. Massaro, R.S. Vasan, Predicting the 30-year risk of cardiovascular disease: the Framingham heart study, Circulation. 119 (24) (2009) 3078–3084.
[20] M.L. Daviglus, Y. Liao, P. Greenland, et al., Association of Nonspecific Minor ST-T abnormalities with cardiovascular mortality: the Chicago Western electric study, JAMA. 281 (6) (1999) 530–536.
[21] Third Report of the National Cholesterol Education Program, (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation*. 106 (25) (2002) 3143 LP–3143-http://circ.ahajournals.org/content/106/25/3143.abstract.
[22] E. Di Angelantonio, R. Chowdhury, N. Sarwar, T. Aspelund, J. Danesh, V. Gudnason, Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study, BMJ. 341 (7776) (2010) 768.
[23] S. Venkatesh, W.T.O. Neal, S.T. Broughton, Utility of Normal findings on electrocardiogram and echocardiogram in subjects ≥ 65 years, Am. J. Cardiol. 119 (6) (2016) 856–861.
[24] Larsen CT, Dahlin J, Blackburn H, et al. Prevalence and prognosis of electrocardiographic left ventricular hypertrophy , ST segment depression and negative T-wave The Copenhagen City Heart Study. 2002:315–324. doi:https://doi.org/10.1053/euhj.2001.2774.
[25] J.H. Ware, The limitations of risk factors as prognostic tools, N. Engl. J. Med. 355 (25) (2006) 2615–2617.
[26] E.P.L. Di Angelantonio, et al., KS. C-reactive protein, fibrinogen, and cardiovascular disease prediction, N. Engl. J. Med. 367 (14) (2012) 1310–1320.
[27] American Academy of Family Physicans. Recommendations for Clinical Preventive Service: Coronary Heart Disease. http://www.aafp.org/patient-care/clinical-recommendations/all/cw-ekg.html. Published 2015.
[28] Consumer Reports survey. Heart Disease Prevention Survey. https://www.consumerreports.org/cro/news/2012/07/study-healthy-adults-should-skip-routine-ekgs/index.htm#. Published 2012.