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ORIGINAL ARTICLE

Prognostic value of myocardial injury-related findings on resting electrocardiography for cardiovascular risk in the asymptomatic general population: the 12-year follow-up report from the Ansan-Ansung cohort

Jinho Shin[a], Yonggu Lee[b], Jin-Kyu Park[a], Jeong-Hun Shin[b], Young-Hyo Lim[a], Heo Ran[a], Hyun-Jin Kim[b] and Hwan-Cheol Park[b]

[a]Division of Cardiology, Department of Internal Medicine, Hanyang University Medical Center, Seoul, Republic of Korea; [b]Division of Cardiology, Department of Internal Medicine, Hanyang University Guri Hospital, Guri City, Republic of Korea

ABSTRACT

Background: We investigated the predictive values of myocardial injury-related findings (MIFs) including ST-T wave abnormalities (STA) and pathologic Q waves (PQ) in electrocardiography for long-term cardiovascular outcomes in an asymptomatic general population.

Methods: We observed 8444 subjects without cardiovascular diseases and related symptoms biennially over a 12-year period. Major cardiovascular adverse events (MACEs) were defined as a composite of cardiovascular death, myocardial infarction, coronary artery disease and stroke.

Results: MACEs occurred more frequently in subjects with STA (9.1% vs. 5.2%, $p < .001$) and in those with anterior PQ (11.5% vs. 5.2%, $p = .001$) than in those without any MIFs, whereas anterolateral/posterior PQ were not associated with a higher incidence of MACEs. Multivariate Cox regression analyses showed that STA and anterior PQ were independently associated with the risk of MACEs. However, survival receiver operating characteristic curve analysis showed that the composite of STA and anterior PQ did not improve the predictive power of the conventional cardiovascular risk estimators when added to the models.

Conclusions: The presence of STA or anterior PQ was associated with worse cardiovascular outcomes in the asymptomatic general population. However, the addition of MIFs to the conventional risk estimators was of limited value in the prediction of MACEs.

KEY MESSAGES

- Myocardial injury-related findings including ST-T wave abnormalities and anterior pathologic Q waves in resting electrocardiography predict long-term cardiovascular outcomes in an asymptomatic low-risk population.
- However, ST-T wave abnormalities and anterior pathologic Q waves add only limited value to conventional cardiovascular risk estimators in the prediction of cardiovascular outcomes.

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Electrocardiography; ST-T wave abnormality; pathologic Q wave; low-risk populations; cardiovascular risk

Introduction

Electrocardiography (ECG) is one of the most useful tools to evaluate myocardial injuries from various causes including coronary artery disease (CAD) and hypertension [1–3]. Myocardial injury-related findings (MIFs), including ST-T wave abnormalities (STAs) and pathologic Q (PQ) waves on resting ECG, could be important diagnostic clues in patients with acute coronary syndrome [4]. The clinical relevance of these resting ECG abnormalities on the prognosis of cardiovascular (CV) disease has also been reported in patients with chronic stable angina [5]. In hypertensive patients, MIFs may represent myocardial remodelling or hypertrophy mediated by hypertension [3]. However, the prognostic value of MIFs on resting ECG has yet to be established in asymptomatic low-risk general populations. Major and minor STAs have been reported to predict CV diseases and deaths in middle-aged and elderly individuals in the general population [6–9]. In addition to STAs on resting 12-lead ECG, asymptomatic STAs on exercise ECG and global electrical heterogeneity on vector ECG have also shown prognostic value in population-based studies [10,11].

CONTACT Yonggu Lee hmedi97@hanyang.ac.kr, hmedi97@naver.com Division of Cardiology, Department of Internal Medicine, Hanyang University Guri Hospital, College of Medicine, Hanyang University, 153 Gyeongchun-ro, Guri-si 11923, Republic of Korea

Supplemental data for this article can be accessed here.

PQ waves have also been reported to be associated with a worse prognosis in the general population with a low CV risk [12]. In contrast, the US Preventive Services Task Force (USPSTF) recently reported that resting ECG has limited value beyond the traditional scores for predicting CV risk in the general population through a systematic review of 9 cohort studies [13,14]. Moreover, while the results from population-based cohort studies could be vastly influenced by population characteristics, none of these studies investigated the prognostic value of resting ECG findings in asymptomatic populations. Therefore, in this study, we investigated the prognostic value of MIFs, including STAs and PQ waves, on resting ECG for CV risk in an asymptomatic general population.

Methods

Study population

This study was conducted with the population of the Ansan-Ansung cohort study, which is an ongoing longitudinal investigation funded by the Korean government (Korean National Research Institute of Health, Korean Centers for Disease Control and Prevention, and the Ministry of Health and Welfare) to examine the association of genetic and environmental factors with frequent metabolic and CV diseases in South Koreans. Detailed information regarding the study protocol and procedures is available in a previous publication [15,16]. Koreans aged 40–69 years, residing in two cities (Ansan and Ansung) were enrolled between June 2001 and January 2003. Comprehensive health evaluations regarding demographic, anthropometric, social and past medical information, physical examinations and laboratory tests were conducted in a tertiary hospital located in Ansan City. Six serial follow-up assessments that completed the baseline protocol were conducted biennially after the baseline assessment through scheduled visits until 2014. At each visit, written informed consent was obtained from all of the participants. The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Korean National Research Institute of Health and the Institutional Review Board of Hanyang University Medical Center (IRB No. 2018-08-001).

Information on lifestyle, past medical history and symptoms

Comprehensive health examinations and face-to-face interviews were conducted with the participants. Through interviews, information regarding demographics, lifestyle including smoking and alcohol intake, and past and present medical conditions including hypertension, diabetes mellitus (DM), dyslipidemia and CV diseases, were obtained by trained investigators using a questionnaire. Angina-related symptoms were defined at baseline when at least one of the following symptoms was present: dyspnoea during exertion $\geq$ New York Heart Association classification 2; and chest pain that was pressure-like, squeezing, burning or fullness in both arms, substernal area, anterior chest wall or jaw, and chest pain during exercise, emotional stress or cold exposure.

Hypertension was defined as a previous diagnosis of hypertension or taking antihypertensive medications. DM was defined as a previous diagnosis of DM, taking oral hypoglycaemic agents, receiving insulin therapy or a haemoglobin A1C level $\geq$6.5%. Dyslipidemia was defined as a previous diagnosis of dyslipidemia, taking statins without a history of CV disease or DM, a total cholesterol level $\geq$240 mg/dl, a triglyceride level $\geq$150 mg/dl or a high-density lipoprotein cholesterol level $<$45 mg/dl. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Study equation, and chronic kidney disease was defined as an eGFR $\leq$60 ml/min/1.73 m^2. The 10-year atherosclerotic CV disease (ASCVD) risk was calculated as previously described in the Korean Heart Study [17].

Measurement of ECG and classification of MIFs

Twelve-lead ECG was obtained using a GE Marquette MAC 5000® (GE Marquette Inc., Milwaukee, WI, USA), recorded in a 25 mm/s with 0.1 mV/mm standardization and interpreted and classified according to the Minnesota codes [18] at the baseline evaluation by one experienced cardiologist affiliated with the tertiary hospital where the evaluations took place. MIFs were defined as STAs or PQ waves. The presence of PQ waves was defined by codes between 1-1-1 and 1-3-3, and the presence of STAs was defined by codes between 4-1-1 and 5-4. The STAs consisted of T-wave inversions (negative T-wave amplitude $\geq$1 mm or biphasic), T-wave flattening (flat T-wave amplitude, negative or biphasic with $<$1 mm negative phase or T/R-wave amplitude ratio $<$1/20) and ST-segment depression (ST junction depression $\geq$1 mm or downward-sloping ST-segment with the nadir $\geq$5 mm). The detailed Minnesota codes for the classification are described in Supplementary Table 1.

Participant selection

Participants who had a prior history of CV diseases, including myocardial infarction (MI), non-MI CADs, congestive heart failure and haemorrhagic/ischaemic stroke, were excluded from the study. These CV diseases were identified through the interviews conducted during the baseline evaluations. Previous diagnoses made by physicians were used as the definitions of these CV diseases. Non-MI CADs were identified through a binary question for the presence of physician-diagnosed angina pectoris without MI. Participants with any angina-related symptoms were also excluded. Participants with pre-excitation syndrome (Minnesota code 6-4-1), left or right bundle branch block (Minnesota code 7-1-1 and 7-2-1, respectively) or tachycardia $\geq$120 bpm were also excluded because of the STAs accompanying these conditions.

Investigation and definition of CV events

The new development of CV diseases was identified through interviews with the participants that were administered at every visit by the trained investigators using the questionnaire. CV death was identified through the cause of death data recoded as ICD-10 codes in the national registry database from the Korean national statistical office, Statistics Korea (KOSTAT). CV death was defined as death from a cardio-cerebrovascular disease (I20-I82) or sudden death from an unknown cause (R96-R99). A major adverse CV event (MACE) was defined as a composite of MI, non-MI CAD, haemorrhagic or ischaemic stroke and CV death.

Statistical analysis

The participants were divided into 2 groups according to the presence of the MIFs (no-MIF group vs. MIF group). The continuous variables were compared between the groups using an independent *t*-test, and the categorical variables were compared using a chi-square test. A Kruskal–Wallis test was employed for variables with a skewed distribution. A Kaplan–Meier survival curve analysis with a log-rank test was employed to compare the incidence of MACE in participants with an individual MIF with those in the no-MIF groups.

Multivariate Cox proportional hazard models were used to evaluate the association between the individual MIF and the risk of MACE in the presence of the confounding variables. The models were reduced through a backward variable selection process with a p value $<.05$ as the retention criterion to prevent overfitting bias. Covariates of the multivariate Cox proportional hazard models included age, sex, DM, hypertension, dyslipidemia, eGFR, low-density lipoprotein cholesterol level, log-transformed C-reactive protein level, current smoking, BMI, waist-to-hip ratio and the presence of left ventricular hypertrophy (LVH) on ECG (ECG-LVH).

To evaluate the predictive value of MIFs for MACE in comparison with the conventional CV risk factors and the 10-year ASCVD risk, receiver operating characteristic (ROC) curve analyses of survival were performed. We estimated statistics including C-indexes, 95% confidence intervals, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at the median follow-up time (162 months). Comparisons between C-indexes of the survival ROC curve models were performed using a Delong test. Comparisons between the global performances of the multivariate Cox proportional hazard models were performed using likelihood ratios and Akaike information criteria (AIC). A difference in AICs (ΔAIC) <2 was considered as no significant difference between the models, and ΔAIC >10 was considered as a substantial difference between the models.

All of the statistical analyses were performed using the statistical software R-3.4.3, Rstudio-1.1.463 and R packages such as descr, tableone, survival, rms, time ROC and coin. A p value $<.05$ was considered significant.

Results

As shown in Supplementary Figure 1, 8444 participants were analyzed after applying inclusion and exclusion criteria. At least one MIF was found in 1463 participants (17.3%) (Table 1). Participants in the MIFs group were older and more frequently male than those in the no-MIFs group. Participants in the MIF group were also more obese, more hypertensive and more dyslipidemic and presented with lower eGFR levels than those in the no-MIF group. Similarly, most laboratory findings, including C-reactive protein and ECG-LVH, were worse in the MIF group than in the no-MIF group. However, current smoking and alcohol intake $\geq$1/week were less frequent in the MIF group. The majority of MIFs were STAs, and the majority of STAs were T-wave inversion/flattening. Posteroinferior PQ waves were most frequent. Only 21 of the participants had both anterior PQ waves and STAs (Figure 1 and Supplementary Table 2).

Table 1. Baseline characteristics and outcomes of the study population.

$N = 8444$	No MIFs $N = 6981$	Any MIFs $N = 1463$	p Value
Age (years)	51.4 ± 8.6	53.9 ± 9.1	<.001
Female (%)	3758 (53.8)	440 (30.1)	<.001
BMI (kg/m^2)	24.4 ± 3.1	25.2 ± 3.2	<.001
Hip circumference (cm)	93.5 ± 5.9	94.0 ± 6.2	.011
Waist circumference (cm)	82.1 ± 8.6	84.0 ± 9.2	<.001
Waist-hip ratio	0.88 ± 0.07	0.89 ± 0.08	<.001
Current smoking (%)	1959 (28.5)	242 (16.8)	<.001
Drinking ≥1/week (%)	3993 (57.7)	613 (42.3)	<.001
Hypertension (%)	854 (12.2)	311 (21.3)	<.001
Diabetes (%)	595 (8.5)	134 (9.2)	.433
Dyslipidemia (%)	3828 (54.9)	852 (58.2)	.018
Chronic kidney disease (%)	261 (3.7)	86 (5.9)	<.001
10-year ASCVD risk (%)[a]	3.8 [1.4, 8.4]	4.1 [1.5, 8.7]	.069
10-year ASCVD risk (%)[b]	5.9 [3.1, 11.9]	8.1 [3.9, 15.5]	<.001
10-year ASCVD risk ≥10% (%)	850 (14.9)	613 (22.5)	<.001
Laboratory tests			
Serum Creatinine (mg/dL)	0.86 ± 0.24	0.81 ± 0.19	<.001
eGFR (ml/min/1.73 m^2)	92.6 ± 14.2	90.9 ± 14.6	<.001
HgA1c (%)	5.8 ± 0.9	5.9 ± 1.0	<.001
Total cholesterol (mg/dL)	190.2 ± 35.1	195.3 ± 36.5	<.001
LDL-C (mg/dL)	113.3 ± 33.2	117.3 ± 33.5	<.001
HDL-C (mg/dL)	44.8 ± 10.1	44.5 ± 10.0	.324
Triglyceride (mg/dL)	133 [98, 188]	142 [106, 196]	<.001
CRP (mg/dL)	0.14 [0.06, 0.24]	0.15 [0.07, 0.26]	.001
ECG LVH (Minnesota)	955 (13.7)	238 (16.3)	.010
Clinical outcomes			
Angina-related symptoms	1488 (21.3)	365 (24.9)	.002
Time to symptoms (months)	159 [116, 167]	159 [95, 167]	.107
FU duration (months)	162 [157, 173]	162 [157, 173]	.892
MACE (%)	357 (5.1)	109 (7.5)	<.001
Myocardial infarction (%)	44 (0.6)	11 (0.8)	.599
Coronary artery disease (%)	131 (1.9)	39 (2.7)	.051
Stroke (%)	111 (1.6)	38 (2.6)	.008
Cardiovascular death (%)	92 (1.3)	31 (2.1)	.020

Data are presented as the mean ± SD or *N* (%).
Data with a skewed distribution was presented as the median [the first quartile, the third quartile].
BMI: body mass index; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.
[a]Calculated by AHA/ACC pooled cohort equation.
[b]Calculated by the Korean Risk Prediction Model equation.

There were 466 MACEs among 8444 participants (5.5%), which demonstrates that our study population is a low-risk population, on average. Clinical events, including angina-related symptoms, non-MI CADs, strokes, CV deaths and MACEs were more frequent in the MIF group, whereas the incidence of MI did not differ between groups according to the presence of MIFs (Table 1).

The cumulative incidence of MACEs was higher in participants with STAs than in those without MIFs, whereas it was not different between participants with PQ waves and those without MIFs. MACEs also occurred more frequently in participants with both T-wave flattening and T-wave inversion than in those without MIFs. However, the cumulative incidence of MACEs was higher only in participants with anterior PQ waves than in those without MIFs (Figure 2). Multivariate Cox proportional hazard models showed that STAs and both T-wave inversion and T-wave flattening were associated with the risk of MACEs, whereas only anterior PQ waves among the PQ waves were associated with the risk of MACEs (Figure 3). When both STAs and PQ waves were included in the model (model 1 in Table 2), STAs (but not PQ waves) were a significant predictor for MACEs. When MIFs were included individually in the model (model 2 in Table 2), only anterior PQ waves among the PQ waves and T-wave abnormalities significantly predicted MACEs. For secondary outcomes, when adjustments were made for the covariates, the presence of STAs was associated with the risk of stroke and CV death. T-wave inversion and T-wave flattening were associated with the risk of stroke and CV death, respectively. Anterior PQ waves were associated with the risk of MI and CV death (Table 3).

MIFs, including STAs and anterior PQ waves, showed lower sensitivity and higher specificity than 10-year ASCVD risk in predicting MACEs. The PPV was highest when both STAs and anterior PQ waves were present, whereas it was similar among the other

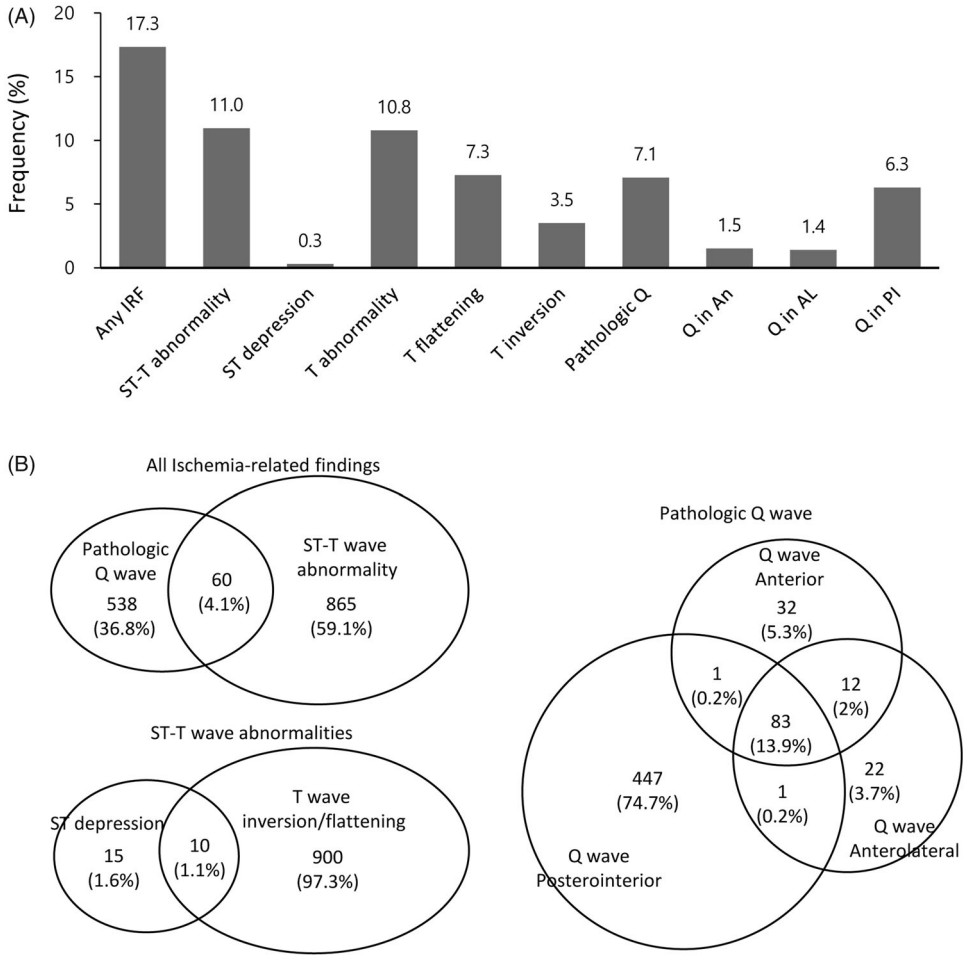

Figure 1. The frequencies and the intersection of MIFs on ECG. (A) STAs were more frequent than PQ waves. T-wave flattening was the most frequent MIF among STAs, while the posterior wall was the most frequent location of PQ waves. (B) STAs and PQ waves were simultaneously present in only a small portion (5.9%) of participants with MIFs.

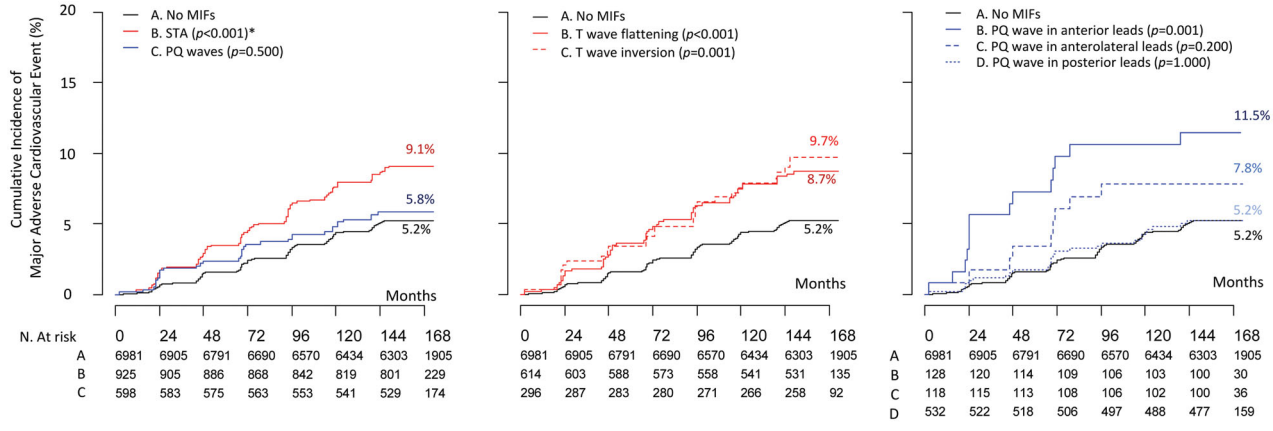

Figure 2. The cumulative incidences and the risk of the MACEs according to the MIFs on ECG. STAs and PQ waves in the anterior leads were associated with the risk of MACEs, whereas PQ waves in the other leads were not. The risk of MACEs did not differ between subjects with T-wave flattening and those with T-wave inversion. *All *p* values were derived from a log-rank test against group A.

criteria, and the NPV was sufficiently high for all of the criteria (Table 4). The ROC curve analyses of survival showed that the model of the conventional risk factors of CAD (model 1) and the model of 10-year ASCVD risk (model 3) had higher C-indexes than the model including only STAs and anterior PQ waves. The

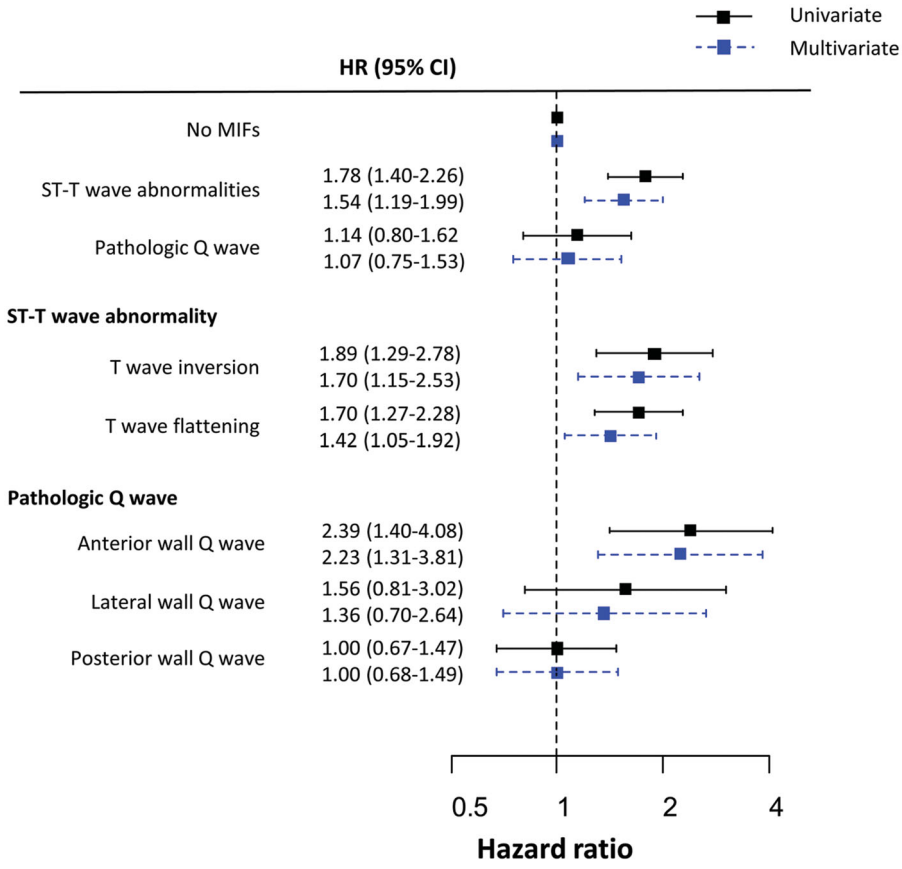

Figure 3. Cox proportional hazard models for the association between various MIFs and the risk of MACEs. In both univariate and multivariate Cox proportional hazard models, STA, T-wave inversion, T-wave flattening and anterior PQ waves were significantly associated with an increase in the risk of MACEs. A backward variable selection process was performed to simplify the models (cut-off point <0.05). Covariates included age, sex, DM, hypertension, dyslipidemia, eGFR, low-density lipoprotein cholesterol level, log-transformed CRP level, current smoking, BMI, waist-to-hip ratio and the presence of ECG-LVH.

Table 2. Multivariate Cox regression analysis for the predictors of MACEs.

	Models	HR	95% CI	*p* Value
Model 1	STA	1.55	1.21–2.00	<.001
	PQ wave	1.02	0.72–1.45	.901
	Age (per 5 years)	1.39	1.32–1.48	<.001
	Male	1.44	1.15–1.80	.001
	Diabetes	1.66	1.30–2.11	<.001
	Hypertension	1.55	1.24–1.92	<.001
	Current smoking	1.35	1.07–1.69	.011
	Waist–hip ratio (per 0.1)	1.21	1.07–1.37	.003
Model 2	Anterior PQ waves	3.60	1.70–7.62	<.001
	Lateral PQ waves	0.54	0.20–1.42	.211
	posterior PQ waves	0.81	0.53–1.25	.347
	T-wave abnormality	1.53	1.18–1.97	.001
	ST-segment depression	1.15	0.29–4.66	.840
	Age (per 5 years)	1.39	1.32–1.47	<.001
	Male	1.43	1.14–1.78	.002
	Diabetes	1.64	1.28–2.10	<.001
	Hypertension	1.55	1.24–1.92	<.001
	Current smoking	1.34	1.06–1.68	.013
	Waist–hip ratio (per 0.1)	1.22	1.07–1.38	.003

A backward variable selection process was performed, and the myocardial injury-related findings in ECG were set to be retained in the final model.

model including only these two MIFs showed a substantially low predictive value (C-index 0.538, 95% confidence interval 0.519–0.557). Likelihood ratios and AICs from the Cox proportional hazard models showed that the addition of STAs and anterior PQ waves slightly improved the performance of the models. However, in the ROC curve analyses of survival, there were no significant increases in the C-indexes when both STAs and anterior PQ waves were added to either the model of the conventional risk factors (model 1) or the model of the 10-year ASCVD risk (model 3) (Table 5 and Supplementary Figure 2).

Discussion

In this study, we found that MIFs including STAs and anterior PQ waves were associated with the risk of composite events including MI, incident CAD, stroke and CV death, independent of the conventional CV risk factors and 10-year ASCVD risk score in an asymptomatic and low-risk general population. In particular, STAs were associated with the risk of stroke, anterior PQ waves were associated with the risk of MI and both STAs and anterior PQ waves were associated with the risk of CV death. However, the presence of

Table 3. The association between the secondary outcomes and each MIF in ECG.

	MI		Non-MI CAD		Stroke		CV death	
	HR (95% CI)	*p* Value	HR (96% CI)	*p* Value	HR (97% CI)	*p* Value	HR (98% CI)	*p* Value
STA	1.58 (0.71–3.49)	.261	1.42 (0.95–2.12)	.086	1.63 (1.03–2.59)	.036	1.65 (1.03–2.64)	.036
T-wave inversion	1.84 (0.55–6.10)	.320	1.46 (0.76–2.80)	.259	2.18 (1.12–4.24)	.022	1.42 (0.61–3.31)	.414
T-wave flattening	1.52 (0.58–4.00)	.394	1.41 (0.87–2.28)	.166	1.37 (0.78–2.40)	.268	1.72 (1.01–2.93)	.044
PQ waves	1.52 (0.64–3.58)	.342	0.95 (0.52–1.72)	.865	1.40 (0.79–2.50)	.252	1.03 (0.50–2.14)	.930
Anterior PQ waves	4.26 (1.32–13.8)	.015	2.16 (0.88–5.29)	.091	2.04 (0.75–5.53)	.161	2.78 (1.13–6.88)	.026
Lateral PQ waves	1.31 (0.18–9.55)	.788	0.83 (0.20–3.36)	.793	1.45 (0.46–4.58)	.525	1.50 (0.48–4.76)	.488
Posterior PQ waves	1.15 (0.41–3.23)	.790	0.80 (0.40–1.57)	.509	1.43 (0.79–2.61)	.236	0.63 (0.23–1.72)	.367

HR was produced in multivariate Cox regression analyses with a backward variable selection process.
The covariates include age, sex, diabetes, hypertension, dyslipidemia, eGFR, low-density lipoprotein cholesterol level, log-transformed CRP level, current smoking, BMI and waist–hip ratio.

Table 4. Predictive values of MIFs in ECG for MACEs.

	Sensitivity	Specificity	PPV	NPV
STA	16.6%	89.9%	8.9%	94.8%
Anterior PQ wave	3.0%	98.7%	11.8%	94.5%
STA and anterior PQ wave	1.0%	99.8%	20.7%	94.4%
STA or anterior PQ wave	18.8%	88.7%	9.0%	94.8%
10-year ASCVD risk ≥5%	87.2%	45.3%	8.7%	98.4%
10-year ASCVD risk ≥8.4%[a]	72.3%	63.8%	10.5%	97.5%
10-year ASCVD risk ≥10.0%	64.8%	70.2%	11.5%	97.1%

[a]Best cut-off point of 10-year ASCVD risk estimated using Youden's J-index.
ASCVD: atherosclerotic cardiovascular diseases; MIFs: myocardial injury-related findings; MACEs: major adverse cardiac events; NPV: negative predictive value; PPV: positive predictive value; PQ: pathologic Q.

MIFs on ECG did not improve the predictive value of the conventional CV risk assessment tools when added to the risk assessment models.

Our results are consistent with the results from previous population studies showing that T-wave inversion or minor changes could predict CV outcomes in low-risk general populations [8,9]. Other previous studies have also reported that STAs on ECG could be useful for predicting the occurrence of stroke [19,20] and coronary events [6]. Nevertheless, the USPSTF published a systematic review stating that ECG would not be recommended for CAD screening in asymptomatic subjects until it achieved a sufficient enhancement of predictive value when combined with the conventional CV risk prediction tools [21,22]. Therefore, our results do not provide evidence that would recommend the use of ECG to predict or prevent CV events in asymptomatic healthy populations, especially to predict CAD, because the ROC statistics failed to show any enhancement of predictive value relative to the conventional risk prediction tools.

However, because the recommendation was focussed on screening for coronary events using ECG, it had to be revised to consider composite CV events or MACEs in 2018 [13,23]. MIFs may not necessarily be abnormal findings entirely related to CAD, but they may also indicate relative myocardial ischaemia due to increased demand or myocardial hypertrophy [24]. In our results, STAs predicted the occurrence of stroke, which suggests that MIFs may reflect LVH or presumably hypertension mediating organ damage. In our results, hypertension, CKD, ECG-LVH and metabolic abnormalities, including obesity, were associated with the presence of MIFs. These findings may also imply the influence of LVH on the association between MIFs and the risk of CV events, given that hypertension, CKD and obesity are known risk factors for LVH. Because the ECG-LVH criteria using only voltage were reported to be not sufficiently sensitive [25] and the relationship between casual blood pressure and LVH has often been reported to be weak or negative [26,27], STAs may still have some implications for CV event prediction in general populations.

On the other hand, the finding that anterior PQ waves could predict MI or CV death suggests that silent infarction or myocardial damage due to compromised coronary blood flow could result in a recurrent fatal/nonfatal MI. Since anterior PQ waves were noted only in 1.5% of our study population, it is difficult to expect anterior PQ waves to improve the performance of the conventional CV risk prediction tools. However, because the prevalence of anterior PQ waves did not differ according to the 10-year ASCVD risk (1.4% in <10% vs. 1.8% in ≥10%, $p = .084$), there might be some additional value of anterior PQ waves in predicting CV events in populations where anterior PQ waves are more prevalent.

Although MIFs have not been shown to provide additional predictive value for CV events, they may still have a role in individualizing management to prevent future CV events. This may include noninvasive testing for myocardial ischaemia for patients with anterior PQ waves to prevent recurrent MI, and optimizing blood pressure management in patients with STAs to prevent future stroke, given that the MIFs showed higher PPVs, while showing similar NPVs with 10-year ASCVD risk.

In addition, our results showed that the 10-year ASCVD risk was not an independent predictor of MACEs in the multivariate Cox proportional hazard

Table 5. Comparisons between multivariate Cox-proportional hazard models including MIFs.

Multivariate Cox proportional hazard models						Survival ROC curve	
Predictors	HR	95% CI	*p* Value	ANOVA[a]	ΔAIC[b]	C-index	Delong test
Model 1							
Age (per 5 years)	1.44	1.37–1.53	<.001			0.728	
Male sex	1.37	1.11–1.70	.004			(0.704–0.751)	
Diabetes	1.71	1.34–2.19	<.001				
Hypertension	1.58	1.27–1.98	<.001				
Current smoking	1.34	1.07–1.69	.011				
Model 2							
STA	2.15	1.26–3.66	.001	$p < .001$ vs. Model 1	11.8 vs. Model 1	0.733 (0.710–0.756)	$p = .093$ vs. Model 1
Anterior PQ wave	1.53	1.18–1.98	.005				
Age (per 5 years)	1.43	1.35–1.51	<.001				
Male sex	1.48	1.18–1.85	<.001				
Diabetes	1.75	1.37–2.23	<.001				
Hypertension	1.55	1.24–1.93	<.001				
Current smoking	1.34	1.07–1.69	.012				
Model 3							
10-year ASCVD risk	1.07	1.06–1.08	<.001			0.729 (0.706–0.752)	
Model 4							
STA	1.38	1.08–1.77	.009	$p = .003$ vs. Model 3	7.6 vs. Model 3	0.731 (0.708–0.754)	$p = .611$ vs. Model 3
Anterior PQ wave	2.03	1.19–3.46	.009				
10-year ASCVD risk	1.07	1.06–1.08	<.001				

10-year ASCVD risk, 10-year atherosclerotic cardiovascular disease risk derived from the Korean Heart Study; AIC: Akaike information criterion; ANOVA: analysis of variance; CI: confidence interval; HR: hazard ratio; LR: likelihood ratio; PQ: pathologic Q; ROC: receiver operating characteristics; STA: ST-T wave abnormality.

[a]ANOVA was performed to compare the likelihood ratios between the two models.

[b]Differences in AICs between the models; ΔAIC< 2 indicates that models are indifferent and ΔAIC > 10 indicates that models are substantially different in terms of information loss.

models, although the C-index of the 10-year ASCVD risk was quite comparable to that of the model containing only the conventional CV risk factors. These results may invoke a feasibility issue for the 10-year ASCVD risk calculation, considering that the estimation of 10-year ASCVD risk requires serum cholesterol measurements, especially in an epidemiologic study setting such as ours.

The 10-year ASCVD risk scoring system used in our study was the Korean Risk Prediction Model (KRPM) introduced in the Korean Heart Study, which when compared with the AHA/ACC pooled cohort equation found that the AHA/ACC equation overestimated CV risk in the Korean population [17]. In our results, the KRPM determined the presence of MIFs better than the AHA/ACC equation did (Table 1). However, KRPM was derived from a multicenter health screening population, and it might not be suitable for estimating CV risk in a low-risk general population of younger individuals, such as our study population. Further studies should be conducted using more appropriate CV risk prediction tools for the study population.

Although the Minnesota code classification system for ECG findings is not widely used in clinical practices, it has been the most popular method to classify ECG findings in epidemiologic and clinical studies for decades [6,8,9,12,28] because it provides a unique ability to archive complex morphological descriptions for electrocardiograms into analyzable datasets [18]. The role of the Minnesota code classification in clinical and epidemiologic studies may grow in the future with the increasing use of digital ECG devices and automatized data processing software. Although there might be some minor morphologic characteristics that the Minnesota codes could not describe, this system provides a practical definition of MIFs.

Limitations

Our study has several limitations. First, our study was observational. Therefore, it is difficult to draw a causal relationship between the underlying pathologies of the MIFs and the clinical outcomes. Our study explored the value of MIFs on ECG as predictors of future CV events and obtained mechanistic insight into the influence of LVH on the association of MIFs with CV events. Second, clinical events other than CV deaths were reported by participants themselves. Although baseline information regarding previous clinical events was obtained through thorough face-to-face interviews with trained investigators using a formal questionnaire, these unascertained clinical events may have contained some information and recall bias. This event identification method may also be vulnerable to underrecognition of clinical events, given that participants who were healthy enough to revisit could report their clinical events, and silent coronary events could not be reported. However, unlike the other clinical events, CV deaths were identified through the national database from KOSTAT, which provides

accurate causes of death. In addition, the underrecognition of silent coronary events may, in contrast, emphasize the role of ECG in epidemiology studies as a safe and feasible tool for screening previous coronary events. Third, because this study is a retrospective investigation of ECG findings that had already been classified using the Minnesota codes, we could not obtain any more information beyond the documentation about ECG morphologies such as the locations of STAs and ECG-LVH criteria other than the Minnesota voltage criteria. Finally, we classified the sudden deaths from unknown causes (R9X codes in ICD-10) as CV deaths, which may have led to some misclassification of causes of death because a minor proportion of the sudden deaths may have not been a result of cardio-cerebrovascular diseases. However, the potential misclassifications may have had limited impact on the results, given that only 14 (11.4%) CV deaths were identified from the unknown causes and that the incidence of death by non-cardio-cerebrovascular causes is low.

In conclusion, STAs and anterior PQ waves on ECG could predict a composite of CV events, including MI, CAD, stroke and CV deaths, independent of the conventional CV risk factors and estimated 10-year ASCVD risk in an asymptomatic low-risk Korean general population. Although MIFs did not show additional predictive value for CV events when combined with the conventional risk estimators, further studies should evaluate the usefulness of MIFs in the prediction and prevention of more specific CV outcomes in more individualized clinical situations.

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No potential conflict of interest was reported by the authors.

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ORCID

Yonggu Lee http://orcid.org/0000-0002-3757-3692

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