SHORT-TERM AND LONG-TERM CHANGES OF SELECT ELECTROCARDIOGRAM VARIABLES PRECEDING HEART FAILURE

Kristal Lea Chichlowska

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology, Gillings School of Global Public Health

Chapel Hill
2009

Approved by:

Lloyd E. Chambless

Patricia P. Chang

Gerardo Heiss (Chair)

Wayne D. Rosamond

Eric A. Whitsel

ABSTRACT

KRISTAL L. CHICHLOWSKA: Short-Term and Long-Term Changes of Select Electrocardiogram Variables Preceding Heart Failure
(Under the direction of Dr. Gerardo Heiss)

Background: The association between long-term changes in electrocardiograph (ECG) abnormalities and incident heart failure in healthy populations is unclear. Furthermore, there is a paucity of data on the short-term repeatability of and the long-term changes of ECG abnormalities.

Methods: This study examined the short-term repeatability of ECG measures (QRS/T angle, Cornell voltage, Cornell product, left ventricular mass (LVM), T wave amplitudes in lead V_5 and V_1, and ST depression) in the ECG Repeatability Study using nested random effects models. In the Atherosclerosis Risk in Communities (ARIC) Study, we described the long-term changes of ECG variables (QRS/T angle, QT interval, Cornell voltage, Cornell product, LVM, T wave amplitudes in leads V_5 and V_1 and ST depression) over repeat ARIC visits and additionally examined their association with incident heart failure. ECG variables were dichotomized (0 or 1, with "1" indicating increased risk for heart failure) and long-term change was defined as moving from "0" at baseline (1987 – 1989) to "1" over any ARIC visit. Continuous long-term change variables for ECG measures were created using the number of ECGs available over ARIC visits and time from baseline. Logistic and linear regression models were used to describe the long-term changes of ECG variables by coronary heart disease (CHD),

diabetes and hypertension status. Cox regression models were used to assess the associations between long-term changes of ECG variables and incident heart failure.

Results: Short-term repeatability of the ECG measures was excellent. Mean values of the annual rate of change in ECG measures differed by CHD, diabetes and hypertension status and a higher proportion of ECG change was present in persons with these conditions. Finally, continuous and categorical ECG measures were associated with incident heart failure, however stronger associations were observed among the latter.

Conclusions: The long-term changes in select ECG measures may be useful for continuous monitoring of heart failure in the clinical setting. Further research to ascertain whether these select ECGs predict incident heart failure above and beyond traditional risk factors for heart failure is warranted and may provide insight into avenues for the prevention of heart failure.

This dissertation is dedicated to my grandmothers, Hust Spiza (Lucille Raymond, August 16, 1918 – January 23, 2004) and Quint Pi (Evelyn Teters, January 28, 1928 – February 7, 2007) and to my daughter, Monika Eve Chichlowska

ACKNOWLEDGEMENTS

It is with sincere gratitude that I acknowledge my committee members: Drs. Lloyd E. Chambless, Patricia P. Chang, Gerardo Heiss, Wayne D. Rosamond and Eric A. Whitsel. I also wish to recognize several individuals who have provided invaluable help with this doctoral work: Drs. Ronald Prineas and Zhu-Ming Zhang of the Epidemiologic Cardiology Research Center and Pentti Rautaharju. Additionally, I thank the participants of the Electrocardiogram Repeatability Study and the Atherosclerosis Risk in Communities Study. Thanks are also due to Dr. Kathryn M. Rose who offered her advisory support in completing my doctoral degree. I am also in debt to the Colville Confederated Tribes for providing years of financial support in completing my educational pursuits and to the Royster Society of Fellows Sequoyah Dissertation Fellowship for allowing me to focus exclusively on my doctoral work in my final year. Finally, I thank my family: my husband Maciej, my mother Slum tah (Charlene), my stepfather Don, my father Glenn, my brother Chi hoot see (George), and my high school friend Rachel for offering encouragement and support.

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities
BMI	Body mass index
BNP	Brain natriuretic peptide
CC	Coordinating center
CHD	Coronary heart disease
CI	Confidence interval
CLR	Confidence limit ratio
CVD	Cardiovascular disease
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EPICARE	Epidemiologic Cardiology Research Center
FHS	Framingham Heart Study
HR	Hazard ratio
ICC	Intraclass correlation
ICD	International Classification of Disease
ID	Identification
LIFE	Losartan Intervention For Endpoint Reduction in Hypertension

LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
MD	Maryland
MI	Myocardial infarction
MN	Minnesota
MS	Mississippi
NC	North Carolina
NDPV	Non-dipolar voltage
NYHA	New York Heart Association
rMSSD	Root mean square of differences in RR intervals
SD	Standard deviation
SDNN	Standard deviation of all RR intervals
SHS	Strong Heart Study
US	United States
WHI	Women's Health Initiative

CHAPTER 1: INTRODUCTION

1.1 Heart failure

Heart failure results from impaired left ventricular systolic function or ventricular diastolic function and other abnormalities that interfere with ventricular filling or emptying (1). Systolic dysfunction is often associated with abnormal contractility and low ejection fraction, while diastolic dysfunction is generally associated with abnormal relaxation of the heart ventricle and normal ejection fraction (1).

Many individuals with heart failure remain asymptomatic for extended periods of time either because the impairment is mild (2) or because of the compensatory mechanisms in heart failure that help to maintain cardiac output and blood pressure including augmented stroke volume, ventricular hypertrophy and activation of neurohormonal systems (3). However, when the compensatory mechanisms fail, the symptoms of heart failure are numerous and non-specific, and while the clinical signs tend to have good specificity, they also tend to have poor sensitivity (4). As a result, mild forms of heart failure may be undiagnosed in the clinical encounter.

In conjunction with the various signs and physical symptoms of heart failure, there exist numerous scoring systems to classify heart failure for use in research: Minnesota Heart Health Study (5), Framingham (6), Rotterdam (7), Gothenburg (8),

Gheorghiade (9), Boston (10), Walma (11), National Health and Nutrition Examination Survey (12), and European Society for Cardiology (13) criteria. Some studies (14-16) have attempted to validate these classification systems. Although there is no gold standard classification system for heart failure, the prognosis tends to be poor regardless of the criteria used (17).

Some of the items included in the above case classification schema are non-specific, such as fatigue and edema, and thus more objective criteria are needed to validly diagnose persons with heart failure. Heart failure is commonly diagnosed by an echocardiogram but is also assessed via radionuclide ventriculograms, cardiac magnetic resonance imaging and/or chest radiographs (18), although chest radiographs tend to have low specificity and sensitivity (18-20). Both B-type brain natriuretic peptide (BNP) and N-terminus proBNP have been used to identify persons with heart failure (21-23) and BNP levels have been shown to correlate well with the New York Heart Association (NYHA) classification (23).

There are two main systematizations of heart failure, the NYHA and the American College of Cardiology-American Heart Association (ACC/AHA) classification for heart failure (18). Four classes encompass the NYHA classification: 1) no limitation of physical activity; 2) slight limitation of physical activity and dyspnea and fatigue with moderate physical activity; 3) marked limitation of activity and dyspnea with minimal activity; and 4) severe limitation of activity and symptoms are present even at rest. The ACC/AHA staging system acknowledges the progression from asymptomatic to symptomatic heart failure and includes the following: 1) at high risk for heart failure but without structural heart disease or symptoms of heart failure; 2) with structural heart

disease but without symptoms; 3) with structural heart disease but with prior or current symptoms; and 4) refractory heart failure and requiring specialized interventions.

Early identification and treatment of risk factors may be the most important step in eliminating the public health burden of heart failure (24). If persons at high risk for heart failure are not treated, then many develop structural heart disease and go on to develop overt heart failure. The prognosis of heart failure is poor after diagnosis, with a 1-year case fatality ranging from 22 to 43 percent (25-27) and a 5-year case fatality ranging from 42 to 75 percent (25-28).

The treatment for heart failure depends on its stage. At Stage A, early modification of factors and behaviors associated with increased risk of heart failure has been shown to be beneficial in reducing risk (29) and treatment often involves modification of the neurohormonal axis with the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (29). Treatment may also involve dietary sodium restriction and moderation of alcohol intake or exercise (30), however there is no direct evidence that these measures can prevent the development of heart failure. At Stages B, C and D, Stage A treatment recommendations also apply. In addition, therapy with β–blockers, digoxin, diuretics and the use of more invasive procedures such as valve replacement, implantable cardioverter defribillator placement and coronary revascularization may be necessary (29). Most of the evidenced-based care for heart failure is based on treatment for systolic heart failure, and although there is no proven therapy for heart failure with preserved systolic function, treatment is similar to that for systolic dysfunction (31).

1.2 Epidemiology of heart failure

The burden of heart failure has increased over the past decades. From 1979 to 2005, hospital discharges for heart failure increased 171% (32, 33). In 2009, estimated heart failure healthcare costs are $37.2 billion, and in 2003 $4.4 billion was paid to Medicare beneficiaries for congestive heart failure (34). As of 2006, there were 5.7 million adults diagnosed with heart failure, and 670,000 incident cases (34). Although incidence remains relatively stable over the past decades (35-37), prevalence has been increasing (38). There is also evidence that the proportion of persons with heart failure with preserved systolic function has increased over time (31). Registry data indicate that half of persons presenting to hospitals with heart failure have preserved systolic function (39, 40).

The trend of increasing incidence of heart failure may be due to decreased case fatality of coronary heart disease (CHD) (41), use of effective medical therapy (42), improved outcomes of surgical intervention (43), or increases in the burden of risk factors for heart failure (44, 45). However, the increasing trend in heart failure may also be an artifact due to more sensitive diagnostic tests, detection of milder cases, greater awareness of heart failure or rehospitalizations (46) of persons with heart failure. Heart failure prevalence is expected to increase with the aging of the population (41, 47) and because of improved survival after myocardial infarction (MI).

An abundance of risk factors for heart failure have been identified: age (48), cigarette smoking (49), low physical activity (49), overweight (49), hypertension (49-

51), diabetes (49-52), obesity (49, 52, 53), CHD (49-52), elevated pulse pressure (52, 54), valvular heart disease (49-51), reduced kidney function (55) and left ventricular hypertrophy (LVH) (50, 51). Other important risk factors are race and sex. In each of the past three decades, black patients had a higher prevalence of heart failure compared with white or Latino patients in the United States (US) (56). While an increase in prevalence of heart failure in men aged 70 years and younger has been observed, women have a higher prevalence of heart failure at age 70 years and older. However, this difference may be due to the increased average life expectancy in women (56).

Heart failure is a burgeoning public health problem, and the prevalence has increased over the past two decades (57). Furthermore, the prognosis of heart failure is grim (25-28). Although, therapy (42, 43, 58) exists that could reduce the mortality rate, the need for hospitalization and delay the progression of heart failure, there is a clear need to focus on primary prevention of heart failure, especially since the majority of heart failure cases are attributable to hypertension, coronary artery disease and diabetes (24, 41), all of which are treatable or preventable conditions. Furthermore, AHA guidelines emphasize the importance of risk factor modification and early detection in addition to the implementation of proven treatments to reduce morbidity and mortality (18). For these reasons, risk stratification of persons is imperative to enable identification of persons who will benefit from further examination, preventive measures and if necessary more aggressive use of pharmacologic and interventional strategies.

1.3 ECG abnormalities and incident heart failure

The results of four (59-62) fairly recent population-based studies have implicated select electrocardiogram (ECG) variables as predictive of incident heart failure in relatively healthy populations (Table 1).

Both Dhingra and colleagues (59) and Okin and colleagues (60) examined the effect of one selected ECG abnormality on incident heart failure, and both QRS duration and ST depression were found to be associated with incident heart failure in their respective studies. Adjusting for age, sex and body mass index (BMI), systolic blood pressure, anti-hypertensive treatment, total high-density lipoprotein cholesterol, diabetes mellitus, smoking status, interim MI and valve disease, a QRS duration between 100 – 119 milliseconds (ms) and a QRS duration ≥ 120 ms were associated with incident heart failure in the Framingham Heart Study (FHS) (59) compared with a QRS duration < 100 ms: hazard ratios (HR) = 1.43 (95% confidence interval (CI) = 1.05, 1.96) and 1.74 (95% CI = 1.28, 2.35), respectively. In analyses with QRS duration in its continuous form, heart failure incidence increased with longer QRS durations in age- and sex-specific models (HR = 1.27, 95% CI = 1.14, 1.41). Although the Strong Heart Study (SHS) was limited by a small number of heart failure events (N = 77), continuous (HR per 10 μV = 1.22, 95% CI = 1.13, 1.32) and categorical (10-24 μV HR = 1.79, 95% CI = 0.56, 5.71; -4-9 μV HR = 2.76, 95% CI = 0.91, 8.34; ≤ -5 μV HR = 5.55, 95% CI = 1.96, 15.74; versus ≥ 25 μV) measures of ST depression in leads V_5 and V_6 were shown to be associated with incident heart failure, adjusting for sex, age, diabetes, CHD and albuminuria (60). Although the categorical measure of ST depression showed a stepwise increasing risk for heart failure as ST depression values decreased, the confidence

intervals were imprecise and should be interpreted with caution. Dhingra and colleagues (59) and Okin and colleagues (60) did not adjust for other ECG variables in the SHS and the FHS, and thus it is difficult to assert that either QRS duration or ST depression predict, independently of other ECG variables, new-onset heart failure. Although, Okin and colleagues recognized the need to control for left ventricular mass (LVM), they did not adjust for Cornell voltage, since it was not found to be a significant predictor of new-onset heart failure in the SHS (60).

Results from the Women's Health Initiative (WHI) Study by Rautaharju and colleagues (61) corroborated the association found between ST depression and new-onset heart failure in the SHS (60). Rautaharju and colleagues (61) found that ST depression in lead V_5 was associated with incident heart failure when the lowest decile (≤ 0 μV) was compared with all other deciles (>0 μV) (HR = 2.11, 95% CI =1.62, 2.52), adjusting for age, ethnicity, systolic blood pressure, BMI, smoking status, hormone therapy use, cholesterol-lowering drugs, diabetes status, use of cardioactive drugs. This association remained, although attenuated (HR = 1.49, 95% CI = 1.17, 1.89), when multiple ECG variables were added to the model, including QRS/T angle, T net amplitude in lead V_1, $QRS_{\text{non-dipolar voltage}}$ ($_{\text{ndpv}}$), QT interval and heart rate variability. All ECG variables under study, QRS/T angle, MI, ST depression, T net amplitude, QRS_{ndpv}, T net amplitude in lead V_5, ST gradient in lead V_5, QT interval, Cornell voltage, T wave roundness index, heart rate variability and T_{ndpv}, were associated with incident heart failure in the WHI (61). It is important to note that only the lowest decile, and not the highest, for T net amplitude in lead V_5, and the highest decile, not the lowest, for T net amplitude in lead V_1, were significantly associated with new-onset heart failure when compared with the

middle deciles collectively. Strengths of this study conducted by Rautaharju and colleagues in the WHI (61) include the evaluation of multiple ECG variables, the additional evaluation of multivariable-adjusted multiple ECG variable models and the use of a large, population-based study. However, this study was limited to women.

Comparable to Dhingra and colleagues (59) and Okin and colleagues (60) in the FHS and the SHS, Rautaharju and colleagues (62) evaluated ST depression and QRS interval in the Atherosclerosis Risk in Communities (ARIC) Study. Similar to results found in the SHS (60) and the WHI (61), Rautaharju and colleagues (62) found that ST depression in lead V_5 in men (HR = 2.11, 95% CI = 1.58, 2.82) and in women (HR = 1.38, 95% CI = 1.01, 1.88), was associated with incident heart failure when the lowest decile (≤ 5 μV in men and ≤ -7 μV in women) was the inference group, adjusting for age, ethnicity, systolic blood pressure, BMI, smoking status, hormone therapy use, cholesterol-lowering drugs, diabetes status, use of cardioactive drugs. With the additional adjustment of multiple ECGs, MI, LVM, QRS/T angle, ST amplitude in lead V_5, QT interval, heart rate, QRS_{ndpv} and T net amplitude in lead V_1, the association remained in men (HR = 1.57, 95% CI = 1.16, 2.06) but not in women (HR = 1.05, 95% CI = 0.77, 1.44). In contrast to Dhingra and colleagues (59), Rautaharju and colleagues (62) were unable to observe a significant association between QRS interval and incident heart failure in additional analyses conducted in the ARIC Study (results not presented).

Many of the ECG variables analyzed in the ARIC Study and the WHI by Rautaharju and colleagues were comparable (61, 63). In multivariable-adjusted single-ECG models, QRS/T angle, ST depression, QRS_{ndpv}, T net amplitude in lead V_1, and Cornell voltage were significantly associated with incident heart failure in the WHI

participants and in women in the ARIC Study (61, 62). Conversely, MI, QT interval and T net amplitude in lead V_5 were not associated with new-onset heart failure in women in the ARIC Study (62), whereas associations were observed between these ECG variables and incident heart failure in women in the WHI (61). In addition to the ECG variables listed above, heart rate and Cornell product were also associated with new-onset heart failure in women in the ARIC Study (62). With the exception of QRS_{ndpv}, all ECG variables entered into multivariable-adjusted single ECG models, MI, LVM, QRS/T angle, ST depression, QT interval, heart rate, T net amplitude in lead V_1, Cornell product, Cornell voltage and T net amplitude in lead V_5, were associated with incident heart failure in men in the ARIC Study (62).

There were notable differences between ECG abnormality and incident heart failure associations observed in the WHI and the ARIC Study when multivariable-adjusted multiple ECG models were used. T amplitude in lead V_1 was significantly associated with incident heart failure in the WHI Study (HR = 1.56, 95% CI = 1.19, 2.05) (61), however, it was not associated with new-onset heart failure in the ARIC Study in both men (HR = 1.21, 95% CI = 0.89, 1.67) and in women (HR = 1.12, 95% CI = 0.89, 1.51) (62). Although QRS_{ndpv} and QRS/T angle were associated with incident heart failure in both the WHI (61) and in women in the ARIC Study (62), MI, ST depression, and QT interval were associated with new-onset heart failure in the WHI and not in the ARIC Study. In addition to the ECG variables listed above, heart rate was also associated with new-onset heart failure in women in the ARIC Study (62). In men in the ARIC Study, all ECG variables, MI, LVM, QRS/T angle, ST depression, QT interval,

and heart rate, with the exception of QRS_{ndpv}, were additionally associated with incident heart failure (62).

The analysis of the effect of ECG abnormalities on the incidence of heart failure in the ARIC Study (62) extends previous studies (59-61) by examining multiple ECG variables by sex. However, varying cut points for ECG measures made comparisons problematic between the studies. For example, in the WHI Study for both T net amplitude in lead V_5 and T net amplitude in lead V_1, the highest and the lowest deciles were inference groups and the remaining deciles were collectively the referent group, whereas in the ARIC Study the lowest decile ($\leq$ 122 μV for men and $\leq$ 107 μV for women) and the highest decile ($\geq$ 307 μV for men and $\geq$ 151 μV for women) for T net amplitude in lead V_1 was the inference group, and "other deciles" was the comparison group.

While these previous studies (59-62) contribute to our understanding of the effects of ECG variables, based on a single measurement, on the incidence of heart failure, these studies use different populations, definitions of heart failure (see Table 1), cut points and inference groups for ECG variables (detailed in the next section). Furthermore, the accuracy of the ECG measures is not well documented in these studies. Sources of error in measurements of ECG variables within a person include within-person biological and methodological variability, which includes variability in placement of electrodes and the precision of the ECG record readings (64). If measurement variability is high (low repeatability), then the ECG variable is likely to have bias associated with its estimate of effect on incident heart failure (65). Despite these limitations, the relationship between select ECG variables and incident heart failure has

been demonstrated in persons with and without cardiovascular disease (CVD) (59, 61, 62, 66), and remains relatively robust after adjustment of clinical and demographic factors and other ECG measures, leading to the hypothesis that there is an independent association between ECG variables and incident heart failure. The mechanisms linking these ECG variables with incident heart failure are unclear. It has been posited that the ECG measures studied may be markers of ventricular remodeling and evolving CHD (59-62), an interpretation that would benefit from consideration of repeat measures of these ECG parameters.

Table 1. Summary of 4 prospective studies examining the relationship between ECG abnormalities and incident heart failure

Author (year)	Study	Study population	Mean follow-up (years)	Incident heart failure	Measure of incident heart failure	ECG variables, estimate (95% confidence interval)
Dhingra (2006)[59]	FHS	Men and women, aged 28-62 years	12.7	324	Framingham criteria and a review of medical records by 3 experienced investigators	QRS duration vs. <100 ms; 100-119 ms: 1.4 (1.1, 2.0); ≥ 120 ms: 1.7 (1.3, 2.4)
Okin (2007)[60]	SHS	American Indian men and women aged 35-74 years	5.7	77	Framingham criteria, a review of medical records	ST depression (per 10 μV): 1.31 (1.24, 1.39) ST amplitude vs. ≥25μV; 10-24 μV: 1.79 (0.56, 5.71); -4-9 μV: 2.76 (0.91, 8.34); ≤-5 μV: 5.55 (1.96, 15.74)
Rautaharju (2006)[61]	WHI	Women, aged 50-79 years	6.2	375	Active follow-up for hospitalized heart failure requiring medical treatment, and a review of medical records	Old MI (Novacode 5.1-5.4) vs. no; yes: 2.0 (1.5, 2.6) QRS/T angle vs. 0-56°; 57-96°: 1.9 (1.4, 2.5); ≥97°: 2.7 (2.1, 3.6) ST depression vs. > 0μV; ≤ 0μV: 2.1 (1.6, 2.5) TV_1 amplitude vs. -41-80μV; <-41μV: 1.1 (0.8,1.5); >80μV: 2.2 (1.7,2.8) QRS_{ndpv} vs. < 65μV; ≥ 65μV: 2.0 (1.5, 2.7) TV_5 amplitude vs. 73-235 μV; <73μV: 1.9 (1.5, 2.4); >235μV: 0.9 (0.5, 1.4) STV_5 gradient vs. ≥3 μV; <3μV: 1.7 (1.3, 2.3) QT interval vs. <437 ms; ≥ 437 ms: 1.8 (1.4, 2.3) Cornell voltage vs. <1800 μV; ≥ 1800 μV: 1.6 (1.3, 2.1) T wave roundness index vs <31%; 31-57%: 1.3 (1.1, 1.7); >57%: 1.6 (1.2, 2.2) Heart rate variability vs. 8-44ms; <8ms:1.3 (1.0, 1.7); >44ms: 1.5 (1.2, 2.0) T_{ndpv} vs. <13μV; ≥13μV: 1.3 (1.0, 1.8)
Rautaharju (2007)[62]	ARIC	Men and women, aged 45-64	14.0	951	ICD-9-CM code 428 or death certificate with ICD-9 code 428 or ICD-10 code 150	Note: reference groups are 'no MI' or 'other deciles' collectively Old MI (Novacode 5.1-5.4); M: 3.1 (1.9, 5.0); W: 1.8 (0.9, 3.7) LVM (M: ≥ 204 g; W: ≥ 162 g); M: 2.4 (1.7, 3.3); W: 1.3 (1.0, 1.9) QRS/T_{simple} angle (M: ≥ 107°; W: ≥ 89°); M: 1.7 (1.2, 2.3); W: 1.9 (1.4, 2.5) QRS/T_{xyz} angle (M: ≥ 110°; W: ≥ 94°); M: 2.0 (1.5, 2.7); W: 2.3 (1.6, 2.8) ST depression (M: <5μV; W: <-7μV); M: 2.1 (1.6, 2.8; W: 1.4 (1.0, 1.9) QT interval (M: > 436ms; W: > 442ms); M: 2.1 (1.6, 2.8); W: 1.1 (0.8, 1.5) Heart rate (M: > 77 cnts/min; W: 79 cnts/min); M: 1.9 (1.4, 2.6); W:1.7 (1.3, 2.3) QRS_{ndpv} (M: ≥ 81μV; W: ≥ 63μV); M: 1.4 (0.9, 2.0); W: 2.1 (1.6, 2.9) TV_1 amplitude (M: ≥ 307μV; W: ≥ 151μV); M: 1.8 (1.3, 2.4); W: 1.6 (1.2, 2.1) Cornell product (M: ≥ 207μV/s; W: ≥ 152μV/s); M: 1.7(1.2,2.3); W:1.6(1.2, 2.2) Cornell voltage (M: ≥ 2650μV; W: ≥ 1673μV); 1.6 (1.1, 2.2); W: 1.5 (1.1, 2.0) TV_5 amplitude (M: < 122μV; W: <107μV); M: 1.8 (1.3, 2.4);W: 1.3 (1.0, 1.8)

Abbreviations: ECG, electrocardiogram; FHS, the Framingham Heart Study; ms, milli-seconds; WHI, Women's Health Initiative; MI, myocardial infarction; μV, microvolts; ndpv, non-dipolar voltage; SHS, Strong Heart Study; ARIC, the Atherosclerosis Risk in Communities Study; ICD, International Classification of Disease; LVM, left ventricular mass; g, gram; M, men; W, women; cnts/min, counts per minute; μV/s, microvolts per second.

1.4 ECG variables

ECG variables shown to be associated with incident heart failure in multivariable-adjusted single ECG models include (59-62) QRS/T angle, MI, ST depression, T net amplitudes in lead V_1 and V_5, QRS_{ndpv}, QT interval, Cornell voltage, QRS duration, LVM, Cornell product and heart rate. In addition, the following were found to be associated with incident heart failure in multivariable-adjusted multiple ECG models (61, 62): QRS/T angle, ST depression, T net amplitude in lead V_1, QRS_{ndpv}, QT interval, MI, LVM and heart rate. The following section provides a brief background of these ECG variables and details how they were defined in their respective studies.

In the analysis conducted by Rautaharju and colleagues in both the WHI and the ARIC Study (61, 62), the QRS/T_{xyz} angle was derived from the X, Y, and Z leads generated from a matrix transformation method. The X, Y, and Z leads refer to one system of spatial vectorcardiography, where the X, Y and Z leads are combined to form three loops: frontal, sagittal and horizontal (67). Vectorcardiography accounts for configuration of the loops in addition to measurement of amplitude and duration. Since the orthogonal X, Y and Z leads are not routinely recorded, they can be obtained from the matrix transformational method, where the mean X, Y and Z values in the QRS and T windows are calculated to obtain QRS and T vectors (68). The QRS/T angle is the spatial angle between the directions of ventricular depolarization and repolarization; greater angles reflect greater abnormalities in repolarization (69). The QRS/T angle has been shown to be positively associated with blood pressure, indicating that it may be a sensitive and early marker of the repolarization alterations in systemic hypertension (70).

Wide QRS/T angles have also been shown to be associated with LVH, bundle-branch block and ischemia (69).

The QRS/T_{simple} angle has been previously shown to detect a QRS/T_{xyz} angle with 88% sensitivity and 91% specificity, and thus may act as an appropriate substitute for the QRS/T_{xyz} angle (63). Rautaharju and colleagues developed a method for estimation of the QRS/T angle using the net QRS and T amplitudes in three standard leads for each (63). The QRS/T_{simple} angle is calculated as the inverse cosine between the mean QRS and T vectors, approximated by the three QRS and T net amplitudes for each vector (61). In the ARIC Study, net T wave amplitudes were calculated by adding signed T' from signed T in leads V_5, aVF and V_2, and net QRS amplitudes were calculated by subtracting the absolute value of S- or QS-waves in leads V_6, aVF and V_2 from the R wave (62).

In the WHI Study, Rautaharju and colleagues obtained T net amplitude by calculating mean and peak T wave values in lead V_5, whereas for T wave amplitude in V_1 only the mean value was used (61), however in the ARIC Study mean values for both T amplitude in leads V_5 and V_1 were used (62). The T wave represents the uncanceled potential differences of ventricular repolarization, and is slightly lower in women than in men (67). Conditions associated with tall T waves are hyperkalemia and intracranial hemorrhage (67).

Cornell voltage, Cornell product, and LVM, are measures of LVH. In both the WHI (61) and the ARIC Study (62), the Cornell voltage was determined by summing the R wave amplitude in the aVL lead, and the Q- or QS-wave amplitude in the V_3 lead (71). The Cornell product has a reported specificity of 95% and a sensitivity of 51% (72).

Although the sensitivity appears to be low, the sensitivity is still higher than for either QRS duration or Cornell voltage alone (72, 73). In the ARIC Study (62), the Cornell product was created by multiplying the Cornell voltage and the QRS duration. The ECG measures for LVM were derived in the ARIC Study using race- and sex-specific calculations (74). LVM is then regressed on Cornell voltage and body weight. An increase in LVM generates leftward and posterior QRS forces which are believed to result from an increase in the size or number of muscle fibers (67). Hypertension often leads to LVH through changes in heart structure (75), and as a result ventricular repolarization and depolarization abnormalities often occur. In fact, repolarization and depolarization abnormalities often precede overt LVH and may be evident on the ECG by changes in QRS/T angle (76). The mechanisms linking LVH to disease are not fully understood. However, hypertrophy results in increased demand for oxygen to the myocardial tissue, which can be decreased in the presence of atherosclerosis and lead to ischemia (77).

Measures of LVM have been shown to differ by sex, race and body mass. Important differences have been observed by sex (78, 79), with men having higher QRS voltages and longer QRS durations than women, and by race (71, 79-82), with blacks having higher QRS voltages than whites and whites having longer QRS durations than blacks. Furthermore, QRS amplitude is reduced in persons with a large body mass, and is believed to result from the increased distance between the precordial electrode and the heart (83). Consequently, persons with low body weight may be over-diagnosed and overweight persons may be under-diagnosed with LVH (83).

Rautaharju and colleagues in the ARIC Study (62), and similarly in the WHI Study (61), calculated the QT interval as sex- and race-specific and adjusted for heart rate as a linear function of the RR interval (84). QT as a linear function of the RR interval was calculated as QT interval – 0.185 x (RR interval – 1) + 0.06 for men and as QT interval – 0.185 x (RR interval – 1) for women (85). The QT interval represents the sum differences in ventricular repolarization and depolarization (67). In relatively healthy individuals, QT varies by sex, race and heart rate. Women tend to have longer QT intervals compared to men and higher heart rates (82, 86), and blacks tend to have shorter QT intervals than whites (82). It is believed that sex hormones play a role in cardiac repolarization, and thus prolong the QT interval in women (87). In addition, the QT interval varies over 24 hours and tends to be longer at night (88, 89). Marked QT lengthening (non-corrected QT interval > 125% of the average normal value) can be attributed to congenital or neurogenic causes, severe hypokalemia, fad diets, antiarrhythmic drugs, myocardial ischemia (67) and may be a marker of subclinical atherosclerosis (90). The causes for prolonged QT intervals are unknown, however cardiac ion channels (91) and autonomic neuropathy (92) involvement have been suggested.

The QRS_{ndpv} variable was also obtained in both the WHI and the ARIC Study (61, 62). Singular value decomposition was used to obtain the QRS_{ndpv} and represents the square root of the sum of the residual variance of the higher order components that are not contained in the X, Y, and Z components of the twelve-lead ECG signal (62). The higher order components (N = 8) are obtained from the matrix report of the Marquette-GE 12SL ECG. The Marquette GE contains 2 ms simultaneous samples of all twelve

ECG leads for one complete cycle per individual. Within the report, the window between the beginning and the end of the QRS complex and the voltage is used to obtain the square root of the total variance of the non-dipolar components. The first three terms are similar to the dipolar X, Y and Z components of an orthogonal lead system obtained from vectorcardiography. The total variance is the summation of the non-dipolar components 4 – 8 and the dipolar components 1 – 3.

A widely used set of criteria for ECG recognition of prior MI, the Novacode (93), provides cut points for separating normal from pathological Q waves. An MI, defined by Novacode criteria (5.1-5.4), was used in both the WHI and the ARIC Study (61, 62), however the prevalence is low in the ARIC Study (2.2% and 0.9% in men and women, respectively). The reasons why some persons have atypical or no symptoms are unknown. Various theories about possible mechanisms have been discussed (94). However, the process is likely to be similar to the processes involved with recognized MI, where an atherosclerotic plaque ruptures and occludes a thrombotic coronary artery. The difference between recognized and unrecognized MI is believed to lie in the interpretation of symptoms. A blunted perception of MI may result from a dysfunction with receptor and afferent neurons, cancellation of multiple stimuli in the thalamus and the dorsal horn of the spinal chord, a defect in the central nervous system and depression may play a role (94). Persons of older age (95), and female sex (96, 97) are at greater risk for undiagnosed MI.

In the FHS, Dhingra and colleagues recorded a twelve-lead configuration and X, Y, and Z orthogonal leads to measure QRS duration (59). QRS duration was defined using World Health Organization criteria for bundle branch block (98): left bundle branch

block was defined as a QRS duration of ≥ 120 ms; absent Q waves; wide-notched R waves in leads V_5 and V_6 present; presence of monophasic QS in leads V_1 and V_2; and absence of secondary R waves in lead V_1. Right bundle branch block was defined as QRS duration ≥ 120 ms; broad, notched R waves in leads V_1 and V_2; and wide, deep and notched S waves in V_5 and V_6. QRS segments that were ≥ 120 ms and did not meet the criteria for either left or right bundle branch block were categorized as indeterminate. Although the normal QRS interval is equal to or less than 0.10 seconds on a twelve-lead ECG, a QRS interval > 100 ms has been associated with reduced left ventricular ejection fraction (99). An increased QRS interval indicates a ventricular ectopic beat, toxic drug effects or severe hypokalemia in addition to bundle branch blocks (3). Lastly, the QRS duration is slightly longer in tall, large persons rather than short, small persons and in males than in females (67).

In the SHS, absolute ST segment deviation was measured at the midpoint of the ST segment on median complexes in leads V_5 and V_6 and the quartiles were based on the maximal magnitude of ST deviation in those leads (60), whereas in the ARIC Study, ST depression was measured using ST amplitude in lead V_5 at 60 ms past the end of the QRS interval (J-point) (62). Lead V_5 was chosen, since it has been shown to be sensitive to the detection of myocardial ischemia, particularly in exercise tests. In the WHI Study, Rautaharju and colleagues (61) defined ST depression as the ST segment (the interval from 20 ms past the J-point to the J-point plus 80 ms or the beginning of the T wave, whichever occurred later) mean value in lead V_5 negative or 0 μV. Eighty ms past the J-point is conventionally used in the clinical encounter (67). However, since this definition of the ST segment originated from exercise testing as a diagnostic test for myocardial

ischemia secondary to CHD, 60 ms was used by Rhautaharju and colleagues to obtain resting ECGs in large population-based studies (62, 100). Although some ST segment elevation has been observed in approximately 90% of normal individuals, any ST segment depression is considered abnormal (67). Ventricular action potentials overlap along the ST segment, as the beginning of the ST segment represents ventricular depolarization and the end involves rapid repolarization of the ventricles (67). Common causes of ST depression are tachycardia, delayed repolarization following slow depolarization resulting from bundle branch block or LVH among other entities, and myocardial ischemia (67).

Heart rate is measured by the twelve-lead ECG via RR intervals (62), and has been known to decrease with age. However, Spodnick and colleagues found that while heart rate decreased with age in men, it increased in women over a 30 year span (101). There are a multitude of factors responsible for variations in heart rate, including physical fitness, sex, temperature and altitude (67). The normal heart rate in adults ranges from 50 to 90 beats per minute (102). Bradycardia is attributed to increased vagal tone and hypothyroidism, hypothermia, hyperkalemia, myocardial ischemia and common drugs (e.g., β – blockers, digitalis and clonidine) have been implicated as potential causes (67). Precipitating conditions for tachycardia include hypotension, heart failure, anemia, hyperthyroidism and myocarditis and result from increased sympathetic activity (67). Sympathetic activity can also be increased with the use of β-adrenergic agonists and anticholinergenic agents, in addition to caffeinated beverages (67).

1.4.1 Coding ECG abnormalities

Many cardiac disorders alter the morphology of the ECG recording in a diagnostically useful way, and these abnormalities can be interpreted by classification systems such as the Minnesota (103) and Novacode (93). Both the Minnesota code and Novacode were developed to standardize the interpretation of ECGs and enhance repeatability, and both provide a clear advantage over visual reading because they are less prone to error (93, 104). As a result, the use of computer processed ECGs has become more frequent and is now the preferred methodology of ECG classification for large prospective studies. The Minnesota Code is a classification system for the ECG that utilizes a defined set of measurement rules to assign specific numerical codes according to the severity of the ECG findings. However, evaluation of serial changes of ECGs becomes much more complex, as the Minnesota Code requires side-by-side comparison of a referent and follow-up ECGs. Data from the Multiple Risk Factor Intervention Trial indicate that misclassification occurs up to 40 to 50% when new abnormalities are coded (105). The Novacode criteria were formulated to include ECG abnormalities not covered by Minnesota Code criteria and were designed to meet the needs of clinical trials (93). The Novacode coding sequence follows the traditional order of interpretation of ECGs in clinical settings (arrhythmic codes followed by antrio-ventricular conduction, ventricular conduction, prolonged repolarization codes and MI codes) (93). Moreover, the Novacode criteria were developed to ease the determination of serial ECG changes associated with pathology (93).

1.5 Short-term changes of ECG variables

Many epidemiologic studies have demonstrated that abnormalities in various resting, standard twelve-lead ECG measures and their changes over time are associated with subsequent cardiovascular morbidity and mortality (59-62, 69, 100, 106-109). However, the accuracy of the ECG measures is often not well documented in those studies. Sources of error in measurements of ECG variables within a person include within-person biological and methodological variability, which includes variability in placement of electrodes and the precision of the ECG record readings (64). If measurement variability is high (low repeatability), then the ECG variable is likely to have bias associated with its estimate of effect on cardiovascular outcomes (65).

The ECG Repeatability Study was conducted in 2001 to estimate the 2-minute and 1-week repeatability of ECG measures in 63 participants, ages 45-64 years (85, 110). Two previous reports (85, 110) from the ECG Repeatability Study quantified the short-term repeatability of T wave axis, QT interval, heart rate and heart rate variability using the standard twelve-lead ECG (Table 2). Vaidean and colleagues (85) investigated spatial T wave axis and QT interval. The intraclass correlation (ICC) coefficients for the T wave axis and heart rate were 0.87 (95% CI: 0.81, 0.93) and 0.82 (95% CI: 0.75, 0.90), respectively, and for QT interval-based indices, ICC coefficients were greater than 0.60. Schroeder and colleagues (110) found that for 10-second recordings, ICC coefficients for mean heart rate and RR interval were greater than 0.80, whereas ICC coefficients for standard deviation of all RR intervals (SDNN) and root mean square of differences in RR intervals (rMSSD), ranged from 0.41 to 0.57.

To our knowledge, the short-term measurement variability of spatial QRS/T angle, Cornell voltage, Cornell product, LVM, T net amplitudes in leads V_1 and V_5, and ST depression as derived from the twelve-lead ECG has yet to be investigated in the ECG Repeatability Study. Past and future studies can benefit from the estimation of short-term repeatability of these ECG measures, since this would enable consideration in measurement protocols and statistical adjustment for variability (111).

Table 2. Summary of 2 studies examining the short-term repeatability of ECG variables in the ECG Repeatability Study

Author (year)	Study	Study population	ECG variables, intraclass correlation coefficient (95% confidence interval)			
Schroeder (2004)[110]	ECGRS	Men and women, aged 45-64 years		10-second	2-minute	6-minute
			HR	0.80 (0.72-0.88)	0.89 (0.85-0.94)	0.90 (0.85-0.94)
			RR	0.85 (0.78-0.91)	0.92 (0.89-0.96)	0.93 (0.90-0.96)
			SDNN	0.41 (0.22-0.59)	0.86 (0.80-0.91)	0.87 (0.81-0.92)
			rMSSD	0.47 (0.30-0.63)	0.91 (0.87-0.95)	0.91 (0.87-0.95)
			HF	.	0.89 (0.86-0.93)	0.85 (0.79-0.91)
			LF	.	0.72 (0.65-0.80)	0.83 (0.77-0.89)
			Hfnu	.	0.60 (0.48-0.73)	0.76 (0.68-0.85)
			Lfnu	.	0.60 (0.48-0.73)	0.76 (0.68-0.85)
			ln HR	0.82 (0.75-0.90)	0.91 (0.87-0.95)	0.92 (0.88-0.95)
			ln RR	0.82 (0.75-0.90)	0.91 (0.87-0.95)	0.92 (0.88-0.95)
			ln SDNN	0.46 (0.31-0.62)	0.70 (0.59-0.80)	0.73 (0.63-0.83)
			ln rMSSD	0.57 (0.43-0.70)	0.82 (0.75-0.89)	0.84 (0.78-0.91)
			ln HF	.	0.69 (0.59-0.79)	0.82 (0.75-0.89)
			ln LF	.	0.55 (0.42-0.68)	0.78 (0.70-0.86)
			ln HFnu	.	0.50 (0.35-0.64)	0.76 (0.68-0.84)
			ln LFnu	.	0.68 (0.58-0.78)	0.73 (0.63-0.83)
Vaidean (2005)[85]	ECGRS	Men and women, aged 45-64 years	T wave axis: 0.87 (0.81, 0.93)			
			QT interval: 0.86 (0.81, 0.92)			
			Bazett heart rate-corrected QT interval: 0.69 (0.59,0.80)			
			Fridericia heart rate-corrected QT interval: 0.73 (0.63, 0.83)			
			QT prolongation index: 0.74 (0.65, 0.83)			
			QT as a linear function of the RR interval: M: 0.92 (0.88, 0.97); W: 0.62 (0.41, 0.83)			
			Heart rate: 0.82 (0.75, 0.90)			

Abbreviations: ECG, electrocardiogram; ECGRS, the Electrocardiogram Repeatability Study; HF, high frequency power; HFnu, normalized high frequency power; HR,mean heart rate; LF, low frequency power; LFnu, normalized low frequency power; rMSSD, root mean square of successive differences in normal-to-normal RR intervals; RR, mean RR interval; SDNN, standard deviation of all normal-to-normal RR intervals.

1.6 Long-term changes of ECG variables

Epidemiologic studies have demonstrated that the changes of abnormalities in various resting, standard twelve-lead ECG measures are associated with subsequent cardiovascular morbidity and mortality (112-115). However, little is known about the long-term changes in ECG measures in groups defined by demographic characteristics, cardiovascular risk or morbidity. This information may aid risk stratification in clinical encounters and assist researchers in characterizing the role of ECG measurements on incident cardiovascular morbidity and mortality.

Despite the important role of the temporal evolution in ECG variables in the context of clinical and demographic risk factors for cardiovascular morbidity and mortality, little prospective research has addressed these associations (113, 116-121) (Table 3). A previous study conducted by Levy and colleagues presented categorical changes of R wave and S wave voltages and repolarization abnormalities by sex in participants with LVH in the FHS (113). Although it would appear that there were no sex-differences in ECG voltages and repolarization abnormalities, no statistical test was performed. An additional limitation of this study was the selection of participants with LVH. Thus results can only be generalized to comparable high-risk populations. In this study, change was defined categorically in two different ways: 1) Participants were classified into one of four quartiles at baseline according to the sum of the R wave in aVL and the S wave in lead V_3. Change (decreased, increased or no change) was defined as moving from one quartile to another during follow-up. 2) At baseline a blinded reviewer of ECGs categorized repolarization as normal, mildly abnormal (ST-T flattening, isolated ST depression, or T wave inversion) or severely abnormal (ST depression in association

with inverted or biphasic T waves). Change (improved, worsened or no change) was defined as moving from one classification to another over follow-up.

Okin and colleagues showed in patients in the Losartan Intervention For Endpoint (LIFE) Reduction in Hypertension Study, that Cornell product and Sokolow-Lyon voltage decreased to a greater degree in men than in women (117, 118), in non-diabetics than in diabetics (116, 117), and in participants < 65 years compared to those ≥ 65 years of age (117). However, patients in the LIFE Study were selected based on moderate-to-severe hypertension and elevated Cornell product and Sokolow-Lyon voltages, and some patients were receiving anti-hypertensive medication, and therefore results cannot be generalized to healthier populations. Change was defined as the difference in baseline values of Cornell product and Sokolow-Lyon voltages and subsequent visits (116-118).

To the authors' knowledge, only three studies have evaluated the long-term changes of ECG measures in relatively healthy persons (119-121). Tasaki and colleagues showed that heart rate in 15 elderly Japanese persons increased over a time span of 15 years, while some measures of heart rate variability decreased with age (121). However, this study was limited by small numbers. Change was defined as the difference between baseline and the follow-up visit 15 years later. Lastly, Schroeder and colleagues evaluated measures of heart rate variability by diabetes (119) and hypertension (120) status in the ARIC Study over a mean of 9 years and concluded that there were no differences in the rate of change in heart rate variability by these conditions. Change was defined as heart rate variability at follow-up minus heart rate variability at baseline divided by the number of years between baseline and follow-up.

Previous studies have several strengths. First, Okin and colleagues described the long term changes of ECG measures of LVH (Cornell product and Sokolow-Lyon voltage) in the LIFE Study, by various CVD risk factors, including age, sex, and diabetes status (116-118). Tasaki and colleagues'(121) results of increasing heart rate and decreasing heart rate variability over a time span of 15 years corroborated cross-sectional results of age-related differences in heart rate and heart rate variability reported in previous studies (122, 123). Although Levy and colleagues primary objective was to examine the effect of changes of ECG measures on CVD, we appreciate their presentation of descriptive results of the long-term changes of ECG measures by sex in the FHS (113). Schroeder and colleagues (119, 120) described the longitudinal changes of heart rate variability in a large population-based cohort by diabetes, fasting glucose, insulin resistance, treated and untreated hypertension status, while controlling for multiple covariates, such as age, sex, race, study center, hypertension or diabetes status, smoking, education, BMI, and baseline heart rate variability and correcting for measurement error in continuous baseline measurements.

The descriptive epidemiology of the ECG measures in these studies has several limitations: Okin and colleagues (116-118) and Levy and colleagues (113) described the changes of ECG measures in participants with LVH at baseline; additionally, persons in the LIFE Study were treated for hypertension during the course of the clinical trial; and results are limited to ECG measures of LVH and heart rate variability. As a result of these limitations, it is difficult to make definite conclusions about the long-term changes of various ECG measures in a relatively healthy population, and to our knowledge, no work has focused on the descriptive epidemiology of the long-term changes of a wide

array of ECG variables in relatively healthy population-based studies, taking into account clinical risk factors for CVD morbidity and mortality.

Table 3. Summary of 7 prospective studies examining the long-term changes of ECG variables by clinical and demographic risk factors for heart failure

Author (year)	Study	Study population	ECG variable	ECG change variable, clinical/demographic factor(s), means (SD if available or confidence interval), N (%) odds ratio (95% confidence interval)
Levy (1994) [113]	FHS	Men and women, aged 28-62 years	R wave and S wave voltage, R wave amplitude in lead aVL, S wave amplitude in lead V_3	Change to another quartile: Decreased: Men (M), 242 (21%); women (W), 193 (21%) No change: M, 638 (56%); W, 537 (59%) Increased: M, 258 (23%); W, 184 (20%) Change in repolarization status: Improved (severely abnormal to mildly abnormal or mildly abnormal to normal): M 104 (10%); W, 90 (11%) No change: M 850 (77%), W, 638 (75%) Worsened (normal to mildly abnormal or mildly abnormal to severely abnormal): M 143 (13%); W,125 (14%)
Okin (2008) [118]	LIFE	Men and women, aged 55-80 years with hypertension and left ventricular hypertrophy	Cornell product, Sokolow-Lyon voltage	Reduction in Cornell product ≥ 236mm/ms: Month 6: M, -146 (631); W,-101 (613) Year 1: M, -202 (690); W,-140 (677) Year 2: M, -266 (731); W,-205 (706) Year 3: M, -282 (756); W,-190 (726) Year 4: M, -281 (815); W,-175 (753) Year 5: M, -305 (814); W,-182 (771) Last: M, -251 (890); W,-149 (823) Reduction in Sokolow-Lyon voltage ≥3.5mm: Month 6: M, -1.8; W,-1.3 Year 1: M, -2.5; W,-1.8 Year 2: M, -3.5; W,-2.4 Year 3: M, -4.0; W,-2.8 Year 4: M, -4.6; W,-3.2 Year 5: M, -5.1; W,-3.4 Last: M, -4.8; W,-3.0 Crude odds ratio (women vs. men): Odds that Cornell product decrease is - 236mm/ms or more: 0.76 (0.70, 0.83) Odds that Sokolow-Lyon voltage decrease is -3.5mm or more: 0.69 (0.64, 0.75) Adjusted odds ratio (women vs. men): Odds that Cornell product decrease is - 236mm/ms or more: 0.68 (0.61, 0.76)

				Odds that Sokolow-Lyon voltage decrease is -3.5mm or more: 0.85 (0.77, 0.95)
Okin (2006) [116]	LIFE	Men and women, aged 55-80 years with hypertension and left ventricular hypertrophy	Cornell product	<u>Change in Cornell product vs. baseline (mm/ms), diabetes:</u> Month 6: -100 (580) Year 1: -126 (687) Year 2: -183 (658) Year 3: -156 (759) Year 4: -162 (820) Year 5: -174 (764) Last: -138 (866) <u>Change in Cornell product vs. baseline (mm/ms), no diabetes:</u> Month 6: -125 (628) Year 1: -174 (683) Year 2: -240 (726) Year 3: -242 (737) Year 4: -231 (778) Year 5: -245 (797) Last: -205 (866)
Okin (2003) [117]	LIFE	Men and women, aged 55-80 years with hypertension and left ventricular hypertrophy	Cornell product, Sokolow-Lyon voltage	<u>Change in Cornell product (difference between last and baseline visit):</u> Female: Losartan group, -249; Atenolol group-66 Male: Losartan group, -338; Atenolol group -192 Diabetes: Losartan group, -245; Atenolol group -17 No diabetes: Losartan group, -296; Atenolol group -140 < 65 years: Losartan group, -313; Atenolol group -195 ≥ 65 years: Losartan group, -275; Atenolol group -78 White: Losartan group, -296; Atenolol group -126 Other ethnicity: Losartan group, -213; Atenolol group -82 <u>Change in Sokolow-Lyon voltage (difference between last and baseline visit):</u> Female: Losartan group, -3.8; Atenolol group -2.1 Male: Losartan group, -5.5; Atenolol group -3.5 Diabetes: Losartan group, -3.9; Atenolol group -1.6 No diabetes: Losartan group, -4.7; Atenolol group -2.9 < 65 years: Losartan group, -4.9; Atenolol group -3.4 ≥ 65 years: Losartan group, -4.4; Atenolol group -2.3 White: Losartan group, -4.5; Atenolol group -2.7 Other ethnicity: Losartan group, -5.7; Atenolol group -3.7

Schroeder (2003) [120]	ARIC	Men and women, aged 45-64	Heart rate and heart rate variability	Normotensives, mean annual decrease (ms/y): SDNN: 0.71 (0.66, 0.77) rMSSD: 0.42 (0.36, 0.48) RR interval: 5.92 (5.53, 6.31) Hypertensives, mean annual decrease (ms/y): SDNN: 0.63 (0.54, 0.72) rMSSD: 0.33 (0.23, 0.43) RR interval: 6.65 (6.01, 7.28) Treated hypertensives, mean annual decrease (ms/y): SDNN: 0.60 (0.50, 0.71) rMSSD: 0.39 (0.27, 0.50) RR interval: 5.93 (5.19, 6.67) Untreated hypertensives, mean annual decrease (ms/y): SDNN: 0.68 (0.52, 0.85) rMSSD: 0.19 (0.01, 0.37) RR interval: 8.53 (7.36, 9.70) Normotensives, mean annual decrease, adjusted for baseline (ms/y): SDNN: 0.67 (0.62, 0.71) rMSSD: 0.39 (0.34, 0.44) RR interval: 5.97 (5.62, 6.33) Hypertensives, mean annual decrease, adjusted for baseline (ms/y): SDNN: 0.74 (0.67, 0.81) rMSSD: 0.40 (0.33, 0.48) RR interval: 6.52 (5.94, 7.10) Treated hypertensives, mean annual decrease, adjusted for baseline (ms/y): SDNN: 0.73 (0.65, 0.80) rMSSD: 0.40 (0.31, 0.49) RR interval: 6.37 (5.70, 7.05) Untreated hypertensives, mean annual decrease, adjusted for baseline (ms/y): SDNN: 0.78 (0.66, 0.91) rMSSD: 0.42 (0.27, 0.56) RR interval: 6.91 (5.83, 8.00) Note: significantly different than normotensives at the 0.05 *p*-level

Schroeder (2005) [119]	ARIC	Men and women, aged 45-64	Heart rate and heart rate variability	NFG, mean annual decrease (ms/y): SDNN: -0.69 (-0.75, -0.62) rMSSD: -0.39 (-0.46, -0.32) RR interval: 6.24 (5.79, 6.68) IFG, mean annual decrease (ms/y): SDNN: -0.67 (-0.75, -0.58) rMSSD: -0.32 (-0.41, -0.24) RR interval: 7.09 (6.52, 7.65) Note: significantly different than NFG group at the 0.05 *p*-level Diabetes, mean annual decrease (ms/y): SDNN: -0.74 (-0.92, -0.56) rMSSD: -0.46 (-0.65, -0.26) RR interval: 5.49 (4.24, 6.74) NFG, mean annual decrease, adjusted for baseline (ms/y): SDNN: -0.66 (-0.71, -0.61) rMSSD: -0.36 (-0.41, -0.30) RR interval: 6.74 (6.33, 7.16) IFG, mean annual decrease, adjusted for baseline (ms/y): SDNN: -0.66 (-0.72, -0.60) rMSSD: -0.34 (-0.41, -0.27) RR interval: 6.61 (6.09, 7.13) Diabetes, mean annual decrease, adjusted for baseline (ms/y): SDNN: -0.95 (-1.08, -0.81) rMSSD: -0.66 (-0.82, -0.50) Note: significantly different than NFG group at the 0.05 *p*-level RR interval: 3.88 (2.72, 5.04) Note: significantly different than NFG group at the 0.05 *p*-level Hyperinsulinemia absent, mean annual decrease (ms/y): SDNN: -0.72 (-0.78, -0.67) rMSSD: -0.42 (-0.47, -0.36) RR interval: 6.35 (5.97, 6.73) Hyperinsulinemia present, mean annual decrease (ms/y): SDNN: -0.44 (-0.58, -0.30) Note: significantly different than the hyperinsulinemia present group at the 0.05 *p*-level rMSSD: -0.11 (-0.26, -0.04) Note: significantly different than the hyperinsulinemia present group at the 0.05 *p*-level RR interval: 8.12 (7.15, 9.10) Note: significantly different than the hyperinsulinemia present

				group at the 0.05 *p*-level <u>Hyperinsulinemia absent,</u> mean annual decrease, adjusted for baseline (ms/y): SDNN: -0.69 (-0.73, -0.65) rMSSD:-0.39 (-0.43, -0.34) RR interval: 6.58 (6.23, 6.93) <u>Hyperinsulinemia present,</u> mean annual decrease, adjusted for baseline (ms/y): SDNN: -0.62 (-0.73, -0.52) rMSSD: -0.28 (-0.40, -0.16) RR interval: 6.78 (5.87, 7.69)
Tasaki (2000) [121]	N=15	Healthy, elderly men and women aged 79-95 years	Heart rate and heart rate variability	<u>Heart rate:</u> Mean values of minimal heart rate (bpm) at baseline and 15 years later (follow-up): Nighttime: baseline 49.2 (5.4); follow-up 55.3 (8.2) (p=0.0018) Daytime: baseline 59.6 (9.1); follow-up 64.1 (9.1) (p=0.0048) Mean values of maximal heart rate (bpm) at baseline and 15 years later: Nighttime: baseline 67.7 (6.6); follow-up 73.8 (11.7) (p=0.0099) Daytime: baseline 86.0 (11.3); follow-up 92.4 (15.6) (p=0.0114) Mean values of average heart rate (bpm) at baseline and 15 years later: Nighttime: baseline 53.6 (5.6); follow-up 59.5 (9.7) (p=0.0054) Daytime: baseline 67.8 (9.8); follow-up 72.5 (9.9) (p=0.0119) <u>Heart rate variability:</u> Mean values of SDNN index (ms) at baseline and 15 years later: Nighttime: baseline 53 (16); follow-up 45 (13) (p=0.0086) Daytime: baseline 53 (19); follow-up 44 (14) (p=0.0574) Mean values of NN50 index (per hour) at baseline and 15 years later: Nighttime: baseline 39.7 (35.1); follow-up 50.1 (55.9) (p=0.2393) Daytime: baseline 22.9 (17.0); follow-up 44.5 (41.7) (p=0.0425) Mean values of the low frequency component (ms^2) at baseline and 15 years later: Nighttime: baseline 339.26 (290.63); follow-up 222.49 (213.52) (p=0.0151) Daytime: baseline 246.76 (170.54); follow-up 145.19 (112.10) (p=0.0032) Mean values of the high frequency component (ms^2) at baseline and 15 years later: Nighttime: baseline 296.76 (229.95); follow-up 407.15 (467.04) (p=0.1932) Daytime: baseline 171.63 (153.81); follow-up 196.33 (194.72) (p=0.3398)

	Mean values of the low frequency/high frequency component ratio at baseline and 15 years later: Nighttime: baseline 1.295 (0.665); follow-up 0.818 (0.531) (p=0.0270) Daytime: baseline 1.923 (0.910); follow-up 1.281 (0.951) (p=0.0371)

Abbreviations: ECG, electrocardiogram; FHS, Framingham Heart Study; M, men; W, women; SBP, systolic blood pressure; DBP, diastolic blood pressure; LIFE, Losartan Intervention For Endpoint reduction in hypertension study; mm, millimeters; RR interval, the mean normal-to-normal RR interval length; SDNN, the standard deviation of all normal-to-normal RR intervals; rMSSD, the root mean square of successive differences in normal-to-normal RR intervals; NFG, normal fasting glucose; IFG, impaired fasting glucose; ms, milliseconds; bpm, beats per minute; NN50, number of instances where the difference between adjacent normal RR intervals exceeds 50 ms.

1.7 Changes in ECG variables and incident heart failure

It has been demonstrated in large-population based studies that select ECG variables, either measured at one point in time (60-62) or entered in a model as a time-varying variable (59), are associated with incident heart failure. Although ECG variables have been known to vary over time due to biological and methodological variability (124), little work has focused on the effect of the long-term changes in these parameters on new-onset heart failure.

To the best of our knowledge, there are only two studies that have examined the association between changes in ECG variables and new-onset heart failure (Table 4), and the results are conflicting (66, 112). In the LIFE Study, Okin and colleagues found that both categorical and continuous measures of reduction of ECG-LVH, were associated with lower likelihood of new-onset heart failure over an average of 4.7 years of follow-up (66). Categorical and continuous measures of reduction in LVH were defined as a Cornell product LVH reduction $\geq$ 236 mm per ms compared with lesser reductions, and as an 817 mm per ms (1 standard deviation of the mean) lower Cornell product, respectively. In contrast, Fagard and colleagues found that change (ECG variable at last visit minus the baseline value), defined as a continuous measure of LVM (sum of 3 voltages, RaVL, SV_1 and RV_5), was not associated with incident heart failure in 4507 elderly patients (112).

Outcome assessment differed between the two studies: Okin and colleagues (66) defined heart failure as hospitalization based on clinical and diagnostic findings and requiring verification by a blinded committee, whereas Fagard and colleagues (112)

defined heart failure as fatal and non-fatal, regardless of hospitalization, and requiring verification by a blinded review committee. Adjustment covariates were diverse and varied by study: Okin and colleagues (66) adjusted for losartan versus atenolol treatment, age, sex, race/ethnicity, diabetes, history of ischemic heart disease, MI, stroke, peripheral artery disease, atrial fibrillation, smoking, albumin-creatinine ratio, serum glucose and creatinine levels, total and high-density lipoprotein cholesterol levels, BMI, Cornell product; baseline and in-treatment systolic and diastolic blood pressures; and baseline and changes of Sokolow-Lyon voltages, while Fagard and colleagues (112) adjusted for age, sex, BMI, smoking, systolic blood pressure, pulse rate, diabetes, previous antihypertensive treatment, cardiovascular complications at baseline and baseline ECG voltage.

Previous studies have several strengths. First, these studies were prospective, based on fairly large clinical trials, and patients had yearly updated ECGs. Second, it is important to note that while Fagard and colleagues (112) used a continuous variable for ECG change, Okin and colleagues (66) focused on change in ECG measures of LVH using both continuous and categorical variables. The use of continuous measures is important, since clinically meaningful changes can still occur within pre-specified categories. There are limitations to these two studies for the readers to consider. First, selection of patients in the LIFE Study was based on LVH, a Cornell product value greater than 2440 mm/msec or a Sokolow-Lyon voltage value of > 38 mm on a screening ECG before baseline, patients were hypertensive and some were receiving anti-hypertension medications, and thus results from this study can only be applied to comparable high-risk populations. Second, these studies did not document whether

measurement error in the ECG variables were accounted for when evaluating their association with incident heart failure. Failure to take intra-individual variation in ECG measures into account may result in substantial bias associated with its estimate of effect on heart failure incidence (65).

Although a few studies have assessed the impact of changes in ECG variables and incident heart failure in clinical trials consisting of high-risk populations (66, 112), there is no current information on whether the effect of changes in ECG variables are associated with incident heart failure in a relatively healthy, population-based cohort.

Table 4. Summary of 2 prospective studies examining the relationship between changes in ECG variables and incident heart failure

Author (year)	Study	Study population	Mean follow-up (years)	Incident heart failure	Measure of incident heart failure	Change in ECG variables, estimate (95% confidence interval)
Fagard (2004) [112]	SHE	Men and women, aged 60 years and older with systolic hypertension	5.1	209	Fatal and non-fatal requiring dyspnea, clinical signs and treatment	Change in left ventricular mass, a 1-mV higher value: Crude: 1.32 (1.16, 1.47) Adjusted: 1.26 (1.11, 1.43)
Okin (2007) [66]	LIFE	Men and women, aged 55-80 years with hypertension and left ventricular hypertrophy	4.7	214	Clinical and diagnostic findings, a review by blinded Endpoint Committee	Change in Cornell product: Crude, continuous, per 817 mm/msec decrease: 0.76 (0.68, 0.85) Adjusted, continuous, per 817 mm/msec decrease: 0.81 (0.74, 0.89) Crude, categorical, ≥ 236 mm/msec decrease: 0.57 (0.44, 0.76) Adjusted, categorical, ≥ 236 mm/msec decrease: 0.64 (0.47, 0.89)

Abbreviations: ECG, electrocardiogram; SHE, the Systolic Hypertension in Europe trial; LIFE, Losartan Intervention for Endpoint reduction in hypertension study.

1.8 References

1. Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, et al. Cardiac Structure and Ventricular-Vascular Function in Persons with Heart Failure and Preserved Ejection Fraction from Olmsted County, Minnesota. Circulation 2007;115:1982-90.

2. Stevenson LW, Perloff JK. The Limited Reliability of Physical Signs for Estimating Hemodynamics in Chronic Heart Failure. JAMA 1989;261:884-8.

3. Lilly L. Heart Failure. Pathophysiology of Heart Disease. Second ed. Baltimore, MD: Lippincott Williams & Wilkins; 1998, p. 193-231.

4. Fonseca C, Morais H, Mota T, Matias F, Costa C, Gouveia-Oliveira A, et al. The Diagnosis of Heart Failure in Primary Care: Value of Symptoms and Signs. Eur J Heart Fail 2004;6:795-800, 21-2.

5. Kim J, Jacobs DR, Jr., Luepker RV, Shahar E, Margolis KL, Becker MP. Prognostic Value of a Novel Classification Scheme for Heart Failure: The Minnesota Heart Failure Criteria. Am J Epidemiol 2006;164:184-93.

6. McKee PA, Castelli WP, McNamara PM, Kannel WB. The Natural History of Congestive Heart Failure: The Framingham Study. N Engl J Med 1971;285:1441-6.

7. Mosterd A. Heart Failure in the Population at Large; News from the Real World. Eur Heart J 1999;20:398-9.

8. Eriksson H, Caidahl K, Larsson B, Ohlson LO, Welin L, Wilhelmsen L, et al. Cardiac and Pulmonary Causes of Dyspnoea--Validation of a Scoring Test for Clinical-Epidemiological Use: The Study of Men Born in 1913. Eur Heart J 1987;8:1007-14.

9. Gheorghiade M, Beller GA. Effects of Discontinuing Maintenance Digoxin Therapy in Patients with Ischemic Heart Disease and Congestive Heart Failure in Sinus Rhythm. Am J Cardiol 1983;51:1243-50.

10. Carlson KJ, Lee DC, Goroll AH, Leahy M, Johnson RA. An Analysis of Physicians' Reasons for Prescribing Long-Term Digitalis Therapy in Outpatients. J Chronic Dis 1985;38:733-9.

11. Walma EP, Hoes AW, Prins A, Boukes FS, van der Does E. Withdrawing Long-Term Diuretic Therapy in the Elderly: A Study in General Practice in the Netherlands. Fam Med 1993;25:661-4.

12. Schocken DD. Epidemiology and Risk Factors for Heart Failure in the Elderly. Clin Geriatr Med 2000;16:407-18.

13. Guidelines for the Diagnosis of Heart Failure. The Task Force on Heart Failure of the European Society of Cardiology. Eur Heart J 1995;16:741-51.

14. Di Bari M, Pozzi C, Cavallini MC, Innocenti F, Baldereschi G, De Alfieri W, et al. The Diagnosis of Heart Failure in the Community. Comparative Validation of Four Sets of Criteria in Unselected Older Adults: The Icare Dicomano Study. J Am Coll Cardiol 2004;44:1601-8.

15. Mosterd A, Deckers JW, Hoes AW, Nederpel A, Smeets A, Linker DT, et al. Classification of Heart Failure in Population Based Research: An Assessment of Six Heart Failure Scores. Eur J Epidemiol 1997;13:491-502.

16. Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of Clinical Diagnosis of Heart Failure in Primary Health Care. Eur Heart J 1991;12:315-21.

17. Schellenbaum GD, Rea TD, Heckbert SR, Smith NL, Lumley T, Roger VL, et al. Survival Associated with Two Sets of Diagnostic Criteria for Congestive Heart Failure. Am J Epidemiol 2004;160:628-35.

18. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. Acc/Aha 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society. Circulation 2005;112:e154-235.

19. Hobbs FD, Korewicki J, Cleland JG, Eastaugh J, Freemantle N. The Diagnosis of Heart Failure in European Primary Care: The Improvement Programme Survey of Perception and Practice. Eur J Heart Fail 2005;7:768-79.

20. Sparrow N, Adlam D, Cowley A, Hampton JR. Difficulties of Introducing the National Service Framework for Heart Failure into General Practice in the Uk. Eur J Heart Fail 2003;5:355-61.

21. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, et al. Value of Natriuretic Peptides in Assessment of Patients with Possible New Heart Failure in Primary Care. Lancet 1997;350:1349-53.

22. Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE. Reliability of N-Terminal Pro-Brain Natriuretic Peptide Assay in Diagnosis of Heart Failure: Cohort Study in Representative and High Risk Community Populations. BMJ 2002;324:1498.

23. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid Measurement of B-Type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure. N Engl J Med 2002;347:161-7.

24. Baker DW. Prevention of Heart Failure. J Card Fail 2002;8:333-46.

25. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the Onset of Congestive Heart Failure in Framingham Heart Study Subjects. Circulation 1993;88:107-15.

26. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart Failure Incidence and Survival (from the Atherosclerosis Risk in Communities Study). Am J Cardiol 2008;101:1016-22.

27. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, et al. Congestive Heart Failure in the Community: A Study of All Incident Cases in Olmsted County, Minnesota, in 1991. Circulation 1998;98:2282-9.

28. Schellenbaum GD, Heckbert SR, Smith NL, Rea TD, Lumley T, Kitzman DW, et al. Congestive Heart Failure Incidence and Prognosis: Case Identification Using Central Adjudication Versus Hospital Discharge Diagnoses. Ann Epidemiol 2006;16:115-22.

29. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of Intensive Blood-Pressure Lowering and Low-Dose Aspirin in Patients with Hypertension: Principal Results of the Hypertension Optimal Treatment (Hot) Randomised Trial. Hot Study Group. Lancet 1998;351:1755-62.

30. Executive Summary: Hfsa 2006 Comprehensive Heart Failure Practice Guideline. J Card Fail 2006;12:10-38.

31. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction. N Engl J Med 2006;355:251-9.

32. Graves EJ, Owings MF. 1996 Summary: National Hospital Discharge Survey. Adv Data 1998:1-12.

33. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart Disease and Stroke Statistics--2008 Update: A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117:e25-146.

34. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart Disease and Stroke Statistics--2009 Update: A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:e21-181.

35. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-Term Trends in the Incidence of and Survival with Heart Failure. N Engl J Med 2002;347:1397-402.

36. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, et al. Trends in Heart Failure Incidence and Survival in a Community-Based Population. JAMA 2004;292:344-50.

37. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, et al. Congestive Heart Failure in the Community: Trends in Incidence and Survival in a 10-Year Period. Arch Intern Med 1999;159:29-34.

38. From AM, Leibson CL, Bursi F, Redfield MM, Weston SA, Jacobsen SJ, et al. Diabetes in Heart Failure: Prevalence and Impact on Outcome in the Population. Am J Med 2006;119:591-9.

39. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. The Euroheart Failure Survey Programme-- a Survey on the Quality of Care among Patients with Heart Failure in Europe. Part 1: Patient Characteristics and Diagnosis. Eur Heart J 2003;24:442-63.

40. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical Presentation, Management, and in-Hospital Outcomes of Patients Admitted with Acute Decompensated Heart Failure with Preserved Systolic Function: A Report from the Acute Decompensated Heart Failure National Registry (Adhere) Database. J Am Coll Cardiol 2006;47:76-84.

41. Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA, et al. Prevention of Heart Failure: A Scientific Statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. Circulation 2008;117:2544-65.

42. Armstrong PW, Moe GW. Medical Advances in the Treatment of Congestive Heart Failure. Circulation 1993;88:2941-52.

43. Baker DW, Jones R, Hodges J, Massie BM, Konstam MA, Rose EA. Management of Heart Failure. Iii. The Role of Revascularization in the Treatment of Patients with Moderate or Severe Left Ventricular Systolic Dysfunction. JAMA 1994;272:1528-34.

44. Ford ES, Williamson DF, Liu S. Weight Change and Diabetes Incidence: Findings from a National Cohort of Us Adults. Am J Epidemiol 1997;146:214-22.

45. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, et al. Diabetes Trends in the U.S.: 1990-1998. Diabetes Care 2000;23:1278-83.

46. Krumholz HM, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, et al. Readmission after Hospitalization for Congestive Heart Failure among Medicare Beneficiaries. Arch Intern Med 1997;157:99-104.

47. Kannel WB, D'Agostino RB, Silbershatz H, Belanger AJ, Wilson PW, Levy D. Profile for Estimating Risk of Heart Failure. Arch Intern Med 1999;159:1197-204.

48. Kannel WB, Belanger AJ. Epidemiology of Heart Failure. Am Heart J 1991;121:951-7.

49. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk Factors for Congestive Heart Failure in Us Men and Women: Nhanes I Epidemiologic Follow-up Study. Arch Intern Med 2001;161:996-1002.

50. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The Progression from Hypertension to Congestive Heart Failure. JAMA 1996;275:1557-62.

51. Kannel WB. Incidence and Epidemiology of Heart Failure. Heart Fail Rev 2000;5:167-73.

52. Chen YT, Vaccarino V, Williams CS, Butler J, Berkman LF, Krumholz HM. Risk Factors for Heart Failure in the Elderly: A Prospective Community-Based Study. Am J Med 1999;106:605-12.

53. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, et al. Obesity and the Risk of Heart Failure. N Engl J Med 2002;347:305-13.

54. Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased Pulse Pressure and Risk of Heart Failure in the Elderly. JAMA 1999;281:634-9.

55. Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, et al. Reduced Kidney Function as a Risk Factor for Incident Heart Failure: The Atherosclerosis Risk in Communities (Aric) Study. J Am Soc Nephrol 2007;18:1307-15.

56. Miller LW, Missov ED. Epidemiology of Heart Failure. Cardiol Clin 2001;19:547-55.

57. American Heart Association: Heart Disease and Stroke Statistics - 2009 Update. Dallas, TX: American Heart Association; 2008.

58. Arnold JM, Yusuf S, Young J, Mathew J, Johnstone D, Avezum A, et al. Prevention of Heart Failure in Patients in the Heart Outcomes Prevention Evaluation (Hope) Study. Circulation 2003;107:1284-90.

59. Dhingra R, Pencina MJ, Wang TJ, Nam BH, Benjamin EJ, Levy D, et al. Electrocardiographic Qrs Duration and the Risk of Congestive Heart Failure: The Framingham Heart Study. Hypertension 2006;47:861-7.

60. Okin PM, Roman MJ, Lee ET, Galloway JM, Best LG, Howard BV, et al. Usefulness of Quantitative Assessment of Electrocardiographic St Depression for Predicting New-Onset Heart Failure in American Indians (from the Strong Heart Study). Am J Cardiol 2007;100:94-8.

61. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic Predictors of Incident Congestive Heart Failure and All-Cause Mortality in Postmenopausal Women: The Women's Health Initiative. Circulation 2006;113:481-9.

62. Rautaharju PM, Prineas RJ, Wood J, Zhang ZM, Crow R, Heiss G. Electrocardiographic Predictors of New-Onset Heart Failure in Men and in Women Free of Coronary Heart Disease (from the Atherosclerosis in Communities [Aric] Study). Am J Cardiol 2007;100:1437-41.

63. Rautaharju PM, Prineas RJ, Zhang ZM. A Simple Procedure for Estimation of the Spatial Qrs/T Angle from the Standard 12-Lead Electrocardiogram. J Electrocardiol 2007;40:300-4.

64. Schijvenaars BJ, van Herpen G, Kors JA. Intraindividual Variability in Electrocardiograms. J Electrocardiol 2008;41:190-6.

65. Armstrong BA WE, Saracci R. Principled of Exposure Measurement in Epidemiology. New york: Oxford; 1992.

66. Okin PM, Devereux RB, Harris KE, Jern S, Kjeldsen SE, Julius S, et al. Regression of Electrocardiographic Left Ventricular Hypertrophy Is Associated with Less Hospitalization for Heart Failure in Hypertensive Patients. Ann Intern Med 2007;147:311-9.

67. Surawicz B KT. Chou's Electrocardiography in Clinical Practice. Fifth Edition ed. Philadelphia, PA: Saunders; 2001.

68. Edenbrandt L, Pahlm O. Vectorcardiogram Synthesized from a 12-Lead Ecg: Superiority of the Inverse Dower Matrix. J Electrocardiol 1988;21:361-7.

69. Triola B, Olson MB, Reis SE, Rautaharju P, Merz CN, Kelsey SF, et al. Electrocardiographic Predictors of Cardiovascular Outcome in Women: The National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (Wise) Study. J Am Coll Cardiol 2005;46:51-6.

70. Dilaveris P, Gialafos E, Pantazis A, Synetos A, Triposkiadis F, Gialafos J. The Spatial Qrs-T Angle as a Marker of Ventricular Repolarisation in Hypertension. J Hum Hypertens 2001;15:63-70.

71. Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, et al. Electrocardiographic Detection of Left Ventricular Hypertrophy: Development and Prospective Validation of Improved Criteria. J Am Coll Cardiol 1985;6:572-80.

72. Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic Detection of Left Ventricular Hypertrophy by the Simple Qrs Voltage-Duration Product. J Am Coll Cardiol 1992;20:1180-6.

73. Okin PM, Roman MJ, Devereux RB, Kligfield P. Electrocardiographic Identification of Increased Left Ventricular Mass by Simple Voltage-Duration Products. J Am Coll Cardiol 1995;25:417-23.

74. Rautaharju PM, Park LP, Gottdiener JS, Siscovick D, Boineau R, Smith V, et al. Race- and Sex-Specific Ecg Models for Left Ventricular Mass in Older Populations. Factors Influencing Overestimation of Left Ventricular Hypertrophy Prevalence by Ecg Criteria in African-Americans. J Electrocardiol 2000;33:205-18.

75. Kannel WB, Gordon T, Castelli WP, Margolis JR. Electrocardiographic Left Ventricular Hypertrophy and Risk of Coronary Heart Disease. The Framingham Study. Ann Intern Med 1970;72:813-22.

76. Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial Qrs-T Angle Predicts Cardiac Death in a General Population. Eur Heart J 2003;24:1357-64.

77. Pringle SD, Macfarlane PW, McKillop JH, Lorimer AR, Dunn FG. Pathophysiologic Assessment of Left Ventricular Hypertrophy and Strain in Asymptomatic Patients with Essential Hypertension. J Am Coll Cardiol 1989;13:1377-81.

78. Chen CY, Chiang BN, Macfarlane PW. Normal Limits of the Electrocardiogram in a Chinese Population. J Electrocardiol 1989;22:1-15.

79. Okin PM, Roman MJ, Devereux RB, Kligfield P. Gender Differences and the Electrocardiogram in Left Ventricular Hypertrophy. Hypertension 1995;25:242-9.

80. Alfakih K, Walters K, Jones T, Ridgway J, Hall AS, Sivananthan M. New Gender-Specific Partition Values for Ecg Criteria of Left Ventricular Hypertrophy: Recalibration against Cardiac Mri. Hypertension 2004;44:175-9.

81. Siegel RJ, Roberts WC. Electrocardiographic Observations in Severe Aortic Valve Stenosis: Correlative Necropsy Study to Clinical, Hemodynamic,, and Ecg Variables Demonstrating Relation of 12-Lead Qrs Amplitude to Peak Systolic Transaortic Pressure Gradient. Am Heart J 1982;103:210-21.

82. Vitelli LL, Crow RS, Shahar E, Hutchinson RG, Rautaharju PM, Folsom AR. Electrocardiographic Findings in a Healthy Biracial Population. Atherosclerosis Risk in Communities (Aric) Study Investigators. Am J Cardiol 1998;81:453-9.

83. Okin PM, Roman MJ, Devereux RB, Kligfield P. Ecg Identification of Left Ventricular Hypertrophy. Relationship of Test Performance to Body Habitus. J Electrocardiol 1996;29 Suppl:256-61.

84. Rautaharju PM, Zhang ZM, Prineas R, Heiss G. Assessment of Prolonged Qt and Jt Intervals in Ventricular Conduction Defects. Am J Cardiol 2004;93:1017-21.

85. Vaidean GD, Schroeder EB, Whitsel EA, Prineas RJ, Chambless LE, Perhac JS, et al. Short-Term Repeatability of Electrocardiographic Spatial T-Wave Axis and Qt Interval. J Electrocardiol 2005;38:139-47.

86. Strohmer B, Schernthanere C, Paulweber B, Pichler M. Gender-Specific Comparison of Five Qt Correction Formulae in Middle-Aged Participants in an Atherosclerosis Prevention Program. Med Sci Monit 2007;13:CR165-71.

87. Drici MD, Burklow TR, Haridasse V, Glazer RI, Woosley RL. Sex Hormones Prolong the Qt Interval and Downregulate Potassium Channel Expression in the Rabbit Heart. Circulation 1996;94:1471-4.

88. Hansen S, Rasmussen V, Larsen K, Torp-Pedersen C, Jensen GB. Circadian Variation in Qt Dispersion Determined from a 12-Lead Holter Recording: A Methodological Study of an Age- and Sex-Stratified Group of Healthy Subjects. Ann Noninvasive Electrocardiol 2007;12:185-96.

89. Lee KT, Lai WT, Chu CS, Su HM, Yen HW, Voon WC, et al. Circadian Variation of Qt Dispersion Determined by Twelve-Lead Holter Electrocardiography. Cardiology 2003;100:101-2.

90. Festa A, D'Agostino R, Jr., Rautaharju P, O'Leary DH, Rewers M, Mykkanen L, et al. Is Qt Interval a Marker of Subclinical Atherosclerosis in Nondiabetic Subjects? The Insulin Resistance Atherosclerosis Study (Iras). Stroke 1999;30:1566-71.

91. Ackerman MJ, Clapham DE. Ion Channels--Basic Science and Clinical Disease. N Engl J Med 1997;336:1575-86.

92. Ewing DJ, Boland O, Neilson JM, Cho CG, Clarke BF. Autonomic Neuropathy, Qt Interval Lengthening, and Unexpected Deaths in Male Diabetic Patients. Diabetologia 1991;34:182-5.

93. Rautaharju PM, Park LP, Chaitman BR, Rautaharju F, Zhang ZM. The Novacode Criteria for Classification of Ecg Abnormalities and Their Clinically Significant Progression and Regression. J Electrocardiol 1998;31:157-87.

94. Sheifer SE, Manolio TA, Gersh BJ. Unrecognized Myocardial Infarction. Ann Intern Med 2001;135:801-11.

95. Nadelmann J, Frishman WH, Ooi WL, Tepper D, Greenberg S, Guzik H, et al. Prevalence, Incidence and Prognosis of Recognized and Unrecognized Myocardial Infarction in Persons Aged 75 Years or Older: The Bronx Aging Study. Am J Cardiol 1990;66:533-7.

96. Jonsdottir LS, Sigfusson N, Sigvaldason H, Thorgeirsson G. Incidence and Prevalence of Recognised and Unrecognised Myocardial Infarction in Women. The Reykjavik Study. Eur Heart J 1998;19:1011-8.

97. Sigurdsson E, Thorgeirsson G, Sigvaldason H, Sigfusson N. Unrecognized Myocardial Infarction: Epidemiology, Clinical Characteristics, and the Prognostic Role of Angina Pectoris. The Reykjavik Study. Ann Intern Med 1995;122:96-102.

98. Willems JL, Robles de Medina EO, Bernard R, Coumel P, Fisch C, Krikler D, et al. Criteria for Intraventricular Conduction Disturbances and Pre-Excitation. World Health Organizational/International Society and Federation for Cardiology Task Force Ad Hoc. J Am Coll Cardiol 1985;5:1261-75.

99. Murkofsky RL, Dangas G, Diamond JA, Mehta D, Schaffer A, Ambrose JA. A Prolonged Qrs Duration on Surface Electrocardiogram Is a Specific Indicator of Left Ventricular Dysfunction [See Comment]. J Am Coll Cardiol 1998;32:476-82.

100. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic Abnormalities That Predict Coronary Heart Disease Events and Mortality in Postmenopausal Women: The Women's Health Initiative. Circulation 2006;113:473-80.

101. Spodick DH, Raju P, Bishop RL, Rifkin RD. Operational Definition of Normal Sinus Heart Rate. Am J Cardiol 1992;69:1245-6.

102. Spodick DH. Survey of Selected Cardiologists for an Operational Definition of Normal Sinus Heart Rate. Am J Cardiol 1993;72:487-8.

103. Blackburn H. Classification of the Electrocardiogram for Population Studies: Minnesota Code. J Electrocardiol 1969;2:305-10.

104. Kors JA, Crow RS, Hannan PJ, Rautaharju PM, Folsom AR. Comparison of Computer-Assigned Minnesota Codes with the Visual Standard Method for New Coronary Heart Disease Events. Am J Epidemiol 2000;151:790-7.

105. Rautaharju PM, Broste SK, Prineas RJ, Eifler WJ, Crow RS, Furberg CD. Quality Control Procedures for the Resting Electrocardiogram in the Multiple Risk Factor Intervention Trial. Control Clin Trials 1986;7:46S-65S.

106. Crow RS, Prineas RJ, Hannan PJ, Grandits G, Blackburn H. Prognostic Associations of Minnesota Code Serial Electrocardiographic Change Classification with Coronary Heart Disease Mortality in the Multiple Risk Factor Intervention Trial. Am J Cardiol 1997;80:138-44.

107. Rautaharju PM, Ge S, Nelson JC, Marino Larsen EK, Psaty BM, Furberg CD, et al. Comparison of Mortality Risk for Electrocardiographic Abnormalities in Men and Women with and without Coronary Heart Disease (from the Cardiovascular Health Study). Am J Cardiol 2006;97:309-15.

108. Rautaharju PM, Nelson JC, Kronmal RA, Zhang ZM, Robbins J, Gottdiener JS, et al. Usefulness of T-Axis Deviation as an Independent Risk Indicator for Incident Cardiac Events in Older Men and Women Free from Coronary Heart Disease (the Cardiovascular Health Study). Am J Cardiol 2001;88:118-23.

109. Robbins J, Nelson JC, Rautaharju PM, Gottdiener JS. The Association between the Length of the Qt Interval and Mortality in the Cardiovascular Health Study. Am J Med 2003;115:689-94.

110. Schroeder EB, Whitsel EA, Evans GW, Prineas RJ, Chambless LE, Heiss G. Repeatability of Heart Rate Variability Measures. J Electrocardiol 2004;37:163-72.

111. Chambless LE, Davis V. Analysis of Associations with Change in a Multivariate Outcome Variable When Baseline Is Subject to Measurement Error. Stat Med 2003;22:1041-67.

112. Fagard RH, Staessen JA, Thijs L, Celis H, Birkenhager WH, Bulpitt CJ, et al. Prognostic Significance of Electrocardiographic Voltages and Their Serial Changes in Elderly with Systolic Hypertension. Hypertension 2004;44:459-64.

113. Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB. Prognostic Implications of Baseline Electrocardiographic Features and Their Serial Changes in Subjects with Left Ventricular Hypertrophy. Circulation 1994;90:1786-93.

114. Prineas RJ, Rautaharju PM, Grandits G, Crow R. Independent Risk for Cardiovascular Disease Predicted by Modified Continuous Score Electrocardiographic Criteria for 6-Year Incidence and Regression of Left Ventricular Hypertrophy among Clinically Disease Free Men: 16-Year Follow-up for the Multiple Risk Factor Intervention Trial. J Electrocardiol 2001;34:91-101.

115. Shamim W, Yousufuddin M, Cicoria M, Gibson DG, Coats AJ, Henein MY. Incremental Changes in Qrs Duration in Serial Ecgs over Time Identify High Risk Elderly Patients with Heart Failure. Heart 2002;88:47-51.

116. Okin PM, Devereux RB, Gerdts E, Snapinn SM, Harris KE, Jern S, et al. Impact of Diabetes Mellitus on Regression of Electrocardiographic Left Ventricular Hypertrophy and the Prediction of Outcome During Antihypertensive Therapy:

The Losartan Intervention for Endpoint (Life) Reduction in Hypertension Study. Circulation 2006;113:1588-96.

117. Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, et al. Regression of Electrocardiographic Left Ventricular Hypertrophy by Losartan Versus Atenolol: The Losartan Intervention for Endpoint Reduction in Hypertension (Life) Study. Circulation 2003;108:684-90.

118. Okin PM, Gerdts E, Kjeldsen SE, Julius S, Edelman JM, Dahlof B, et al. Gender Differences in Regression of Electrocardiographic Left Ventricular Hypertrophy During Antihypertensive Therapy. Hypertension 2008;52:100-6.

119. Schroeder EB, Chambless LE, Liao D, Prineas RJ, Evans GW, Rosamond WD, et al. Diabetes, Glucose, Insulin, and Heart Rate Variability: The Atherosclerosis Risk in Communities (Aric) Study. Diabetes Care 2005;28:668-74.

120. Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. Hypertension, Blood Pressure, and Heart Rate Variability: The Atherosclerosis Risk in Communities (Aric) Study. Hypertension 2003;42:1106-11.

121. Tasaki H, Serita T, Irita A, Hano O, Iliev I, Ueyama C, et al. A 15-Year Longitudinal Follow-up Study of Heart Rate and Heart Rate Variability in Healthy Elderly Persons. J Gerontol A Biol Sci Med Sci 2000;55:M744-9.

122. Shannon DC, Carley DW, Benson H. Aging of Modulation of Heart Rate. Am J Physiol 1987;253:H874-7.

123. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-Four Hour Time Domain Heart Rate Variability and Heart Rate: Relations to Age and Gender over Nine Decades. J Am Coll Cardiol 1998;31:593-601.

124. de Bruyne MC, Kors JA, Visentin S, van Herpen G, Hoes AW, Grobbee DE, et al. Reproducibility of Computerized Ecg Measurements and Coding in a Nonhospitalized Elderly Population. J Electrocardiol 1998;31:189-95.

CHAPTER 2: SPECIFIC AIMS

The goals of this doctoral work were to determine the short-term repeatability of select twelve-lead electrocardiogram (ECG) variables in the ECG Repeatability Study, to describe the long-term changes of the ECG variables and to assess the association between the long-term changes of ECG variables and incident heart failure in the Atherosclerosis Risk in Communities (ARIC) Study. Manuscripts I (Chapter 4), II (Chapter 5) and III (Chapter 6) correspond to Aims 1, 2 and 3, respectively.

1) Estimate the short-term (2-minute and 1-week) repeatability of ECG variables (QRS/T angle, Cornell voltage, Cornell product, left ventricular mass (LVM), T wave amplitude in lead V_5, T wave amplitude in lead V_1, and ST depression in lead V_5).

Research question: Are the ECG variables highly repeatable in the short-term?

2) Describe the long-term changes of ECG variables (QRS/T angle, QT interval, Cornell voltage, Cornell product, LVM, T wave amplitude in lead V_5, T wave amplitude in lead V_1, and ST depression in lead V_5) by coronary heart disease, diabetes and hypertension status.

Research question: Do the long-term changes of ECG variables differ by coronary heart disease, diabetes and hypertension status?

3) Estimate the association between the long-term changes of ECG variables and incident heart failure, while considering their short-term repeatability.

Research question: Are the long-term changes of ECG variables associated with incident heart failure, while considering their short-term repeatability?

CHAPTER 3: STUDY POPULATIONS AND METHODS

3.1 Study populations

The aims of this doctoral work were addressed in two separate studies. The first, the electrocardiogram (ECG) Repeatability Study was used to investigate Aim 1. The second study, the Atherosclerosis Risk in Communities (ARIC) Study was used to investigate Aims 2 and 3.

3.1.1 The ECG Repeatability Study

This ECG Repeatability Study included 63 volunteers, aged 45 to 64 years, recruited from the Chapel Hill, NC area between July and October, 2001 (1, 2). Participants were invited to attend two examination visits, separated on average by 10 days, with a standard deviation of 4 days. At each visit, participants had two ECG recordings. Recruitment was limited to those without reported use of type Ia anti-arrhythmics (quinidine, procainamide, disopyramide or moricizine), an artificial pacemaker or conditions such as renal failure, heart failure, diabetes mellitus or pregnancy. Furthermore, participants were excluded if they smoked, ate or drank anything but water less than ten hours prior to the visit(s). Age, race/ethnicity and sex

were self-reported and body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

The race/ethnicity, sex, BMI and age of those who participated in the ECG Repeatability Study are listed in Table 5; for comparison, the characteristics of the original ARIC Study participants are listed as well.

Table 5. Characteristics of the ECG Repeatability Study and the Atherosclerosis Risk in Communities (ARIC) Study participants

	N (%) or mean (standard deviation)	
Characteristic	**ECG Repeatability Study (N = 63)**	**ARIC Study (N = 15792)**
Race/ethnicity		
Black	19 (31.8%)	4266 (25.4%)
White	43 (68.3%)	11478 (74.6%)
Asian	1 (1.6%)	34 (0.2%)
American Indian	.	14 (0.1%)
Sex		
Men	32 (50.8%)	7082 (44.9%)
Women	31 (49.2%)	8710 (55.2%)
Body mass index (kg/m^2)	26.9 (5.3)	27.7 (5.4)
Age (years)	52.0 (5.0)	54.2 (5.8)

3.1.2 The ARIC Study

The ARIC Study combines epidemiologic surveillance of four communities and a community-based prospective cohort designed to investigate the etiology and natural history of atherosclerosis and its sequelae. From1987 to 1989, the ARIC Study cohort of 15,792 black and white participants aged 45 to 64 years was drawn from four communities in North Carolina (NC), Mississippi (MS), Minnesota (MN), and Maryland (MD). Two of the population samples (Washington County, MD and Minneapolis, MN suburbs) were mostly white. Blacks were over-sampled in Forsyth County, NC (12% black) and were exclusively sampled in Jackson, MS to provide statistical power to investigate findings by race/ethnicity. The overall recruitment response proportion at

baseline was 60%: black men (42%), black women (49%), women (67%) and white women (68%). A comparison of study participants to non-respondents has been described (3).

After a home interview which established a baseline socio-demographic and cardiovascular (CVD) profile of all enumerated residents in each study community who were willing to have an interview, age-eligible residents were invited to participate in a baseline, and three subsequent clinical examinations, scheduled at three year intervals. The baseline examination (Visit 1) was conducted between 1987 and 1989; Visit 2 was held between 1990 and 1992; Visit 3 between 1993 and 1995; and the last clinic visit (Visit 4) was conducted between 1996 and 1998. Each clinical examination consisted of standardized interviews pertaining to CVD risk factors, medical history and obtainment of extensive clinical data and a twelve-lead standard ECG. After Visit 1, the ARIC Study participants were followed annually via telephone interviews to establish vital status and assess indices of CVD, and surveillance of hospitalizations and ongoing record abstraction for hospitalized events and deaths. Annual follow-up interviews and surveillance have continued after Visit 4, and those data will be available to the investigators in this study on a continuing basis.

Construction of the cohort samples used to address Aim 2

We excluded participants with fewer than two ECGs (n = 1340), with a QRS interval greater than or equal to 120 ms (n = 574), with a race/ethnicity other than black or white (n = 48), and black participants in Minneapolis, MN or Washington County, MD

(n = 55). The final sample size for a cohort so defined (cohort 1) was 13,901. Analyses evaluating the continuous change of ECG variables utilized cohort 1 data, whereas analyses evaluating categorical ECG change variables required the exclusion of participants with missing ECGs at baseline (n range = 228 – 287) and whose measurements parameters at baseline exceeded the established cut points detailed in Section 3.4 (cohorts 2 – 9; n range = 1287 – 4148). Cohorts 2 through 9 excluded those whose ECG measures at baseline exceeded the established cut point because they already had a higher risk for incident heart failure at baseline. The final sample sizes for cohorts 2, 3, 4, 5, 6, 7, 8 and 9 were 10239, 12870, 12735, 12230, 12142, 12033, 12126 and 12004, respectively. Cohorts 1 through 9 were used to address Aim 2.

Construction of the cohort samples used to address Aim 3

We excluded participants with fewer than two ECGs (n = 1340), with a QRS interval greater than or equal to 120 ms (n = 574), with a race/ethnicity other than black or white (n = 48), black participants in Minneapolis, MN or Washington County, MD (n = 55), those with prevalent heart failure at baseline (n = 752), with missing information on heart failure at the baseline examination (n = 287) and those who were censored prior to ARIC Visit 4 (n = 4486). The final sample size for a cohort so defined (cohort 10) was 10,313. Analyses evaluating the continuous change of ECG variables utilized cohort 10 data, whereas analyses evaluating categorical ECG change variables required the exclusion of participants with missing ECGs at baseline (n range = 228 – 287) and whose measurements parameters at baseline exceeded the established cut points detailed in

Section 3.4 (cohorts 11 – 18; n range = 1287 – 4148). The final sample sizes for cohorts 2, 3, 4, 5, 6, 7, 8 and 9 were 7812, 9637, 9554, 9205, 9152, 9110, 9086 and 9044, respectively. Cohorts 10 through 18 were used to address Aim 3.

3.2 ECG methods

3.2.1 The ECG Repeatability Study ECG methods

The ECG Repeatability Study followed the standardized protocol used in the ARIC Study for placing electrodes, room condition and data collection (4). All ECG recordings were carried out in a quiet, temperature-controlled room. Participants reported for the visits between 7:30 and 11:30 am. After participants rested in the supine position for fifteen minutes, one of four trained and certified ECG technicians recorded ten-second, twelve-lead ECGs using Kendall Q-Trace 5400 Ag/AgCl electrodes (Ludlow Co, Chicopee, Mass). The E-V6 Halfpoint method (5) was used when recording the first of two ECGs using a MAC Personal Cardiographer (Marquette Electronics, Inc, Milwaukee, WI). The E-V6 Halfpoint method improves the precision and the repeatability of chest electrode positioning by placing the V_4 electrode at the horizontal level of the fifth intercostal space at the half-way point between the midsternal line and the left midaxillary line (V_6 location). Without removal of the electrodes, the recording was repeated after 1 to 2 minutes. ECGs were digitized and sent via modem after each recording session to the Epidemiological Cardiology Research (EPICARE) Center at the Wake Forest University School of Medicine. The EPICARE Center, blinded to participant identity and previous ECG readings, processed the ECGs using the most

recent version of the Marquette GE program, version 12SL. Following an identical protocol, a second set of ECGs from the same participants were obtained on the second visit.

3.2.2 The ARIC Study ECG methods

The ARIC Study used standardized protocol for the acquisition of and processing of ECGs (4). All ECG recordings were carried out in a quiet, temperature-controlled room. After participants rested in the supine position for fifteen minutes, trained and certified ECG technicians recorded ten-second, twelve-lead ECGs using Kendall Q-Trace 5400 Ag/AgCl electrodes (Ludlow Co, Chicopee, Mass). The E-V6 Halfpoint method (5) was used when recording ECGs using a MAC Personal Cardiographer (Marquette Electronics, Inc, Milwaukee, WI). The E-V6 Halfpoint method improves the precision and the repeatability of chest electrode positioning by placing the V_4 electrode at the horizontal level of the fifth intercostal space at the half-way point between the midsternal line and the left midaxillary line (V_6 location). ECGs were digitized and sent via modem after each recording session to the EPICARE Center (Wake Forest University, Winston-Salem, NC). The EPICARE Center, blinded to participant identity processed the ECGs using the 12SL version of the Marquette GE program.

The ARIC Study standardized procedure for data collection of ECGs

The ARIC Study standardized procedure for data collection of ECGs and quality control are briefly described below (6).

Each participant, chest exposed, was instructed to lie on the recording bed with arms relaxed at the sides. The individual was asked to avoid movements which might cause errors in marking the electrode locations. A felt tip pin was used to mark the six chest electrode positions. In order to increase the electrode/skin interface, the electrodes were placed on the skin for at least 2 to 3 minutes before taking the ECG. The 10 electrode sites (6 chest and four limb sites) were wiped with sterile alcohol in order to remove skin oil and perspiration. The four limb leads were placed on the medial side of the left ankle, right ankle, the left wrist and the right wrist. The six chest leads were placed as follows: Electrode V_2 was placed in the intercostals space immediately to the left of the sternal border. Electrode V_1 was placed in the fourth intercostal space immediately to the right of the sternal border. The E point was defined as the space horizontally to the midsternal line and parallel with the fifth intercostal space. Electrode 6 was the same location as the E point in the midaxillary line (straight down from the center of the armpit). Electrode V_4 was located using the E-V_6 halfpoint method. A measuring tape was placed over the skin between the E point and the V_6 marking. V_4 was midway between the E and V_6. Likewise, V_3 was midway between V_2 and V_4. V_5 was midway between the location between V_4 and V_6. If technical problems were observed due to poor electrode contact then it was necessary to do further preparation: 1) remove excess hair with a razor; or 2) brush sandpaper over the skin three times using light pressure. When placing each electrode, it was massaged in a circular motion to maximize the contact with the skin.

After placing the electrodes on the skin, the 'record' key was pressed. The machine read, 'acquiring data.' The machine automatically printed the ECG after it acquired 10 seconds of good data. The ECG was torn off the machine and filed at the field center, and read locally by clinical physicians for notification and referral. The records were then placed in participants' local data files.

Additionally, the ECGs were transmitted to the EPICARE Center. If there was a problem transmitting to the EPICARE Center, ECGs were transmitted to the MAC 12 at the Minneapolis ECG Coding Center. Every morning, the EPICARE Center notified each ARIC field center of the identification numbers (IDs) received. After successful confirmation that EPICARE received the transmission, and it was of good quality, the ECG was deleted from the Mac PC Storage Directory. Every other week EPICARE sent these data to the Coordinating Center (CC). All resting twelve-lead ECG records with computer generated ECG findings listed below, which qualified for serial change coding at follow-up visits, and at least a 10% random sample of the remaining ECGs were visually coded at the Minnesota Coding Center by the Minnesota Code: 1) any 1-code; 2) and 4-1, 4-2, 5-1 or 5-2 code; 3) any 9-2, 6-4, 7-1-1, 7-2-1 or 7-4 code; and 4) any 6-1, 6-8 or heart rate $\geq$ 140. The visual Minnesota Codes were sent to the CC for data comparison with the computer generated codes. Adjudication of computer codes was made only on ECGs that had a discrepancy involving any Q-code, ST, or T wave changes from Visit 1 to Visit 2. The CC determined the IDs that had any of these discrepancies and sent a report form to the Minnesota Coding Center. These ECGs were examined and the adjudicated record was sent to the CC. The CC added the adjudicated codes to the database as the definitive Minnesota codes for the IDs involved.

The computer assigned codes were used in the Study Data in all cases except when adjudication resulted in a code different from the original EPICARE code. If the two centers disagreed on 'minor' codes (codes other than Q waves, ST depression, T waves, ST-elevation, bundle branch block, Wolf-Parkinson-White, complete atrio-ventricular block, heart rate ≥ 140), the EPICARE reading prevailed. For major codes, the adjudicated reading prevailed.

Baseline and follow-up ECGs were compared. When two (adjudicated) ECGs were available from two separate visits, a determination was made at the CC as to whether the Minnesota code change criteria were met. Determination was made by a computer algorithm and not by Minnesota Coders. IDs that fit the change in criteria were examined side by side for serial ECG change at the Minnesota ECG Reading Center. Objective rules for side-by-side ECG evaluation were used to determine whether a Minnesota code change between ECG pairs was significant between visits, using the first clinic visit ECG as the referent.

All ECG technicians were certified and were required to take an average of 3 ECGs per week over a two-month period in order to remain familiar with the procedures and equipment. Each technician was observed quarterly by senior technicians while taking a participant's ECG, and performance was documented. EPICARE checked the quality of the data.

3.3 ECG Repeatability Study variables

The following ECG measures were generated at the EPICARE Center using methods previously described (7): QRS/T angle, Cornell voltage, Cornell product, left ventricular mass (LVM), net T wave amplitude in lead V_5, net T wave amplitude in lead V_1, and ST depression. The QRS/T angle was defined as the angle between the net QRS and T wave vectors (8). QRS/T angle was calculated using a simplified method from the net QRS amplitudes (R – absolute value of S or QS, whichever was larger, in leads V_6, aVF and V_2) and the net T wave amplitudes (signed T +signed T prime) in leads V_5, aVF and V_2. T waves were obtained by calculating mean and peak T wave values in lead V_5, whereas for T wave amplitude in lead V_1, only the mean value was used. ST depression was evaluated using ST amplitude in lead V_5 at 60 ms past the end of the QRS interval (the J-point) from the Marquette-GE program. Cornell-voltage (R wave amplitude in lead aVL + Q or QS wave amplitude in lead V_3) (9), Cornell product (Cornell voltage x QRS duration) (10), and LVM predicted by a multivariate model (11) were used as measures of left ventricular hypertrophy (LVH). The LVM model adjusted for Cornell voltage and body weight. Age, race/ethnicity and sex were self-reported and BMI was calculated as weight (kg) divided by height (m) squared. A summary of demographic characteristics and ECG variables are presented in Table 6.

Table 6. Summary of variables for the short-term repeatability analysis, the ECG Repeatability Study (N = 63)

Variable Name	Variable Description	Coding	N (%) or mean (standard deviation)
BMI	Body mass index (kg/m^2)	Continuous	26.9 (5.3)
AGE	Age at Visit 1 (years)	Continuous	52.0 (5.0)
		1 = White	43 (68.3%)
		2 = Black	19 (30.2%)
RACE	Race/ethnicity	4 = Asian Indian	1 (1.6%)
		0 = White	43 (68.3%)
RACE2	Race/ethnicity	1 = Nonwhite	20 (31.8%)
		1 = Male	32 (50.8%)
SEX	Sex	0 = Female	31 (49.2%)
HR	Mean heart rate (beats/min)	Continuous	59.6 (8.7)

QRST	QRS/T angle using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2 (°)	Continuous	78.4 (26.0)
QTRR	Heart rate- and sex-adjusted QT as a linear function of the RR interval (ms)	Continuous	415.8 (17.6)
CV	Cornell voltage (μV) (RaVL + SV_3)	Continuous	1213.8 (501.2)
CP	Cornell product (μV.s) (Cornell voltage (μV) x QRS(s))	Continuous	115.6 (50.3)
ECGLVM	Left ventricular mass as measured by ECG (g)	Continuous	154.1 (27.3)
TAMP_V5	T amplitude in lead V_5 (μV)	Continuous	408.6 (213.7)
TAMP_V1	T amplitude in lead V_1 (μV)	Continuous	90.3 (154)
ST60V5	ST segment amplitude at time point 60 ms past end of QRS in lead V_5 (μV)	Continuous	50.5 (31.6)

*The study sample included 63 healthy participants, aged 45 to 64 years, with no reported use of class Ia antiarrhythmics, or conditions such as heart failure, pregnancy or diabetes mellitus.

3.4 ARIC Study variables

3.4.1 Exposure assessment

The following ECG measures were generated at the EPICARE Center using methods previously described (7): spatial QRS/T angle, QT interval, Cornell voltage, Cornell product, LVM, T net amplitudes in leads V_5 and V_1, and ST depression. The QRS/T angle was defined as the angle between the net QRS and T wave vectors (8). QRS/T angle was calculated using a simplified method from the net QRS amplitudes (R – absolute value of S or QS, whichever was larger, in leads V_6, aVF and V_2) and the net T wave amplitudes (signed T +signed T prime) in leads V_5, aVF and V_2. QTrr, used to evaluate QT prolongation, was the sex- and race/ethnicity-specific QT adjusted for heart rate as a linear function of the RR interval (2). Cornell voltage (R wave amplitude in lead aVL + Q or QS wave amplitude in lead V_3) (9), Cornell product (Cornell voltage x QRS duration) (10), and LVM predicted by a multivariate model (11) were used as measures of LVH. The LVM model adjusted for Cornell voltage and body weight. T waves were

obtained by calculating mean and peak T wave values in lead V_5, whereas for T wave amplitude in lead V_1, only the mean value was used. ST depression was evaluated using ST amplitude in lead V_5 at 60 ms past the end of the QRS interval (the J-point) from the Marquette-GE program.

The coding schemes for ECG abnormalities in the ARIC Study are presented in Table 7.

Table 7. Summary of ECG variables, the Atherosclerosis Risk in Communities (ARIC) Study

Variable Name	Variable Description	Coding
QRST	QRS/T angle using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2 (°)	Continuous
QTRR	Heart rate- and sex-adjusted QT as a linear function of the RR interval (ms)	Continuous
CV	Cornell voltage (μV) (RaVL + SV_3)	Continuous
CP	Cornell product (μV.s) (Cornell voltage (μV) x QRS (s))	Continuous
ECGLVM	Left ventricular mass (g)	Continuous
TAMP_V5	T amplitude in lead V_5 (μV)	Continuous
TAMP_V1	T amplitude in lead V_1 (μV)	Continuous
ST60V5	ST segment amplitude at time point 60 ms past end of QRS in lead V_5 (μV)	Continuous

Construction of continuous ECG change variables used to address Aims 2 and 3

The following linear regression model was used to derive the continuous exposure variable, long-term change of the ECG measure (B_i), for each participant: $y_{ij} = A_i + B_i t_{ij} + \varepsilon_{ijk}$, where y = the predicted ECG abnormality value, i = 1, 2, 3…n participants, j = 1, 2…4 visits, k = 1 to 2 ECG measures, t was the time between ARIC Visit 1 and subsequent visits and ε was the error term. In the regression model used to derive B_i, $y_{ij} = A_i + B_i t_{ij} + \varepsilon_{ijk}$, the random variability in y, σ^2, was assumed to be the same for all participants and at all visits: Var $(y_{ijk} \mid t_{ij})$ = Var $(\varepsilon_{ijk} \mid t_{ij}) = \sigma^2$.

Construction of the categorical ECG change variables used to address Aims 2 and 3

We additionally constructed categorical change ECG variables. To provide comparability with an earlier analysis in the ARIC Study, we used cut points for ECG variables shown to be associated with incident heart failure used by Rautaharju and colleagues (7). ECG variables were defined using the following cut points for men (M) and women (W): QRS/T angle (°): M ≥ 107, W ≥ 89; QT interval (ms): M ≥ 436, W ≥ 442; Cornell voltage (μV): M ≥ 2650, W ≥ 1673; Cornell product (μV.s): M ≥ 207, W ≥ 152; LVM (g): M ≥ 204, W ≥ 162; $T_{net}V_5$ amplitude (μV): M ≤ 122, W ≤ 107; $T_{net}V_1$ amplitude (μV): M ≥ 307, W ≥ 151; and $ST_{60}V_5$ (μV): M ≤ 5, W ≤ -7. For each ECG variable, categorical change was defined as ever exceeding the cut point ("1") over ARIC visits, or else "0".

3.4.2 Outcome assessment

Incident heart failure

Incident heart failure was defined as the first hospital discharge associated with a diagnosis of heart failure (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM code 428 or 518.4) or death certificates with an underlying cause of death coded as heart failure (ICD-9-CM code 428 or ICD-10 code I50). All cohort hospitalizations that occurred before January 1, 2005 were included. The ICD-9 codes and descriptions used in these analyses are reported in Table 8.

Prevalent heart failure at baseline

Table 8. Hospital discharge diagnoses of International Classification of Diseases (ICD), 9th Revision, Clinical Modification codes used to define heart failure by the Atherosclerosis Risk in Communities (ARIC) Study investigators

ICD-9 Code	Description
428	Heart failure
428.0	Congestive heart failure, unspecified
428.1	Left heart failure
428.2	Systolic heart failure
428.3	Diastolic heart failure
428.4	Combined systolic and diastolic heart failure
428.9	Heart failure, unspecified
518.4	Acute edema of the lung, unspecified

If the participant reported s/he had taken any medication for heart failure or qualified for stage 3 of the Gothenburg Criteria (Table 10) for heart failure which requires specific cardiac, pulmonary and heart failure indicators to be present (12, 13) then the participant had prevalent heart failure (PREVHF01 = 1) at Visit 1, and they were excluded (see Table 9).

Table 9. Prevalent heart failure (PREVHF01), derived from the heart failure medication (HFMEDS) and Gothenburg (GOTHENBURG) variables utilized by Atherosclerosis Risk in Communities (ARIC) Study investigators

PREVHF01	HFMEDS	GOTHENBURG
	1	Any
1	Any	1
0	0	0
	Missing	0 or missing
Missing	0 or missing	Missing

Table adapted from the ARIC Manual of Procedures

The heart failure medication variable (HFMEDS) takes on a value of 1 (yes) or 0 (no). The value for heart failure medication was 1 if the participant reported s/he had taken heart failure medication in the last two weeks.

The Gothenburg Score (GOTHENBURG) can take on the values of 0, 1, 2, 3 or missing. The Gothenburg score consists of cardio, pulmonary and heart failure therapy binary variables, with missing variables excluded. A value of 1 was given for CARDIAC if the participant had any of the following variables: edema (swelling in the feet or ankles during the day), paroxysmal nocturnal dyspnea, coronary heart disease (CHD), angina, rales, or atrial fibrillation. A value of 1 was given for PULMONARY if the participants had any of the following variables: history of bronchitis, history of asthma, rhonchi or chronic cough. A value of 1 was given for heart failure therapy if the participant received either digitalis or diuretic therapy.

Table 10. Gothenburg criteria score for heart failure utilized by the Atherosclerosis Risk in Communities (ARIC) Study investigators

Score	Cardiac	Pulmonary	Heart Failure Therapy
3	1	1	1
	1	1	0 or missing
2	1	0 or missing	1
1	1	0 or missing	0 or missing
0	0	.	.
Missing	Missing	.	.

Table adapted from the ARIC Manual of Procedures

3.4.3 Covariate assessment

Covariates used to address Aim 2

Variables of interest included: age, race/ethnicity, sex, hypertension, diabetes, and CHD. These variables were considered because they are biologically or clinically relevant to the occurrence of heart failure (14, 15), or they were determined to be relevant based on a review of the literature. A detailed description of the ARIC Study

demographic and clinical measures and the processing have been published elsewhere (16). ARIC Study Visit 1 covariates are briefly described below.

The covariates selected for the analysis were age (years), sex (male or female), self-reported race/ethnicity (black or white). A race/center variable was created by combining each participant's race/ethnicity with their respective study center. Additional covariates selected for the analysis include CHD (yes or no), diabetes (yes or no) and hypertension (yes or no). Each participant was asked to indicate whether they were white, black/African American, American Indian or Asian. CHD at baseline was defined from a reported history of physician-diagnosed myocardial infarction (MI), coronary artery bypass surgery, coronary angioplasty, or evidence of a previous MI on an ECG. Blood pressure, lipids and glucose were measured according to standard ARIC procedures (4). Participants were asked to fast twelve hours before blood draw and actual fasting times were recorded. Blood was drawn from an antecubital vein of seated participants, serum was centrifuged, and frozen samples were shipped to central laboratories for analysis (16). The mean of the last two of three systolic and diastolic sitting blood pressure measurements obtained from a random-zero sphygmomanometer was used for measures of blood pressure. Hypertension was defined as a systolic blood pressure value equal to or greater than 140 mmHg, a diastolic blood pressure value equal to or greater than 90 mmHg, or use of blood pressure lowering medications in the past two weeks. Pre-hypertension was defined as a systolic blood pressure value equal to or greater than 120 mm Hg but less than 140 mm Hg or a diastolic blood pressure value equal to or greater than 80 mm Hg but less than 90 mm Hg (17). Type II diabetes mellitus was defined as a fasting serum glucose level of 7.0 mmol/L or more (126

mg/dL), nonfasting glucose level of 11.1 mmol/L or more (200 mg/dL), participant report of a physician diagnosis of diabetes, or current use of diabetes medication (18). Pre-diabetes was defined as a fasting serum glucose level of 6.1 mmol/L (110 mg/dL) or more but less than 7.0 mmol/L (126 mg/dL) (18).

Table 11. Summary of clinical and demographic variables used to address Aim 2, the Atherosclerosis Risk in Communities (ARIC) Study

Variable Name	Variable Description	Coding
V1AGE01	Age at Visit 1 in years	Continuous
PRVCHD05	Coronary heart disease: history of myocardial infarction, coronary artery bypass surgery or coronary angioplasty	1 = CHD 0 = No CHD
RACECTR	Combination of race/ethnicity and study center	0 = White/Minneapolis, MN 1 = White/Washington County,MD 2 = Black/Jackson, MS 3 = White/Foryth County, NC 4 = Black/Forsyth County, NC
GENDER	Sex	1 = Male 0 = Female
HTN	Hypertension was defined as physician-diagnosed or use of anti-hypertension medications. Pre-hypertension was defined as a systolic blood pressure ≥ 120 mm Hg but < 140 mm Hg or a diastolic blood pressure ≥ 80 mm Hg but less than 90 mm Hg.	2= Hypertension 1= Pre-hypertension 0= No hypertension
DIAB	Diabetes was defined as self-reported physician diagnosed or use of hypoglycemic medications. Pre-diabetes was defined as a fasting glucose level ≥ 110 mg/dL but < 126 mg/dL.	2= Diabetes 1= Prediabetes 0= No diabetes

*All data were derived from the ARIC Study at Visit 1 (1987-1989).

Covariates used to address Aim 3

The covariates selected for the analysis were age (years), sex (male or female), self-reported race/ethnicity (black or white). Additional covariates selected for the analysis include CHD (yes or no), diabetes (yes or no), hypertension (yes or no), smoking status (current or not current), use of cholesterol-lowering medication (yes or no), and BMI (continuous) at the Visit 4 examination and physical activity (continuous) at the Visit 3 examination. These variables were considered because they are biologically or

clinically relevant to the occurrence of heart failure (14, 15), or they were determined to be relevant based on a review of the literature. ARIC Study Visit 4 covariates, with the exception of physical activity (physical activity was obtained at ARIC Visit 3), were used for this analysis. However, if participants were missing covariate information for Visit 4, then Visit 3 covariates were used. Likewise, if participants were missing Visit 3 covariates, then covariate information for Visit 2 was used.

A detailed description of the ARIC Study demographic and clinical measures and the processing have been published elsewhere (16). Each participant was asked to indicate whether they were white, black/African American, American Indian or Asian. CHD at baseline was defined from a reported history of physician-diagnosed MI, coronary artery bypass surgery, coronary angioplasty, or evidence of a previous MI on an ECG. Blood pressure, lipids and glucose were measured according to standard ARIC procedures (4). Participants were asked to fast twelve hours before blood draw and actual fasting times were recorded. Blood was drawn from an antecubital vein of seated participants, serum was centrifuged, and frozen samples were shipped to central laboratories for analysis (16). The mean of the last two of three systolic and diastolic sitting blood pressure measurements obtained from a random-zero sphygmomanometer was used for measures of blood pressure. Hypertension was defined as a systolic blood pressure value equal to or greater than 140 mmHg, a diastolic blood pressure value equal to or greater than 90 mmHg, or use of blood pressure lowering medications in the past two weeks. Use of cholesterol-lowering medications was self-reported. Type II diabetes mellitus was defined as a fasting serum glucose level of 7.0 mmol/L or more (126 mg/dL) (19), nonfasting glucose level of 11.1 mmol/L or more (200 mg/dL), participant report of

a physician diagnosis of diabetes, or current use of diabetes medication. BMI was calculated as measured weight (kg) divided by height (m^2). Physical activity was measured using the sport during leisure time activity index (range 1-5) of Baecke's questionnaire (20). The appropriateness of coding schemes was confirmed in univariate analyses. The coding schemes for covariates at ARIC Visit 4 (and Visit 3 for physical activity) are presented in Table 12.

Table 12. Summary of clinical and demographic variables used to address Aim 3, the Atherosclerosis Risk in Communities (ARIC) Study

Variable Name	Variable Description	Coding
BMI41	Body mass index (kg/m^2)	Continuous
V4AGE41	Age in years	Continuous
PRVCHD43	Coronary heart disease: history of myocardial infarction, coronary artery bypass surgery or coronary angioplasty	1 = CHD 0 = No CHD
RACEGRP	Race/ethnicity	1 = Black 0 = White
GENDER	Sex	1 = Male 0 = Female
HYPERT45	Physician-diagnosed hypertension or use of anti-hypertension medications	1 = Hypertension 0 = No hypertension
DIABTS42	Self-reported physician diagnosed diabetes or use of hypoglycemic medications	1 = Diabetes 0 = No diabetes
CURSMK41	Current cigarette smoking status	1 = Current smoker 0 = Not smoking
SPRT_I31	Sport during leisure time activity: 5 ordinal variables (low=1, high=5) derived from Baecke's survey	Continuous
CHOLMD41	Cholesterol-lowering medications	1 = Yes 0 = No

*All data were derived from the ARIC Study at Visit 4 (1996-1998), with the exception of SPRT_I31 at Visit 3. However, if participants were missing covariate information for Visit 4, then Visit 3 covariates were used. Likewise, if participants were missing Visit 3 covariates, then covariate information for Visit 2 was used.

3.5 Statistical analysis

3.5.1 Analytic plan for Aim 1

Nested random effects models were used to partition the total variance into between-participant, between-visit and within-visit components of variance: $y_{ijk} = \mu + p_i +$

$v_{j(i)} + \varepsilon_{k(ij)}$, where y = ECG abnormality, i = 1, 2, 3…63 participants, j = 1, 2 visits and k = 1, 2 ECG recordings. p_i was the effect of the ith participant. $v_{j(i)}$ was the effect of the jth visit nested within the ith participant. $\varepsilon_{k(ij)}$ was the error term and was the effect of the kth ECG recording nested within the ith participant on the jth visit. The total variance in the data was: $\sigma^2_T = \sigma^2_p + \sigma^2_v + \sigma^2_\varepsilon$, where σ^2_p was the between-participant component of variation, σ^2_v was the between-visit component of variation, σ^2_ε was the within-visit component of variation and σ^2_T was the total variance. The within-visit component of variation represents methodological variability. The within-participant component of variation, the summation of the between-visit and within-visit components of variance, represents a combination of temporal biological and methodological variability.

The intra-class correlation (ICC) coefficient is the between-participant component of variation over the total variance (sum of between-participant, between-visit and within-visit variance) and can be interpreted as the correlation between ECG measures at different visits. The ICC coefficient can also be calculated by subtracting the within-person variance over the total variance from 1. In these analyses, we assumed that: 1) the ECG measures were normally distributed; 2) the between-participant variation followed a normal distribution ($p_i \sim N(0, \sigma^2_s)$); 3) the between-visit variation was normally distributed ($v_{j(i)} \sim N(0, \sigma^2_v)$); 4) the residual variation followed a univariate normal distribution ($\varepsilon_{k(ij)} \sim N(0,\sigma^2_\varepsilon)$); and 5) p_i, $v_{j(i)}$ and $\varepsilon_{k(ij)}$ were independent of each other. If the normality assumptions were not met, then we planned to log-transform ECG variables. However, all ECG measures met the normality assumption. The ICC coefficient was calculated for each of the ECG measures and 95% confidence intervals were derived using the Delta method (21). The following criteria were used to

characterize short-term repeatability: poor, 0-0.40; moderate, 0.41-0.60; good, 0.61-0.80; and excellent, 0.81-1.0.

When we calculated sex-specific ICC coefficients for each of the ECG measures, we found that the normality assumptions were not met. It is recognized that a logarithmic transformation could diminish the skewness of the distribution of the data and even achieve a normal distribution. This would permit the construction of confidence intervals for the sex-specific ICC coefficients, since they were limited by small numbers. However, logarithmically-transformed sex-specific ICC coefficients were non-normal, and as a result, we used the measured values of sex-specific ECG variables rather than their logarithmic transformation and bootstrapping methods to construct their confidence intervals. A bootstrapping procedure was used to construct 95% confidence intervals using 2000 samples with replacement (22). Lastly, the square roots of the between-participant, between-visit and within visit variances were calculated and the coefficient of variation for each component was calculated as the ratio of its square root to its grand mean, multiplied by 100.

3.5.2 Analytic plan for Aim 2

Logistic and linear regression were used to compare adjusted categorical and continuous changes in the ECG measures over ARIC visits 1 through 4, stratified by CHD, diabetes and hypertension status at baseline. QRS/T angle, Cornell voltage, Cornell product, T net amplitudes in leads V_5 and V_1, and ST depression were adjusted for age, race/center-, sex- and baseline ECG measure, while QT interval and LVM were

adjusted for age and baseline ECG measure only. A two-tailed p-value<0.05 was required for statistical significance.

3.5.3 Analytic plan for Aim 3

We employed Cox proportional hazard regression modeling to assess the association between change, continuous (per one standard deviation change) and categorical, in ECG measures and incident heart failure. For all survival analyses of time to heart failure the follow-up time was defined as the period from the third re-examination (Visit 4) to the first hospitalization for heart failure, heart failure death, December 31, 2004, or the last date of contact if lost-to-follow-up. The assumption of proportional hazard over time was verified by Cox tests and visual inspection of log(-log) plots.

Assessing effect measure modification

For assessment of effect measure modification on the multiplicative scale, Cox proportional hazard models of the association between each ECG abnormality change variable and incident heart failure with and without interaction terms between potential effect measure modifiers were compared using the likelihood ratio test. An α of 0.15 was used for the likelihood ratio test when comparing models with and without interaction term(s). When the likelihood ratio test was significant, the interaction terms were deemed significant to the association between the ECG change variable and incident

heart failure, and thus the interaction term remained in the model. However, if the likelihood ratio test was not significant, then the covariate did not modify the relation between the ECG change variable and incident heart failure, and the interaction term was removed from the model. The backward elimination method was used to examine the interaction terms one at a time in order to eliminate insignificant variables from the model. Any covariates found to be effect measure modifiers were not assessed for confounding.

Assessing confounding

To assess for confounding by the covariates that were not effect measure modifiers, the crude and adjusted hazard ratios were compared. Each of the covariates was removed from the model, one at a time and the likelihood ratio test was used to determine if the potential confounder can be removed from the model. An α of 0.05 was used for the likelihood ratio test when comparing models with and without potential confounder(s). If the likelihood ratio test was significant, then the covariate was deemed to be a significant confounder of the ECG change variable and incident heart failure association, and thus the confounder remained in the model. However, if the likelihood ratio test was not significant, then the covariate did not confound the relation between the ECG change variable and incident heart failure, and the covariate was removed from the model. The backward elimination method was used to examine potential confounders one at a time in order to eliminate insignificant variables from the model.

Correction for measurement error in continuous ECG change variables

We incorporated variance estimates derived from the ECG Repeatability Study in Aim 1 to adjust for intra-individual variation (measurement error) in continuous ECG change variables using regression calibration methods (23).

As mentioned in Section 3.4, the following linear regression model was used to derive the exposure variable, long-term change in the ECG measure (B_i), for each participant: $y_{ij} = A_i + B_i t_{ij} + \varepsilon_{ijk}$, where y = the ECG measure value, i = 1, 2, 3…n participants, j = 1, 2…4 visits, and t was the time between ARIC Visit 1 and subsequent visits. We included participants in the study who had 2 or more ECG measures for any of the ARIC Visits 1 through 4, for each ECG variable. In the regression model used to derive B_i, $y_{ij} = A_i + B_i t_{ij}$, the random variability in y, σ^2, was assumed to be the same for all participants and at all visits: Var $(y_{ijk} \mid t_{ij})$ = Var $(\varepsilon_{ijk} \mid t_{ij}) = \sigma^2$. It was also assumed that ε_{ijk} were independent, and were independent of A_i and B_i. Furthermore, the regression estimator of B_i, our measure of long-term continuous change in ECG variable, for some given $y_{i1k}, y_{i2k}, y_{i3k}, y_{i4k}$ was $\widehat{B_{i,k}} = \sum_{j=1}^{n_i} c_{ij}\, y_{ijk} = \sum_{j=1}^{n_i} c_{ij}\,(A_i + B_i t_{ij}) + \sum_{j=1}^{n_i} c_{ij}\,\varepsilon_{ijk}$, where $c_{ij} = \frac{t_{ij} - \bar{t}_i}{\sum_{j1} (t_{ij1} - \bar{t}_{i1})^2} = \frac{t_{ij} - \bar{t}_i}{(n_i - 1) S_{t,i}}$, and where S^2_{t1i} was the sample variance of the (t_{i1}, t_{i2}, t_{i3}, t_{i4}).

However, in contrast with the usual regression assumption, the within-participants error variance of the continuous ECG change variable, σ^2, was not constant across participants. The within-participant component of variance of the change in ECG

exposure variable, depends on the number of ECG measurements (n_i) and on the spread of the t_{ij}, $S^2_{t,i}$, and hence, the following calculations were implemented to account for participant-dependent variability:

$$\sigma^2_{B,e,i} = Var\left(\widehat{B_{ik}} \mid i\right) = Var(\sum_{j=1}^{n_i} c_{ij}^2 \varepsilon_{ijk}) = \sum_{j=1}^{n_i} c_{ij}^2 Var\left(\varepsilon_{ijk}\right) = (\sum_{j=1}^{n_i} c_{ij}^2)\ \sigma^2 = \frac{\sigma^2}{(n_i - 1)S^2_{t,i}}$$

In order to derive, σ^2, the variance of the random within-participant component of variance in *y*, we estimated *R* from the ECG Repeatability Study in fulfillment of Aim 1 and assumed that it applied to the ARIC Study data using the following calculation:

$\sigma^2 = \sigma^2_{y,e} = (1 - R)\sigma^2_{y,T}$,where *R* was the ICC calculated for an ECG measure and $\sigma^2_{y,T}$ was the total variance of the ECG measure in the ARIC Study.

We replaced the observed continuous ECG change exposure variable, $B_{i,obs}$, in the regression model with a Stein estimator (transformed ECG measure) of the true continuous ECG change exposure variable; $B_i^* = \widehat{B_i}(z)(1 - \widetilde{R_i}) + B_{i,obs}\widetilde{R_i}$, where $\widehat{B_i}(z)$ was the predicted value of the regression of $B_{i,obs}$ on *z* . The other covariates in the model, *z*, were assumed to have no intra-individual variation. $\widetilde{R_i}$ was 1 – the product of the mean squared error $(MSE)^{-1}$ and the average within-participant error variance, $\sigma^2_{B,e,i}$, in the study population, where the MSE was derived from the regression of $B_{i,obs}$ on *z*. Lastly, the transformed ECG measure and its corresponding baseline ECG measure were jointly corrected for intra-individual variation.

3.6 References

1. Schroeder EB, Whitsel EA, Evans GW, Prineas RJ, Chambless LE, Heiss G. Repeatability of Heart Rate Variability Measures. J Electrocardiol 2004;37:163-72.

2. Vaidean GD, Schroeder EB, Whitsel EA, Prineas RJ, Chambless LE, Perhac JS, et al. Short-Term Repeatability of Electrocardiographic Spatial T-Wave Axis and Qt Interval. J Electrocardiol 2005;38:139-47.

3. Jackson R, Chambless LE, Yang K, Byrne T, Watson R, Folsom A, et al. Differences between Respondents and Nonrespondents in a Multicenter Community-Based Study Vary by Gender Ethnicity. The Atherosclerosis Risk in Communities (Aric) Study Investigators. J Clin Epidemiol 1996;49:1441-46.

4. The Atherosclerosis Risk in Communities (Aric) Study: Manual of Procedures.

5. Rautaharju PM, Wolf HK, Eifler WJ, Blackburn H. A Simple Procedure for Positioning Precordial Ecg and Vcg Electrodes Using an Electrode Locator. J Electrocardiol 1976;9:35-40.

6. Atherosclerosis Risk in Communities Study, Manual 5, Electrocardiography. 1987, p. http://www.cscc.unc.edu/aric/visit/Electrocardiography.1_5.pdf

7. Rautaharju PM, Prineas RJ, Wood J, Zhang ZM, Crow R, Heiss G. Electrocardiographic Predictors of New-Onset Heart Failure in Men and in Women Free of Coronary Heart Disease (from the Atherosclerosis in Communities [Aric] Study). Am J Cardiol 2007;100:1437-41.

8. Rautaharju PM, Prineas RJ, Zhang ZM. A Simple Procedure for Estimation of the Spatial Qrs/T Angle from the Standard 12-Lead Electrocardiogram. J Electrocardiol 2007;40:300-4.

9. Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, et al. Electrocardiographic Detection of Left Ventricular Hypertrophy: Development and Prospective Validation of Improved Criteria. J Am Coll Cardiol 1985;6:572-80.

10. Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic Detection of Left Ventricular Hypertrophy by the Simple Qrs Voltage-Duration Product. J Am Coll Cardiol 1992;20:1180-6.

11. Rautaharju PM, Park LP, Gottdiener JS, Siscovick D, Boineau R, Smith V, et al. Race- and Sex-Specific Ecg Models for Left Ventricular Mass in Older Populations. Factors Influencing Overestimation of Left Ventricular Hypertrophy Prevalence by Ecg Criteria in African-Americans. J Electrocardiol 2000;33:205-18.

12. Eriksson H, Caidahl K, Larsson B, Ohlson LO, Welin L, Wilhelmsen L, et al. Cardiac and Pulmonary Causes of Dyspnoea--Validation of a Scoring Test for Clinical-Epidemiological Use: The Study of Men Born in 1913. Eur Heart J 1987;8:1007-14.

13. Fonseca C, Oliveira AG, Mota T, Matias F, Morais H, Costa C, et al. Evaluation of the Performance and Concordance of Clinical Questionnaires for the Diagnosis of Heart Failure in Primary Care. Eur J Heart Fail 2004;6:813-20, 21-2.

14. American Heart Association: Heart Disease and Stroke Statistics - 2009 Update. Dallas, TX: American Heart Association; 2008.

15. Baker DW. Prevention of Heart Failure. J Card Fail 2002;8:333-46.

16. The Atherosclerosis Risk in Communities (Aric) Study: Design and Objectives. The Aric Investigators. Am J Epidemiol 1989;129:687-702.

17. Verdecchia P, Angeli F. [the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure: The Weapons Are Ready]. Rev Esp Cardiol 2003;56:843-7.

18. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2003;26 Suppl 1:S5-20.

19. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-97.

20. Baecke JA, Burema J, Frijters JE. A Short Questionnaire for the Measurement of Habitual Physical Activity in Epidemiological Studies. Am J Clin Nutr 1982;36:936-42.

21. Bishop YMM FS, Holland PW. Discrete Multivariate Analysis: Theory and Practice. Cambridge: The MIT Press; 1975.

22. Carpenter J, Bithell J. Bootstrap Confidence Intervals: When, Which, What? A Practical Guide for Medical Statisticians. Stat Med 2000;19:1141-64.

23. Chambless LE, Davis V. Analysis of Associations with Change in a Multivariate Outcome Variable When Baseline Is Subject to Measurement Error. Stat Med 2003;22:1041-67.

CHAPTER 4

Manuscript I: Short-term repeatability of ECG variables predictive of cardiovascular morbidity and mortality

4.1 Abstract

Background: Various electrocardiogram (ECG) abnormalities and their changes over time are associated with excess risk of cardiovascular mortality and morbidity. Knowledge of the short-term repeatability of these ECG measures, which have not been characterized for many ECG parameters, can allow for its correction in prediction analysis.

Methods: We measured the two-minute and one-week repeatability of seven ECG variables measured by a computer-ECG software (spatial QRS/T angle, Cornell voltage, Cornell product, left ventricular mass, T net amplitudes in leads V_5 and V_1, and ST depression) in 63 middle-aged, white and black men and women in a ECG repeatability study and we assessed the contribution of between-participant, between-visit and within-visit components of variance.

Results: Short-term repeatability of the ECG measures was excellent. Intra-class correlation **(**ICC) coefficients ranged from 0.86 to 0.99.

Conclusions: Our results suggest that select ECG measures employed for prediction in clinical and epidemiologic settings were highly reliable in the short-term. Estimation of their predicted effect on cardiovascular outcomes may not be subject to substantial bias due to short-term variability if measurements are obtained under standardized conditions. Under such circumstances, analytic adjustment for short-term measurement variability may not be essential.

4.2 Introduction

Many epidemiologic studies have demonstrated that abnormalities in various resting, standard twelve-lead electrocardiogram (ECG) measures and their changes over time are associated with subsequent cardiovascular morbidity and mortality (1-8). However, the short-term repeatability of the ECG measures is often not well documented in those studies. Sources of error in measurements of ECG variables within a person include within-person biological and methodological variability, which includes variability in placement of electrodes and the precision of the ECG record readings (9). If measurement variability is high (low repeatability), then the ECG variable is likely to have bias associated with its estimate of effect on cardiovascular outcomes (10). Past and future studies can benefit from the estimation of short-term repeatability of ECG measures, since this would enable consideration in measurement protocols and statistical adjustment for variability (11).

The ECG Repeatability Study was conducted in 2001 to estimate the two-minute and one-week repeatability of ECG measures in 63 participants, ages 45-64 years (12, 13). Two previous reports (12, 13) from the ECG Repeatability Study quantified the short-term repeatability of T wave axis, QT interval, heart rate and heart rate variability using the standard twelve-lead ECG. Vaidean and colleagues (13) investigated spatial T wave axis and QT interval. The intra-class correlation (ICC) coefficients for the T wave axis and heart rate were 0.87 (95% confidence interval: 0.81, 0.93) and 0.82 (95% confidence interval: 0.75, 0.90), respectively, and for QT interval-based indices ICC coefficients were greater than 0.60. Schroeder and colleagues (12) found that for ten-second recordings, ICC coefficients for mean heart rate and RR interval were greater than 0.80, whereas ICC coefficients for standard deviation of all RR intervals (SDNN) and root mean square of differences in RR intervals (rMSSD), ranged from 0.41 to 0.57.

Our aim of the study was to quantify the short-term measurement variability of spatial QRS/T angle, Cornell voltage, Cornell product, left ventricular mass (LVM), T net amplitudes in leads V_5 and V_1, and ST depression, in middle-aged, white and black men and women in the ECG Repeatability Study. The ECG measures were chosen based on demonstrated relevance as cardiovascular risk predictors (3, 6). To the authors' knowledge, this is the first study to quantify the short-term repeatability of these ECG measures.

4.3 Material and methods

4.3.1 Study population

This ECG Repeatability Study included 63 volunteers, aged 45 to 64 years, recruited from the Chapel Hill, North Carolina area between July and October, 2001. Participants were invited to attend two examination visits, separated on average by ten days, with a standard deviation of four days. At each visit, participants had two ECG recordings. Recruitment was limited to those without reported use of type Ia anti-arrhythmics (quinidine, procainamide, disopyramide or moricizine), an artificial pacemaker or conditions such as renal failure, heart failure, diabetes mellitus or pregnancy. Furthermore, participants were excluded if they smoked, ate or drank anything but water less than ten hours prior to the visit(s). Age, race/ethnicity and sex were self-reported and body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Detailed descriptions of the ECG Repeatability Study have been published (12, 13). The Institutional Review Board of the University of North Carolina at Chapel Hill approved the study, and all participants gave informed, written consent.

4.3.2 ECG methods

The ECG Repeatability Study followed the standardized protocol used in the Atherosclerosis Risk in Communities (ARIC) Study for placing electrodes, room condition and data collection (14). All ECG recordings were carried out in a quiet, temperature-controlled room. Participants reported for the visits between 7:30 and 11:30 am. After participants rested in the supine position for fifteen minutes, one of four trained and certified ECG technicians recorded ten-second, twelve-lead ECGs using Kendall Q-Trace 5400 Ag/AgCl electrodes (Ludlow Co, Chicopee, MA). The E-V6

Halfpoint method (15) was used when recording the first of two ECGs using a MAC Personal Cardiographer (Marquette Electronics, Inc, Milwaukee, WI). The E-V6 Halfpoint method improves the precision and the repeatability of chest electrode positioning by placing the V_4 electrode at the horizontal level of the fifth intercostal space at the half-way point between the midsternal line and the left midaxillary line (V_6 location). Without removal of the electrodes, the recording was repeated after one to two minutes. ECGs were digitized and sent via modem after each recording session to the Epidemiological Cardiology Research (EPICARE) Center (Wake Forest University, Winston-Salem, NC). The EPICARE Center, blinded to participant identity and previous ECG readings, processed the ECGs using the most recent version of the Marquette GE program, version 12SL. Following an identical protocol, a second set of ECGs from the same participants were obtained on the second visit.

The following ECG measures were generated at the EPICARE Center using methods previously described (6): QRS/T angle, Cornell voltage, Cornell product, LVM, net T wave amplitude in leads V_5 and V_1, and ST depression. The QRS/T angle was defined as the angle between the mean QRS and T wave vectors (16). QRS/T angle was calculated using a simplified method from the net QRS amplitudes (R – absolute value of S or QS, whichever is larger, in leads V_6, aVF and V_2) and the net T wave amplitudes (signed T +signed T prime) in leads V_5, aVF and V_2. Cornell-voltage (R wave amplitude in lead aVL + Q or QS wave amplitude in lead V_3) (17), Cornell product (Cornell voltage x QRS duration) (18), and LVM predicted by a multivariate model (19) were used as measures of left ventricular hypertrophy (LVH). The LVM model adjusted for Cornell voltage and body weight. T waves were obtained by calculating mean and peak T wave

values in lead V_5, whereas for T wave amplitude in lead V_1, only the mean value was used. ST depression was evaluated using ST amplitude in lead V_5 at 60 ms past the end of the QRS interval (the J-point) from the Marquette-GE program.

4.3.3 Statistical analysis

All analyses were performed with SAS 9.1 (SAS Institute, Inc., Cary, NC). Nested random effects models were used to partition the total variance into between-participant, between-visit and within-visit components of variance. The within-visit component of variation represents methodological variability. The within-participant component of variation, the summation of the between-visit and within-visit components of variance, represents a combination of temporal biological and methodological variability. In addition, the square roots of the between-participant, between-visit and within visit variances were calculated. The coefficient of variation for each component was calculated as the ratio of the square root of its variance to its grand mean, multiplied by 100. The ICC coefficient was calculated for each of the ECG measures and 95% confidence intervals were derived using the Delta method (20). The ICC coefficient is the between-participant variance over the total variance (sum of between-participants, between-visits and within-visit variance) and can be interpreted as the correlation between ECG measures at different visits. Furthermore, the sex-specific ICC coefficient was calculated for each of the ECG measures and 2000 samples were used to calculate confidence intervals using bootstrapping methods (21). The following criteria were used

to characterize short-term repeatability: poor, 0-0.40; moderate, 0.41-0.60; good, 0.61-0.80; and excellent, 0.81-1.0.

4.4 Results

Age in years, race/ethnicity, sex and BMI of the population were described as means or proportions (Table 1). Table 2 presents mean values and standard deviations calculated by visit (1 or 2) and measurement of ECG (1 – 4) for each ECG measure. The mean values for the ECG measures were fairly stable across ECG recording sessions (Table 2). Most of the total variation of ECG variables was due to between-participant variation (Table 3), with coefficients of variation ranging from 31.07 to 159.06. The ICC coefficients were greater than 0.86, and thus indicate excellent short-term repeatability (Table 4). The LVM measure had the highest short-term repeatability value (ICC coefficient = 0.99). The sex-specific ICC coefficients were greater than 0.73, and thus indicate good to excellent short-term repeatability.

4.5 Discussion

The data from this study indicate excellent short-term repeatability of spatial QRS/T angle, Cornell voltage, Cornell product, LVM, T net amplitudes in leads V_5 and V_1, ST depression measured from a twelve-lead ECG.

Previous studies (12, 13) have examined the short-term repeatability of T wave axis, QT interval, heart rate and heart rate variability in the ECG Repeatability Study using a standard ten-second, twelve-lead ECG. In general, they found that the between-participant component represented most of the total variability compared to between-visit and within-visit components of variance, with the exception being SDNN and rMSSD, measures of heart rate variability. The high between-participant component of variance has been attributed to the highly standardized procedures for collection and reading of ECGs which maximizes between-participant biological variability (13). Similar to Schroeder and colleagues (12), who evaluated mean heart rate and RR interval, our ICC coefficients for ECG measures represent excellent short-term repeatability. Vaidean and colleagues (13) observed a range ICC coefficients (0.61 to 0.92) for measures of the QT interval, whereas, comparable to our study, both T wave axis and heart rate had excellent short term repeatability, 0.87 and 0.82, respectively.

Within-participant variability can be explained by a combination of temporal biological and methodological variation. In order to minimize the influence of methodological variation, the ECG Repeatability Study applied strict quality control approaches that were comparable to standardized protocol used in the ARIC Study (22). Despite adherence to a standardized measurement protocol for data acquisition and processing by trained and certified technicians, operator-related, procedure-related and biological sources of variability may exist. Electrode misplacement can occur and in a systematic fashion even when staff are trained and aware that they are being evaluated (23). The electrodes in our study remained in place within visits, but electrode placement between visits may have contributed to variability (24). As a weakness of this study, we

were unable to compare between-technician and within-technician differences, because many ECG recordings had to be performed by the same technician in the same visit. Various within-participant sources of variability in ECG measures are known to exist that are subject to change between visits (9). However, our study indicates that most of the total variation in ECG measurements was due to the between-participant rather than to the between-visit component of variance.

When Vaidean and colleagues (13) evaluated the sex-specific short-term repeatability of QT interval, calculated as a linear function of the RR interval, higher ICC coefficient values were observed for men (0.92; 95% confidence interval: 0.88, 0.97) than women (0.62; 95% confidence interval:0.41, 0.83). Although, in our study, there were no sex-specific differences in ICC coefficients for Cornell voltage, Cornell product, LVM, and net T wave amplitude in leads V_5, and V_1, there were notable differences for QRS/T angle, and ST depression, with women having lower values than men. Replication studies using larger numbers of participants may be informative for the extent of variability of spatial QRS/T angle, Cornell voltage, Cornell product, LVM, T net amplitudes in leads V_1 and V_5, and ST depression, by important demographic factors, such as age, race/ethnicity and BMI.

We found that women had lower ICC coefficients for QRS/T angle and ST depression than men. BMI has been known to impact short-term repeatability of ECG measures (9) and may have influenced the ICC coefficient estimates in our study. In support of this hypothesis, we found higher mean BMI values for women than men (data not shown). However, despite sex-specific differences in BMI in our analysis, ICC

coefficients for net T wave amplitude in leads V_5 and V_1, and ECG measures of LVH (LVM, Cornell voltage, and Cornell product) were identical by sex.

Adding new information to the published literature, we estimated the short-term repeatability of spatial QRS/T angle, Cornell voltage, Cornell product, LVM, T net amplitudes in leads V_1 and V_5, and ST depression. Complementing this, we presented the proportion of total variance due to between-participant, between-visit and within-visit components of variance. We additionally presented our short-term repeatability results by sex. Lastly, our study employed the data collecting and processing protocols used by the ARIC Study (22), which is comparable to that used by several other large-scale population-based studies. Generalizability of our estimates to other comparable populations is aided by this.

In conclusion, high short-term repeatability results for select ECG measures in the present study indicate that they can be reliably measured in epidemiologic studies when carefully standardized protocols for ECG acquisition and processing are employed. The high short-term repeatability supports analyses of their effects on cardiovascular disease outcomes.

ACKNOWLEDGEMENTS

This work was supported in part by a grant (RR00046) from the General Clinical Research Centers program of the Division of Research Resources, National Institutes of Health, and by grants (N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019,

N01-HC-55020, N01-HC-55021 and N01-HC-55022) from the US National Heart, Lung, and Blood Institute. K.L.C. was supported by a Royster Society Sequoyah Dissertation Fellowship from the University of North Carolina Graduate School. The authors thank the staff and participants of the ECG Repeatability Study and the staff of the Atherosclerosis Risk in Communities (ARIC) Study for their important contributions.

4.6 References

1. Crow RS, Prineas RJ, Hannan PJ, Grandits G, Blackburn H. Prognostic Associations of Minnesota Code Serial Electrocardiographic Change Classification with Coronary Heart Disease Mortality in the Multiple Risk Factor Intervention Trial. Am J Cardiol 1997;80:138-44.

2. Rautaharju PM, Ge S, Nelson JC, Marino Larsen EK, Psaty BM, Furberg CD, et al. Comparison of Mortality Risk for Electrocardiographic Abnormalities in Men and Women with and without Coronary Heart Disease (from the Cardiovascular Health Study). Am J Cardiol 2006;97:309-15.

3. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic Predictors of Incident Congestive Heart Failure and All-Cause Mortality in Postmenopausal Women: The Women's Health Initiative. Circulation 2006;113:481-9.

4. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic Abnormalities That Predict Coronary Heart Disease Events and Mortality in Postmenopausal Women: The Women's Health Initiative. Circulation 2006;113:473-80.

5. Rautaharju PM, Nelson JC, Kronmal RA, Zhang ZM, Robbins J, Gottdiener JS, et al. Usefulness of T-Axis Deviation as an Independent Risk Indicator for Incident Cardiac Events in Older Men and Women Free from Coronary Heart Disease (the Cardiovascular Health Study). Am J Cardiol 2001;88:118-23.

6. Rautaharju PM, Prineas RJ, Wood J, Zhang ZM, Crow R, Heiss G. Electrocardiographic Predictors of New-Onset Heart Failure in Men and in Women Free of Coronary Heart Disease (from the Atherosclerosis in Communities [Aric] Study). Am J Cardiol 2007;100:1437-41.

7. Robbins J, Nelson JC, Rautaharju PM, Gottdiener JS. The Association between the Length of the Qt Interval and Mortality in the Cardiovascular Health Study. Am J Med 2003;115:689-94.

8. Triola B, Olson MB, Reis SE, Rautaharju P, Merz CN, Kelsey SF, et al. Electrocardiographic Predictors of Cardiovascular Outcome in Women: The National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (Wise) Study. J Am Coll Cardiol 2005;46:51-6.

9. Schijvenaars BJ, van Herpen G, Kors JA. Intraindividual Variability in Electrocardiograms. J Electrocardiol 2008;41:190-6.

10. Armstrong BK WE, Saracci R. Principles of Exposure Measurement in Epidemiology. New York: Oxford University Press; 1992.

11. Chambless LE, Davis V. Analysis of Associations with Change in a Multivariate Outcome Variable When Baseline Is Subject to Measurement Error. Stat Med 2003;22:1041-67.

12. Schroeder EB, Whitsel EA, Evans GW, Prineas RJ, Chambless LE, Heiss G. Repeatability of Heart Rate Variability Measures. J Electrocardiol 2004;37:163-72.

13. Vaidean GD, Schroeder EB, Whitsel EA, Prineas RJ, Chambless LE, Perhac JS, et al. Short-Term Repeatability of Electrocardiographic Spatial T-Wave Axis and Qt Interval. J Electrocardiol 2005;38:139-47.

14. The Atherosclerosis Risk in Communities (Aric) Study: Manual of Procedures.

15. Rautaharju PM, Wolf HK, Eifler WJ, Blackburn H. A Simple Procedure for Positioning Precordial Ecg and Vcg Electrodes Using an Electrode Locator. J Electrocardiol 1976;9:35-40.

16. Rautaharju PM, Prineas RJ, Zhang ZM. A Simple Procedure for Estimation of the Spatial Qrs/T Angle from the Standard 12-Lead Electrocardiogram. J Electrocardiol 2007;40:300-4.

17. Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, et al. Electrocardiographic Detection of Left Ventricular Hypertrophy: Development and Prospective Validation of Improved Criteria. J Am Coll Cardiol 1985;6:572-80.

18. Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic Detection of Left Ventricular Hypertrophy by the Simple Qrs Voltage-Duration Product. J Am Coll Cardiol 1992;20:1180-6.

19. Rautaharju PM, Park LP, Gottdiener JS, Siscovick D, Boineau R, Smith V, et al. Race- and Sex-Specific Ecg Models for Left Ventricular Mass in Older Populations. Factors Influencing Overestimation of Left Ventricular Hypertrophy Prevalence by Ecg Criteria in African-Americans. J Electrocardiol 2000;33:205-18.

20. Bishop YMM FS, Holland PW. Discrete Multivariate Analysis: Theory and Practice. Cambridge: The MIT Press; 1975.

21. Carpenter J, Bithell J. Bootstrap Confidence Intervals: When, Which, What? A Practical Guide for Medical Statisticians. Stat Med 2000;19:1141-64.

22. Atherosclerosis Risk in Communities Study, Manual 5, Electrocardiography. 1987, p. http://www.cscc.unc.edu/aric/visit/Electrocardiography.1_5.pdf

23. Wenger W, Kligfield P. Variability of Precordial Electrode Placement During Routine Electrocardiography. J Electrocardiol 1996;29:179-84.

24. Willems JL, Poblete PF, Pipberger HV. Day-to-Day Variation of the Normal Orthogonal Electrocardiogram and Vectorcardiogram. Circulation 1972;45:1057-64.

Table 13. (MS I: Table 1) Characteristics of participants, the ECG Repeatability Study(N=63)

Characteristic	Mean (standard deviation) or N (percent)
Age (years)	52 (5)
Black ethnicity	20 (32%)
Female sex	31 (49%)
Body mass index (kg/m^2)	27 (5)

* The study population included 63 healthy participants, ages 45 to 64 years, with no reported use of class Ia antiarrhythmics, no artificial pacemaker or conditions such as renal failure, heart failure, diabetes mellitus or pregnancy.
† Abbreviations: ECG, electrocardiogram; kg, kilogram; m, meter.

Table 14. (MS I: Table 2) Means (standard deviations) for ECG measures, the ECG Repeatability Study (N=63)

ECG Measure	First Visit		Second Visit	
	ECG1	ECG2	ECG3	ECG4
QRS/T angle (°)	79 (26)	80 (26)	78 (26)	77 (27)
Cornell voltage (μV)	1213 (509)	1224 (517)	1214 (496)	1204 (494)
Cornell product (μV.s)	114 (51)	116 (53)	114 (49)	114 (49)
Left ventricular mass (g)	154 (28)	154 (28)	154 (27)	154 (27)
$T_{net}V_5$ amplitude (μV)	404 (211)	398 (207)	418 (224)	415 (218)
$T_{net}V_1$ amplitude (μV)	84 (155)	88 (149)	92 (160)	98 (155)
$ST_{60}V_5$ (μV)	49 (31)	50 (31)	52 (33)	51 (33)

* The study sample included 63 healthy participants, ages 45 to 64 years, with no reported use of class Ia antiarrhythmics, no artificial pacemaker or conditions such as renal failure, heart failure, diabetes mellitus or pregnancy.
† Abbreviations: ECG, electrocardiogram; °, degree; μV, micro-volts; g, gram; s, seconds.
‡ Definitions: ECG1, ECG parameter estimate at visit 1; ECG2, ECG parameter estimate at visit 1, approximately 1 minute after ECG1; ECG3, ECG parameter estimate at visit 2; ECG4; ECG parameter estimate at visit 2, approximately 1 minute after ECG3; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1; $ST_{60}V_5$, ST segment amplitude at time point 60 ms past end of QRS in lead V_5.

Table 15. (MS I: Table 3) Square root of variance components and coefficients of variation of ECG measures, the ECG Repeatability Study (N=63)

ECG Measure	Square Root	Coefficient of Variation
QRS/T angle (°)		
Between-participant	24.36	31.07
Between-visit	9.28	11.84
Within-visit	2.21	2.82
$ST_{60}V_5$ (μV)		
Between-participant	29.57	58.61
Between-visit	10.79	21.39
Within-visit	4.61	9.14
$T_{net}V_5$ amplitude (μV)		
Between-participant	203.70	49.85
Between-visit	65.96	16.14
Within-visit	18.59	4.55
$T_{net}V_1$ amplitude (μV)		
Between-participant	143.55	159.06
Between-visit	52.68	58.37
Within-visit	24.40	27.04
Left ventricular mass (g)		
Between-participant	27.32	17.73
Between-visit	2.55	1.65
Within-visit	1.19	0.77
Cornell voltage (μV)		
Between-participant	496.722	40.92
Between-visit	73.58	6.06
Within-visit	45.17	3.72
Cornell product (μV.s)		
Between-participant	49.67	43.35
Between-visit	8.04	7.02
Within-visit	5.10	4.45

* The study sample included 63 healthy participants, ages 45 to 64 years, with no reported use of class Ia antiarrhythmics, no artificial pacemaker or conditions such as renal failure, heart failure, diabetes mellitus or pregnancy. The coefficient of variation is the product of 100 and the square root of its variance/grand mean.

† Abbreviations: ECG, electrocardiogram; °, degree; μV, micro-volts; g, gram; s, seconds.

‡ Definitions: QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1; $ST_{60}V_5$, ST segment amplitude at time point 60 ms past end of QRS in lead V_5.

Table 16. (MS I: Table 4) Reliability coefficients for ECG measures, the ECG Repeatability Study (N=63)

ECG Measure	Reliability Coefficient		
	Female and Male	**Female**	**Male**
QRS/T angle (°)	0.87 (0.81, 0.93)	0.75 (0.73, 0.78)	0.93 (0.92, 0.95)
Cornell voltage (μV)	0.97 (0.96, 0.98)	0.97 (0.97, 1.00)	0.97 (0.00, 1.00)
Cornell product (μV.s)	0.96 (0.95, 0.98)	0.97 (0.75, 0.98)	0.96 (0.97, 1.00)
Left ventricular mass (g)	0.99 (0.98, 0.99)	0.99 (0.99, 0.99)	0.97 (0.97, 0.98)
$T_{net}V_5$ amplitude (μV)	0.90 (0.85, 0.95)	0.85 (0.83, 1.00)	0.91 (0.81, 1.00)
$T_{net}V_1$ amplitude (μV)	0.86 (0.85, 0.86)	0.74 (0.70, 1.00)	0.86 (0.00, 1.00)
$ST_{60}V_5$ (μV)	0.86 (0.80, 0.92)	0.73 (0.70, 0.75)	0.84 (0.82, 0.85)

***** The study sample included 63 healthy participants, ages 45 to 64 years, with no reported use of class Ia antiarrhythmics, no artificial pacemaker or conditions such as renal failure, heart failure, diabetes mellitus or pregnancy. The reliability coefficient is the between-participant variance/total variance of the ECG measure.

† Abbreviations: ECG, electrocardiogram; °, degree; μV, micro-volts; g, gram; s, seconds.

‡ Definitions: QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1; $ST_{60}V_5$, ST segment amplitude at time point 60 ms past end of QRS in lead V_5.

CHAPTER 5

Results Manuscript II: Long-term changes of ECG predictor variables. The Atherosclerosis Risk in Communities (ARIC) Study

5.1 Abstract

Background: Few have described the long-term changes in electrocardiogram (ECG) variables in population samples, or in individuals with coronary heart disease (CHD), diabetes or hypertension status. Since a number of ECG measurements are predictive of downstream cardiovascular and cerebrovascular diseases, their changes over time are of clinical and public health interest.

Methods: We evaluated the changes over an average of 9 years (range = 7 – 12 years) in selected ECG measures (spatial QRS/T angle, QT interval, Cornell voltage, Cornell product, left ventricular mass (LVM), T net amplitudes in leads V_5 and V_1, and ST depression) in the population-based cohort of the Atherosclerosis Risk in Communities (ARIC) Study. These changes were characterized by diabetes, hypertension and CHD status at intake. Linear and logistic regression modeling was used to evaluate the long-term changes of ECG measures, as continuous (n = 13901) and

categorical variables (n range = 10239 – 12870), adjusting for age, race/center, sex and baseline ECG measure.

Results: In general, higher mean annual rates of change in QRS/T angle, QT interval, Cornell voltage, Cornell product, LVM, and T net amplitude in lead V_1, and lower mean annual rates of change in T net amplitude in lead V_5 and ST depression, were observed in persons with CHD, diabetes and hypertension compared to those without; and thus, a higher proportion of ECG change was present in persons with these conditions; the exception being with LVM, where lower values, rather than the expected higher values, of mean rates of change per year were observed in diabetics and hypertensives.

Conclusions: Our results suggest that long-term changes in ECG measures are of small magnitude in mostly healthy adults sampled from the population. Long-term changes of ECG measures associated with cardiovascular risk are of greater magnitude in persons with CHD, diabetes or hypertension, compared with persons without these conditions.

5.2 Introduction

Epidemiologic studies have demonstrated that the changes of abnormalities in various resting, standard twelve-lead electrocardiogram (ECG) measures are associated with subsequent cardiovascular morbidity and mortality (1-4). However, little is known about the long-term changes in ECG measures in groups defined by demographic

characteristics, cardiovascular risk or morbidity. This information may aid risk stratification in clinical encounters and assist researchers in characterizing the role of ECG measurements on incident cardiovascular morbidity and mortality. There is a paucity of information describing the changes of ECG variables over the long term. Research has focused on the long-term changes of ECG variables in the course of disease (2, 5-7) and in response to treatments (5-7), but only two studies to our knowledge evaluated the long-term changes of ECG measures, specifically heart rate and heart rate variability, in relatively healthy persons (8, 9).

To our knowledge, no work has focused on the descriptive epidemiology of the long-term changes of various ECG variables in relatively healthy middle-aged populations, taking into account clinical risk factors for cardiovascular disease morbidity and mortality. Therefore, we examined the changes of several continuous and categorical ECG measurements over the course of an average of nine years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study. Because of their demonstrated relevance as cardiovascular risk predictors we focused on spatial QRS/T angle, QT interval, Cornell voltage, Cornell product, left ventricular mass (LVM), T net amplitudes in leads V_5 and V_1, and ST depression, and examined whether temporal changes in these measures differed by coronary heart disease (CHD), diabetes and hypertension status at cohort intake. We stratified by CHD, diabetes and hypertension status, since the majority of heart failure cases are attributable to these conditions (10), all of which are treatable or preventable (11).

5.3 Material and methods

5.3.1 Study population

The ARIC Study combines epidemiologic surveillance of four communities and a community-based prospective cohort designed to investigate the etiology and natural history of atherosclerosis and its sequelae. From 1987 to 1989, the ARIC Study cohort of 15,792 black and white participants aged 45 to 64 years was drawn from four communities in North Carolina (NC), Mississippi (MS), Minnesota (MN), and Maryland (MD). Two of the population samples (Washington County, MD and Minneapolis, MN suburbs) were mostly white. Blacks were over-sampled in Forsyth County, NC (12% black) and were exclusively sampled in Jackson, MS to provide statistical power to investigate findings by race/ethnicity. Following an extensive baseline examination participants were followed via annual telephone interviews, clinical examinations approximately every three years from 1987 to 1999, and ongoing medical record abstraction for hospitalized events and deaths. Each clinical examination consisted of standardized interviews, anthropometric and blood pressure measurements, venipuncture for blood samples and a twelve-lead standard ECG. A comparison of study participants to non-respondents has been described (12). The Institutional Review Boards at each of the institutions involved approved the study, and all participants gave informed, written consent.

5.3.2 ECG methods

The ARIC Study used a standardized protocol for the acquisition of and processing of ECGs (13). All ECG recordings were carried out in a quiet, temperature-controlled room. After participants rested in the supine position for fifteen minutes, trained and certified ECG technicians recorded ten-second, twelve-lead ECGs using Kendall Q-Trace 5400 Ag/AgCl electrodes (Ludlow Co, Chicopee, Mass). The E-V6 Halfpoint method (14) was used when recording ECGs using a MAC Personal Cardiographer (Marquette Electronics, Inc, Milwaukee, WI). The E-V6 Halfpoint method improves the precision and the repeatability of chest electrode positioning by placing the V_4 electrode at the horizontal level of the fifth intercostal space at the half-way point between the midsternal line and the left midaxillary line (V_6 location). ECGs were digitized and sent via modem after each recording session to the Epidemiological Cardiology Research (EPICARE) Center (Wake Forest University, Winston-Salem, NC). The EPICARE Center, blinded to participant identity processed the ECGs using the 12SL version of the Marquette GE program.

The following ECG measures were generated at the EPICARE Center using methods previously described (15): spatial QRS/T angle, QT interval, Cornell voltage, Cornell product, LVM, T net amplitudes in leads V_5 and V_1, and ST depression. The QRS/T angle was defined as the angle between the mean QRS and T wave vectors (16). The QRS/T angle was defined as the angle between the mean QRS and T-wave vectors (16). QRS/T angle was calculated using a simplified method from the net QRS amplitudes (R – absolute value of S or QS, whichever is larger, in leads V_6, aVF and V_2) and the net T wave amplitudes (signed T +signed T prime) in leads V_5, aVF and V_2. QT interval, used to evaluate QT prolongation, is the sex- and race-specific QT adjusted for

heart rate as a linear function of the RR interval (17). Cornell voltage (R wave amplitude in lead aVL + Q or QS wave amplitude in lead V_3) (18), Cornell product (Cornell voltage x QRS duration) (19), and LVM predicted by a multivariate model (20) were used as measures of left ventricular hypertrophy. The LVM model adjusted for Cornell voltage and body weight. T waves were obtained by calculating mean and peak T wave values in lead V_5, whereas for T wave amplitude in lead V_1, only the mean value was used. ST depression was evaluated using ST amplitude in lead V_5 at 60 ms past the end of the QRS interval (the J-point) from the Marquette-GE program.

The following participant-specific linear regression model was used to derive the exposure variable, continuous change of the ECG measure (B_i): $y_{ij} = A_i + B_i\, t_{ij}$, where y = the ECG variable value, i = 1, 2, 3…n participants, j = 1, 2, 3 or 4 visits, and t was the time between ARIC Visit 1 and subsequent visits. The continuous change ECG variable is the average rate of change per year and summarizes the longitudinal information for each participant.

We additionally constructed categorical change ECG variables. To provide comparability with an earlier analysis in the ARIC Study, we used cut points for ECG variables shown to be associated with incident heart failure used by Rautaharju and colleagues (15). ECG variables were defined using the following cut points for men (M) and women (W): QRS/T angle (°): M ≥ 107, W ≥ 89; QT interval (ms): M ≥ 436, W ≥ 442; Cornell voltage (μV): M ≥ 2650, W ≥ 1673; Cornell product (μV.s): M ≥ 207, W ≥ 152; LVM (g): M ≥ 204, W ≥ 162; $T_{net}V_5$ amplitude (μV): M ≤ 122, W ≤ 107; $T_{net}V_1$ amplitude (μV): M ≥ 307, W ≥ 151; and $ST_{60}V_5$ (μV): M ≤ 5, W ≤ -7. For each ECG

variable, categorical change was defined as ever exceeding the cut point ("1") over ARIC visits, or else "0".

5.3.4 Covariates

The covariates selected for the analysis were age (years) and sex (male or female). A race/center variable was created by combining each participant's self-reported race/ethnicity (black or white) with their respective study center (Forsyth County, NC, Jackson, MS, Minneapolis, MN and Washington County, MD). Additional covariates selected for the analysis include hypertension (yes or no), diabetes (yes or no) and CHD (yes or no) at the baseline examination. Blood pressure, lipids and glucose were measured according to standard ARIC procedures (13). Participants were asked to fast twelve hours before blood draw and actual fasting times were recorded. Blood was drawn from an antecubital vein of seated participants, serum was centrifuged, and frozen samples were shipped to central laboratories for analysis. The mean of the last two of three systolic and diastolic sitting blood pressure measurements obtained from a random-zero sphygmomanometer was used for measures of blood pressure.

Hypertension was defined as a systolic blood pressure value equal to or greater than 140 mmHg, a diastolic blood pressure value equal to or greater than 90 mmHg, or use of blood pressure lowering medications in the past two weeks (21). Pre-hypertension was defined as a systolic blood pressure value equal to or greater than 120 mm Hg but less than 140 mm Hg or a diastolic blood pressure value equal to or greater than 80 mm Hg but less than 90 mm Hg (21). Type II diabetes mellitus was defined as a fasting

serum glucose level of 7.0 mmol/L or more (126 mg/dL), nonfasting glucose level of 11.1 mmol/L or more (200 mg/dL), participant report of a physician diagnosis of diabetes, or current use of diabetes medication (22). Pre-diabetes was defined as a fasting serum glucose level of 6.1 mmol/L (110 mg/dL) or more but less than 7.0 mmol/L (126 mg/dL) (22). CHD at baseline was defined from a reported history of physician-diagnosed myocardial infarction, coronary artery bypass surgery, coronary angioplasty, or evidence of a previous myocardial infarction on an ECG.

5.3.5 Statistical analysis

We excluded participants with fewer than two ECGs (n = 1340), with a QRS interval greater than or equal to 120 ms (n = 574), with a race/ethnicity other than black or white (n = 48), and black participants in Minneapolis, MN or Washington County, MD (n = 55). The final sample size for a cohort so defined ("cohort 1") was 13,901. Analyses evaluating the continuous change of ECG variables utilized cohort 1 data, whereas analyses evaluating categorical ECG change variables required the exclusion of participants with missing ECGs at baseline (n range = 228 – 287) and whose measurements parameters at baseline exceeded the established cut points mentioned above (n range = 1287 – 4148; cohorts 2 – 9). Cohorts 2 through 9 excluded those whose ECG measures at baseline exceeded the established cut point because they already had a higher risk for incident heart failure at baseline. The final sample sizes for cohorts 2, 3, 4, 5, 6, 7, 8 and 9 were 10239, 12870, 12735, 12230, 12142, 12033, 12126 and 12004, respectively.

Baseline characteristics and ECG measures were described as means and proportions in the full cohort and cohort 1. Logistic and linear regression were used to compare adjusted categorical and continuous changes of the ECG measures over ARIC visits 1 through 4, stratified by CHD, diabetes and hypertension status at baseline. QRS/T angle, Cornell voltage, Cornell product, T net amplitudes in leads V_5 and V_1, and ST depression were adjusted for age, race/center-, sex- and baseline ECG measure, while QT interval and LVM were adjusted for age and baseline ECG measure only since by definition these ECG measures were already adjusted for race/ethnicity and sex. A two-tailed *p*-value <0.05 was required for statistical significance. All analyses were performed with SAS 9.1 (SAS Institute, Inc., Cary, NC).

5.4 Results

Selected baseline characteristics of the full ARIC cohort and cohort 1 (see Methods), are presented in Table 1. Participants in cohort 1 and cohorts 2 – 9 (data not shown) were comparable to the full ARIC cohort in terms of age and sex, were more likely to be white and female and were less likely to have CHD, diabetes and hypertension.

Table 2 presents an overview of the ECG measures at baseline for the full cohort and cohort 1. It is important to note that only 13725 participants have ECGs information for the baseline visit; however these same participants still have two or more ECGs and thus qualify for inclusion into cohort 1. Compared to the full cohort, participants in cohort 1 had lower mean values for Cornell voltage, Cornell product, T net amplitude in

lead V_1, had a higher mean value for T net amplitude in lead V_5, had similar values for QRS/T angle, QT interval, LVM, and ST depression, and were less likely to cross the threshold cut points established for categorical ECG variables.

The age-, race/center-, sex and baseline ECG-adjusted changes of ECG variables over the average length of follow-up (9 years) are presented in Table 3, stratified by CHD status at baseline. Participants with a CHD manifestation at cohort intake had higher mean rates of change per year for QRST/T angle, QT interval, Cornell voltage, Cornell product, LVM, T net amplitude in lead V_1, and lower mean rates of change per year for T net amplitude in lead V_5 and ST depression. Participants with CHD were more likely to cross pre-specified cut points over ARIC visits for QRS/T angle, QT interval, Cornell voltage, Cornell product, T net amplitudes in leads V_5 and V_1 and ST depression, compared to participants without CHD; no differences were observed by CHD status for LVM.

The age-, race/center-, sex and baseline ECG-adjusted mean changes of ECG variables per year, stratified by diabetes and hypertension status are presented in Tables 4 and 5, respectively. The mean changes per year of continuous ECG variables differed by diabetes status, with greater values observed for the temporal change in QRS/T angle and T net amplitude in leads V_5 and V_1 in pre-diabetics compared to non-diabetics. Lower values were observed for continuous annual change in Cornell voltage, Cornell product, and LVM when pre-diabetics were compared to non-diabetics, while mean annual change values were comparable for QT interval and ST depression. Participants with diabetes at baseline had higher mean rates of change per year for QRST/T angle, QT interval,

Cornell voltage, Cornell product and T net amplitude in lead V_1, and lower mean rates of change per year for LVM, T net amplitude in lead V_5 and ST depression compared with non-diabetics. When comparing the changes in categorical ECG variables, minimal changes were observed among pre-diabetics compared with non-diabetics, although statistically significant differences were observed for QRS/T angle, QT interval, Cornell voltage, Cornell product and ST depression. Whereas, larger proportions of participants with diabetes crossed pre-specified cut points during follow-up for all ECG measures (QRS/T angle, QT interval, Cornell voltage, Cornell product, LVM, T net amplitudes in leads V_1 and V_5 and ST depression) compared with non-diabetics.

As shown in Table 5, all continuous measures of annualized change differed significantly by hypertension status for all ECG variables when pre-hypertensives and hypertensives were compared with normotensives; the only exception being LVM when pre-hypertensives were compared with normotensives. Greater mean values of rate of change per year were observed for QRS/T angle, QT interval, Cornell voltage, Cornell product and T net amplitude in lead V_1 and lower values were observed for T net amplitude in lead V_5 and ST depression when pre-hypertensives or hypertensives were compared with normotensives. A lower mean value of rate of change per year was observed for LVM when hypertensives were compared with normotensives. Furthermore, changes in categorical ECG variables statistically significantly differed by hypertension status for all ECG measures, where larger proportions of pre-hypertensive and hypertensive participants crossed the pre-specified ECG measure cut points compared with normotensives.

5.5 Discussion

Our results indicate that the long-term changes in ECG measures in mostly healthy, middle-aged adults sampled from the population are of small magnitude. Our analyses also show that such long-term changes of ECG measures are generally greater in magnitude in persons with CHD, diabetes or hypertension, compared to their peers in this cohort without these conditions.

Long-term changes of small magnitude in QRS/T angle, QT interval, Cornell voltage, Cornell product, LVM, T net amplitude in leads V_5 and V_1, and ST depression were observed during a follow-up ranging from 7 to 12 years (average 9 years), but often statistically significant changes were observed by CHD, diabetes and hypertension status, adjusting for age, race/center, sex and baseline ECG measure.

Higher values of QRS/T angle, QT interval, Cornell voltage, Cornell product, LVM and T net amplitude in lead V_1, and lower values for T net amplitude in lead V_5 and ST depression have been shown to be associated with increased risk for heart failure in the ARIC Study, the Women's Health Initiative and the Strong Heart Study (15, 23, 24). The mechanisms linking these ECG variables with incident heart failure are unclear. It has been posited that the ECG measures studied may be markers of ventricular remodeling and evolving CHD (15, 23-25). In our study and as expected, the observed temporal change in ECG measures tended to be in the direction of increasing risk among those with CHD, diabetes, or hypertension manifest at the baseline examination. Exceptions include LVM in diabetics and in hypertensives, where mean rates of change per year were lower in diseased participants compared with non-diseased.

Despite the important role of the temporal evolution in ECG variables in the context of clinical and demographic risk factors for predictions of cardiovascular morbidity and mortality, little prospective research has described the long-term changes of ECG measures in relatively healthy populations. A previous study conducted by Levy and colleagues presented categorical changes of R wave and S wave voltages and repolarization abnormalities by sex in participants with left ventricular hypertrophy in the Framingham Heart Study (2). Although it would appear that there were no sex-differences in ECG voltages and repolarization abnormalities, no statistical test was performed. Okin and colleagues showed in hypertensive patients with ECG left ventricular hypertrophy receiving antihypertensive treatment, that Cornell product and Sokolow-Lyon voltage decreased to a greater degree in men than in women (6, 7), in non-diabetics than in diabetics (5, 6), and in participants < 65 years compared to those ≥ 65 years of age (6). However, patients in this study were selected based on moderate-to-severe hypertension and elevated Cornell product and Sokolow-Lyon voltages, and thus results cannot be generalized to healthier populations. Lastly, Schroeder and colleagues evaluated measures of heart rate variability by diabetes (8) and hypertension (9) status in the ARIC Study over a mean of 9 years of follow-up and concluded that there were no differences in the rate of change in heart rate variability by these conditions.

In contrast to previous studies of the long-term changes of ECG measures, our study is the first to quantify the long-term changes of a wide array of ECG measures, inclusive of categorical and continuous measures, and to examine their temporal change by CHD, diabetes and hypertension status while adjusting for baseline ECG, age, race/ethnicity and sex. Our study was based on an extended follow-up of a large cohort,

with standardized risk factor assessment of men and women from diverse communities in the US population. Lastly, an important strength of this study is its reliance on a strict and standardized protocol for data collection and processing of ECGs throughout the study.

There are limitations to this study for the readers to consider. The yearly rates of change were estimated from triennial re-examination points. Considering the small magnitude of the average change in ECG measures seen in individuals without manifest morbidity at baseline our inability to measure change in intervals smaller than three years does not represent a significant shortcoming, although estimated from middle-aged persons who survived from one ARIC visit to the next. As another limitation, mean annual changes in ECG measures were assessed in populations (cohort 1 and cohorts 2-9 [data not shown]) that tended to be healthier than the original cohort. As a result, the long-term changes in ECG measures by CHD, diabetes and hypertension status were probably underestimated. Lastly, fixed sex-specific cut point values were used to classify the ECG measures in our analysis. It is possible that the appropriateness of these cut points may not generalize to other population groups. It should also be mentioned that other risk factors such as low physical activity, body mass index, and smoking status deserve attention in future analyses of the long-term changes of ECG variables.

To our knowledge, ours is the most extensive study of the long-term changes of select ECG measures to date. Our results suggest that mean long-term changes in most ECG measures known to predict cardiovascular events are of small magnitude in mostly healthy, middle-aged adults sampled from the population and followed for an average of 9 years. Our results also suggest that CHD, diabetes and hypertension can modify the

rate of long-term change in these ECG measures: the magnitude of the changes observed in the latter groups was greater than that seen in the cohort members without these morbid conditions. Replication of these analyses in different populations and with consideration of other conditions associated with cardiovascular risk will improve our understanding of the contribution of ECG measures and their change on the risk of cardiovascular outcomes.

ACKNOWLEDGEMENTS

K.L.C was supported by a University of North Carolina at Chapel Hill, Royster Society of Fellows Dissertation Completion fellowship. The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by contracts from the National Heart, Lung, and Blood Institute (N01-55015, N01-55016, N01-55018, N01-55019, N01-55020, N01-55021, N01-55022, and R01-HL064142). The authors thank the staff and participants of the ARIC Study for their important contributions.

5.6 References

1. Fagard RH, Staessen JA, Thijs L, Celis H, Birkenhager WH, Bulpitt CJ, et al. Prognostic Significance of Electrocardiographic Voltages and Their Serial Changes in Elderly with Systolic Hypertension. Hypertension 2004;44:459-64.

2. Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB. Prognostic Implications of Baseline Electrocardiographic Features and Their Serial Changes in Subjects with Left Ventricular Hypertrophy. Circulation 1994;90:1786-93.

3. Prineas RJ, Rautaharju PM, Grandits G, Crow R. Independent Risk for Cardiovascular Disease Predicted by Modified Continuous Score Electrocardiographic Criteria for 6-Year Incidence and Regression of Left Ventricular Hypertrophy among Clinically Disease Free Men: 16-Year Follow-up for the Multiple Risk Factor Intervention Trial. J Electrocardiol 2001;34:91-101.

4. Shamim W, Yousufuddin M, Cicoria M, Gibson DG, Coats AJ, Henein MY. Incremental Changes in Qrs Duration in Serial Ecgs over Time Identify High Risk Elderly Patients with Heart Failure. Heart 2002;88:47-51.

5. Okin PM, Devereux RB, Gerdts E, Snapinn SM, Harris KE, Jern S, et al. Impact of Diabetes Mellitus on Regression of Electrocardiographic Left Ventricular Hypertrophy and the Prediction of Outcome During Antihypertensive Therapy: The Losartan Intervention for Endpoint (Life) Reduction in Hypertension Study. Circulation 2006;113:1588-96.

6. Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, et al. Regression of Electrocardiographic Left Ventricular Hypertrophy by Losartan Versus Atenolol: The Losartan Intervention for Endpoint Reduction in Hypertension (Life) Study. Circulation 2003;108:684-90.

7. Okin PM, Gerdts E, Kjeldsen SE, Julius S, Edelman JM, Dahlof B, et al. Gender Differences in Regression of Electrocardiographic Left Ventricular Hypertrophy During Antihypertensive Therapy. Hypertension 2008;52:100-6.

8. Schroeder EB, Chambless LE, Liao D, Prineas RJ, Evans GW, Rosamond WD, et al. Diabetes, Glucose, Insulin, and Heart Rate Variability: The Atherosclerosis Risk in Communities (Aric) Study. Diabetes Care 2005;28:668-74.

9. Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. Hypertension, Blood Pressure, and Heart Rate Variability: The Atherosclerosis Risk in Communities (Aric) Study. Hypertension 2003;42:1106-11.

10. Baker DW. Prevention of Heart Failure. J Card Fail 2002;8:333-46.

11. Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA, et al. Prevention of Heart Failure: A Scientific Statement from the American

Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. Circulation 2008;117:2544-65.

12. Jackson R, Chambless LE, Yang K, Byrne T, Watson R, Folsom A, et al. Differences between Respondents and Nonrespondents in a Multicenter Community-Based Study Vary by Gender Ethnicity. The Atherosclerosis Risk in Communities (Aric) Study Investigators. J Clin Epidemiol 1996;49:1441-46.

13. The Atherosclerosis Risk in Communities (Aric) Study: Manual of Procedures.

14. Rautaharju PM, Wolf HK, Eifler WJ, Blackburn H. A Simple Procedure for Positioning Precordial Ecg and Vcg Electrodes Using an Electrode Locator. J Electrocardiol 1976;9:35-40.

15. Rautaharju PM, Prineas RJ, Wood J, Zhang ZM, Crow R, Heiss G. Electrocardiographic Predictors of New-Onset Heart Failure in Men and in Women Free of Coronary Heart Disease (from the Atherosclerosis in Communities [Aric] Study). Am J Cardiol 2007;100:1437-41.

16. Rautaharju PM, Prineas RJ, Zhang ZM. A Simple Procedure for Estimation of the Spatial Qrs/T Angle from the Standard 12-Lead Electrocardiogram. J Electrocardiol 2007;40:300-4.

17. Vaidean GD, Schroeder EB, Whitsel EA, Prineas RJ, Chambless LE, Perhac JS, et al. Short-Term Repeatability of Electrocardiographic Spatial T-Wave Axis and Qt Interval. J Electrocardiol 2005;38:139-47.

18. Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, et al. Electrocardiographic Detection of Left Ventricular Hypertrophy: Development and Prospective Validation of Improved Criteria. J Am Coll Cardiol 1985;6:572-80.

19. Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic Detection of Left Ventricular Hypertrophy by the Simple Qrs Voltage-Duration Product. J Am Coll Cardiol 1992;20:1180-6.

20. Rautaharju PM, Manolio TA, Siscovick D, Zhou SH, Gardin JM, Kronmal R, et al. Utility of New Electrocardiographic Models for Left Ventricular Mass in Older Adults. The Cardiovascular Health Study Collaborative Research Group. Hypertension 1996;28:8-15.

21. Verdecchia P, Angeli F. [the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure: The Weapons Are Ready]. Rev Esp Cardiol 2003;56:843-7.

22. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2003;26 Suppl 1:S5-20.

23. Okin PM, Roman MJ, Lee ET, Galloway JM, Best LG, Howard BV, et al. Usefulness of Quantitative Assessment of Electrocardiographic St Depression for Predicting New-Onset Heart Failure in American Indians (from the Strong Heart Study). Am J Cardiol 2007;100:94-8.

24. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic Predictors of Incident Congestive Heart Failure and All-Cause Mortality in Postmenopausal Women: The Women's Health Initiative. Circulation 2006;113:481-9.

25. Dhingra R, Pencina MJ, Wang TJ, Nam BH, Benjamin EJ, Levy D, et al. Electrocardiographic Qrs Duration and the Risk of Congestive Heart Failure: The Framingham Heart Study. Hypertension 2006;47:861-7.

Table 17. (MS II: Table 1) Means (standard deviations) and proportions of participants' characteristics at the baseline examination (1987-1989), the Atherosclerosis Risk in Communities (ARIC) Study

Covariate	Mean (Standard deviation) or n (percent)	
	Full cohort (n=15792)	**Cohort 1* (n=13901)**
Age (years)		
< 50	4235 (26.8%)	3827 (27.5%)
50-54	4097 (25.9%)	3681 (26.5%)
55-59	3852 (24.4%)	3372 (24.3%)
≥ 60	3608 (22.9%)	3021 (21.7%)
Mean	54.2 (5.8)	54.0 (5.7)
Sex		
Women	8710 (55.2%)	7829 (56.3%)
Men	7082 (44.9%)	6072 (43.7%)
Race/ethnicity		
White	11478 (72.7%)	10420 (75.0%)
Black	4266 (27.0%)	3481 (25.0%)
Race/Center		
White/Minneapolis, MN	4009 (25.4%)	3662 (26.3%)
White/Washington County, MD	4020 (25.5%)	3581 (25.8%)
Black/Jackson, MS	3728 (23.6%)	3103 (22.3%)
White/Foryth County, NC	3531 (22.4%)	3177 (22.9%)
Black/Forsyth County, NC	483 (3.1%)	378 (2.7%)
Coronary heart disease		
No	14682 (95.0%)	13072 (96.0%)
Yes	766 (5.0%)	551 (4.0%)
Non-diabetic	12051 (77.0%)	10871 (78.7%)
Prediabetic	1723 (11.0%)	1452 (10.5%)
Diabetic	1870 (12.0%)	1486 (10.8%)
Normotensive	6441 (41.0%)	5880 (42.5%)
Pre-hypertensive	3767 (24.0%)	3349 (24.2%)
Hypertensive	5504 (35.0%)	4605 (33.3%)

Definitions: *Cohort 1, black or white participants with at least two electrocardiograms (ECGs) between visits 1-4, with a QRS interval < 120 ms; coronary heart disease, history of myocardial infarction, coronary artery bypass surgery or coronary angioplasty; non-diabetics, fasting blood glucose < 110 mg/dL; pre-diabetics, fasting blood glucose 110-125 mg/dL; diabetics, fasting blood glucose level ≥ 126 mg/dL, a nonfasting blood glucose level ≥ 200 mg/dL, use of hypoglycemic medications, or self-reported physician diagnosis; normotensives, systolic blood pressure < 120 mm Hg or diastolic blood pressure < 80 mm Hg; pre-hypertensives, systolic blood pressure 120-140 mm Hg or diastolic blood pressure 80-90 mm Hg; hypertensives, systolic blood pressure >140 mm Hg, or diastolic blood pressure > 90 mm Hg, and/or use of anti-hypertension medications.

Table 18. (MS II: Table 2) Means (standard deviations) of ECG measures and proportion exceeding thresholds for risk of heart failure at the baseline examination (1987-1989), the Atherosclerosis Risk in Communities (ARIC) Study

ECG Measure	Mean (Standard deviation) or n (percent)	
	Full cohort* (n=15564)	**Cohort 1† (n=13725)**
QRS/T angle (°)	78.1 (31.5)	77.0 (30.2)
Male ≥ 107, female ≥ 89	4148 (26.7%)	3480 (25.4%)
QT interval (ms)	416.4 (17.4)	415.2 (15.7)
Male ≥ 436, female ≥ 442	1287 (8.3%)	866 (6.3%)
Cornell voltage (μV)	1248.7 (562.8)	1220.6 (524.6)
Male ≥ 2650, female ≥ 1673	1307 (8.4%)	1003 (7.3%)
Cornell product (μV.s)	117.8 (64.5)	112.7 (54.8)
Male ≥ 207, female ≥ 152	2023 (13.0%)	1508 (11.0%)
Left ventricular mass (g)	153.9 (30.3)	152.8 (29.6)
Male ≥ 204, female ≥ 162	1979 (12.8%)	1584 (11.5%)
$T_{net}V_5$ amplitude (μV)	281.3 (186.6)	287.5 (178.3)
Male ≤ 122, female ≤ 107	2116 (13.6%)	1702 (12.4%)
$T_{net}V_1$ amplitude (μV)	71.1 (159.0)	67.4 (146.6)
Male ≥ 307, female ≥ 151	2003 (12.9%)	1614 (11.8%)
$ST_{60}V_5$ (μV)	33.7 (38.6)	33.9 (35.9)
Male ≤ 5, female ≤ -7	2106 (13.5%)	1734 (12.6%)

Abbreviation: ECG. Electrocardiograph

Definitions: *Full cohort with ECGs at Visit 1, approximately 15564 depending on the ECG measure; † Cohort 1, black or white participants with at least two ECGs between visits 1-4, with a QRS interval < 120 ms. It is important to note that approximately 13725 participants have ECGs information for the baseline visit; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QTrr, used to evaluate QT prolongation, is the sex- and race-specific QT adjusted for heart rate as a linear function of the RR-interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1; $ST_{60}V_5$, ST segment amplitude at time point 60 ms past end of QRS in lead V_5.

Table 19. (MS II: Table 3) Race/center-, sex-, age- and baseline ECG-adjusted* means (standard deviations) of change in ECG measures and proportions of participants that exceed thresholds for risk of heart failure over mean follow-up of 9 years, by CHD status at baseline, the Atherosclerosis Risk in Communities (ARIC) Study

Measures of ECG change	Mean (95% confidence interval) or percent (95% confidence interval)	
	No CHD (n=13072)†	CHD (n=551)†
QRS/T angle (°)		
Mean rate of change per year	0.0014 (0.0013, 0.0014)	0.0056 (0.0052, 0.0060)‡
+ change across threshold of risk	22% (22%, 23%)	41% (37%, 45%)‡
QT interval (ms)		
Mean rate of change per year	0.0020 (0.0019, 0.0020)	0.0026 (0.0023, 0.0029)‡
+ change across threshold of risk	17% (17%, 18%)	21% (19%, 23%)‡
Cornell voltage (μV)		
Mean rate of change per year	0.0394 (0.0382, 0.0406)	0.0709 (0.0650, 0.0767)‡
+ change across threshold of risk	8% (7%, 9%)	14% (12%, 17%)‡
Cornell product (μV.s)		
Mean rate of change per year	0.0046 (0.0044, 0.0047)	0.0099 (0.0092, 0.0106)‡
+ change across threshold of risk	11% (10%, 12%)	21% (18%, 24%)‡
Left ventricular mass (g)		
Mean rate of change per year	0.0017 (0.0017, 0.0018)	0.0026 (0.0024, 0.0028)‡
+ change across threshold of risk	11% (11%, 11%)	10% (9%, 12%)
$T_{net}V_5$ amplitude (μV)		
Mean rate of change per year	-0.0078 (-0.0083, -0.0073)	-0.0282 (-0.0307, -0.0258)‡
+ change across threshold of risk	16% (16%, 17%)	24% (21%, 27%)‡
$T_{net}V_1$ amplitude (μV)		
Mean rate of change per year	0.0021 (0.0017, 0.0025)	0.0113 (0.0094, 0.0132)‡
+ change across threshold of risk	13% (13%, 14%)	22% (20%, 25%)‡
$ST_{60}V_5$ (μV)		
Mean rate of change per year	-0.0029 (-0.0030, -0.0028)	-0.0055 (-0.0060, -0.0051)‡
+ change across threshold of risk	16% (16%, 17%)	25% (22%, 28%)‡

Abbreviations: ECG, electrocardiograph; CHD, coronary heart disease

Definitions: *QT interval and left ventricular mass were adjusted for age and baseline ECG only; †the N presented is derived from Cohort 1; CHD, history of myocardial infarction, coronary artery bypass surgery or coronary angioplasty; ‡$p < 0.05$ compared with no CHD; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QT interval is the sex- and race-specific QT interval adjusted for heart rate as a linear function of the RR interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1;$ST_{60}V_5$,ST segment amplitude at time point 60 ms past end of QRS in lead V_5; mean rate of change per year, function of 2 or more ECG measures over visits 1-4 and time from baseline; + change across threshold of risk, crossing the threshold cut point at visits 2, 3 or 4, indicating increased risk for heart failure.

Table 20. (MS II: Table 4) Race/center-, sex-, age- and baseline ECG-adjusted* means (standard deviations) of change in ECG and proportions of participants that exceed thresholds for risk of heart failure over a mean follow-up of 9 years, by diabetes status at baseline, the Atherosclerosis Risk in Communities (ARIC) Study

Measures of ECG change	Mean (95% confidence interval) or percent (95% confidence interval)		
	Non-diabetics (n=10871)†	Pre-diabetics (n=1452)†	Diabetics (n=1486)†
QRS/T angle (°)			
Mean rate of change per year	0.0010 (0.0010, 0.0011)	0.0021 (0.0018, 0.0023)‡	0.0045 (0.0043, 0.0048)‡
+ change across threshold of risk	21% (21%, 22%)	25% (23%, 26%)‡	36% (34%, 38%)‡
QT interval (ms)			
Mean rate of change per year	0.0019 (0.0019, 0.0020)	0.0019 (0.0017, 0.0021)	0.0026 (0.0024, 0.0028)‡
+ change across threshold of risk	17% (16%, 17%)	19% (18%, 20%)‡	20% (19%, 21%)‡
Cornell voltage (μV)			
Mean rate of change per year	0.0401 (0.0.0388, 0.0414)	0.0320 (0.0290, 0.0361)‡	0.0503 (0.0468, 0.0539)‡
+ change across threshold of risk	8% (7%, 9%)	7% (6%, 8%)‡	10% (9%, 12%)‡
Cornell product (μV.s)			
Mean rate of change per year	0.0046 (0.0045, 0.0048)	0.0040 (0.0036, 0.0048)‡	0.0065 (0.0061, 0.0070)‡
+ change across threshold of risk	11% (11%, 12%)	10% (9%, 11%)‡	13% (11%, 14%)‡
Left ventricular mass (g)			
Mean rate of change per year	0.0019 (0.0018, 0.0019)	0.0014 (0.0013, 0.0015)‡	0.0011 (0.0009, 0.0012)‡
+ change across threshold of risk	10% (10%, 11%)	11% (10%, 12%)	15% (14%, 16%)‡
$T_{net}V_5$ amplitude (μV)			
Mean rate of change per year	-0.0066 (-0.0071, -0.0060)	-0.0110 (-0.0125, -0.0095)‡	-0.0215 (-0.0230, -0.0200)‡
+ change across threshold of risk	16% (15%, 17%)	17% (16%, 18%)	21% (19%, 22%)‡
$T_{net}V_1$ amplitude (μV)			
Mean rate of change per year	0.0011 (0.0006, 0.0015)	0.0032 (0.0020, 0.0043)‡	0.0111 (0.0100, 0.0123)‡
+ change across threshold of risk	13% (13%, 14%)	12% (11%, 13%)	19% (17%, 20%)‡
$ST_{60}V_5$ (μV)			
Mean rate of change per year	-0.0028 (-0.0029, -0.0027)	-0.0029 (-0.0032, -0.0026)	-0.0047 (-0.0050, -0.0044)‡
+ change across threshold of risk	16% (16%, 17%)	15% (13%, 16%)‡	21% (19%, 23%)‡

Abbreviation: ECG, electrocardiograph

Definitions: *QT interval and left ventricular mass were adjusted for age and baseline ECG only; †the N presented is derived from Cohort 1; non-diabetics, fasting blood glucose < 110 mg/dL;

pre-diabetics, fasting blood glucose 110-125 mg/dL; diabetics, fasting blood glucose level ≥ 126 mg/dL, a nonfasting blood glucose level ≥ 200 mg/dL, use of hypoglycemic medications, or self-reported physician diagnosis; ‡$p < 0.05$ compared with non-diabetics; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QT interval is the sex- and race-specific QT interval adjusted for heart rate as a linear function of the RR interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1; $ST_{60}V_5$, ST segment amplitude at time point 60 ms past end of QRS in lead V_5; mean rate of change per year, function of 2 or more ECG measures over visits 1-4 and time from baseline; + change across threshold of risk, crossing the threshold cut point at visits 2, 3 or 4, indicating increased risk for heart failure.

Table 21. (MS II: Table 5) Race/center-, sex-, age- and baseline ECG-adjusted* means (standard deviations) of change in ECG measures and proportions of participants that exceed thresholds for risk of heart failure over a mean follow-up of 9 years, by hypertension status at baseline, the Atherosclerosis Risk in Communities (ARIC) Study

Measures of ECG change	Mean (95% confidence interval) or percent (95 % confidence interval)		
	Normotensives (n=5880)†	Pre-hypertensive (n=3349)†	Hypertensivess (n=4605)†
QRS/T angle (°)			
Mean rate of change per year	0.0007 (0.0006, 0.0008)	0.0013 (0.0012, 0.0015)‡	0.0028 (0.0026, 0.0029)‡
+ change across threshold of risk	18% (18%, 19%)	22% (21%, 23%)‡	30% (29%, 32%)‡
QT interval (ms)			
Mean rate of change per year	0.0016 (0.0015, 0.0016)	0.0020 (0.0018, 0.0021)‡	0.0026 (0.0024, 0.0027)‡
+ change across threshold of risk	14% (14%, 15%)	17% (16%, 18%)‡	22% (21%, 23%)‡
Cornell voltage (μV)			
Mean rate of change per year	0.0338 (0.0320, 0.0356)	0.0422 (0.0398, 0.0445)‡	0.0473 (0.0452, 0.0494)‡
+ change across threshold of risk	7% (6%, 7%)	9% (8%, 10%)‡	10% (9%, 11%)‡
Cornell product (μV.s)			
Mean rate of change per year	0.0039 (0.0037, 0.0042)	0.0049 (0.0046, 0.0052)‡	0.0057 (0.0055, 0.0060)‡
+ change across threshold of risk	10% (9%, 10%)	12% (11%, 13%)‡	13% (13%, 14%)‡
Left ventricular mass (g)			
Mean rate of change per year	0.0018 (0.0017, 0.0019)	0.0017 (0.0016, 0.0018)	0.0017 (0.0016, 0.0017)‡
+ change across threshold of risk	8% (8%, 9%)	10% (10%, 11%)‡	15% (15%, 16%)‡
$T_{net}V_5$ amplitude (μV)			
Mean rate of change per year	-0.0044 (-0.0051, -0.0036)	-0.0070 (-0.0079, -0.0060)‡	-0.0152 (-0.0160, -0.0143)‡
+ change across threshold of risk	14% (13%, 14%)	16% (16%, 17%)‡	21% (20%, 22%)‡
$T_{net}V_1$ amplitude (μV)			
Mean rate of change per year	-0.0006 (-0.0012, -0.0000)	0.0023 (0.0015, 0.0030)‡	0.0061 (0.0054, 0.0068)‡
+ change across threshold of risk	12% (11%, 13%)	14% (13%, 15%)‡	16% (15%, 17%)‡
$ST_{60}V_5$ (μV)			
Mean rate of change per year	-0.0025 (-0.0027, -0.0024)	-0.0029 (-0.0031, -0.0028)‡	-0.0037 (-0.0039, -0.0035)‡
+ change across threshold of risk	13% (12%, 14%)	17% (16%, 18%)‡	21% (20%, 22%)‡

Abbreviation: ECG, electrocardiograph

Definitions: *QT interval and left ventricular mass were adjusted for age and baseline ECG only; †the N presented is derived from Cohort 1; normotensives, systolic blood pressure (SBP) <

120 mm Hg or diastolic blood pressure (DBP) < 80 mm Hg; pre-hypertensives, SBP 120-140 mm Hg or DBP 80-90 mm Hg; hypertensives, SBP >140 mm Hg, or DBP > 90 mm Hg, and/or use of anti-hypertension medications; ‡$p < 0.05$ compared with non-hypertensives; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QT interval is the sex- and race-specific QT interval adjusted for heart rate as a linear function of the RR interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1; $ST_{60}V_5$, ST segment amplitude at time point 60 ms past end of QRS in lead V_5; mean rate of change per year, function of 2 or more ECG measures over visits 1-4 and time from baseline; + change across threshold of risk, crossing the threshold cut point at visits 2, 3 or 4, indicating increased risk for heart failure.

CHAPTER 6

Results Manuscript III: Temporal changes in ECG variables and incident heart failure. The Atherosclerosis Risk in Communities (ARIC) Study

6.1 Abstract

Background: It has been demonstrated in clinical trials of high risk populations that temporal changes in select electrocardiogram (ECG) variables are associated with incident heart failure. However, their impact on heart failure incidence in a relatively healthy, population-based cohort has not been assessed.

Methods: We examined the association between selected ECG measures (spatial QRS/T angle, QT interval, Cornell voltage, and Cornell product, left ventricular mass, T net amplitudes in leads V_1 and V_5, and ST depression) and incident heart failure hospitalization or death in the Atherosclerosis Risk in Communities (ARIC) Study**.** The long-term ECG change variables were analyzed as categorical (n range = 9637 – 7812), based on sex-specific cut points, and continuous, based on a one standard deviation change (n = 10313). Heart failure was defined using International Classification of Diseases codes, 9^{th} Revision/10^{th} Revision, 428/I50. Cox proportional hazards regression modeling was used to control for clinical and demographic risk factors for heart failure.

Results: During a mean follow-up of 7 years, 670 participants developed heart failure in cohort 1. A 1 standard deviation increase in mean annual rate of change in QRS/T angle, Cornell voltage, Cornell product, left ventricular mass and T net amplitude in lead V_5 were statistically significantly associated with incident heart failure and the most precise predictor of incident heart failure was mean rate of change in Cornell voltage (hazard ratio [HR] = 1.18; 95% confidence interval [CI] = 1.09, 1.27; confidence limit ratio [CLR] = 1.17). All categorical ECG change variables were statistically significantly associated with new onset heart failure, with the exception of QT interval and Cornell voltage; the most precise predictors of incident heart failure were categorical changes in QRS/T angle (HR = 1.97; 95% CI = 1.57, 2.48; CLR: 1.58) and T net amplitude in lead V_1 (HR = 1.33; 95% CI = 1.06, 1.68; CLR: 1.58).

Conclusions: Our results suggest that longitudinal changes in ECG measures are predictive of incident heart failure, independent of clinical and demographic risk factors for heart failure. Further studies aimed at identifying mechanisms which explain the variations in the impact of changes in ECG measures on heart failure incidence are warranted and may provide insight into avenues for the prevention of heart failure.

6.2 Introduction

The burden of heart failure has increased over the past decades. From 1979 to 2005, hospital discharges for heart failure increased 171% (1, 2). In 2009, estimated heart failure healthcare costs are $37.2 billion, and in 2003 $4.4 billion was paid to Medicare beneficiaries for congestive heart failure (3). As of 2006, there were 5.7

million adults diagnosed with heart failure, and 670,000 incident cases (3). Although incidence remains relatively stable over the past decades (4-6), prevalence has been increasing (7). Early identification and treatment of risk factors may be the most important step in eliminating the public health burden of heart failure (8). It has been demonstrated in large-population based studies that certain electrocardiogram (ECG) variables, either measured at one point in time (9-11) or entered in a model as a time-varying covariate (12), are predictive of incident heart failure.

Although ECG variables have been known to vary over time due to biological and methodological variability (13), little work has focused on the changes in these parameters long-term and their relation to new-onset heart failure. To our knowledge, no work has focused on the examination of the effect of the long-term changes of various ECG variables in relatively healthy middle-aged populations, on incident heart failure. Therefore, we examined the changes of several continuous and categorically defined ECG measurements over the course of an average of nine years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study. Because of their demonstrated relevance as cardiovascular risk predictors we focused on spatial QRS/T angle, QT interval, Cornell voltage, Cornell product, left ventricular mass (LVM), T net amplitudes in leads V_5 and V_1, and ST depression, and examined the association between the long-term changes of the ECG measures and incident heart failure. We additionally corrected for short-term variability of continuous ECG change variables.

6.3 Material and methods

6.3.1 Study population

The ARIC Study combines epidemiologic surveillance of four communities and a community-based prospective cohort designed to investigate the etiology and natural history of atherosclerosis and its sequelae. From 1987 to 1989, the ARIC Study cohort of 15,792 black and white participants ages 45 to 64 years was drawn from four communities in North Carolina (NC), Mississippi (MS), Minnesota (MN), and Maryland (MD). Two of the population samples (Washington County, MD and Minneapolis, MN suburbs) were mostly white. Blacks were over-sampled in Forsyth County, NC (12% black) and were exclusively sampled in Jackson, MS to provide statistical power to investigate findings by ethnicity. Following an extensive baseline examination participants were followed via annual telephone interviews, clinical examinations approximately every three years from 1987 to 1999, and ongoing medical record abstraction for hospitalized events and deaths. Each clinical examination consisted of standardized interviews, anthropometric and blood pressure measurements, venipuncture for blood samples and a twelve-lead standard ECG. A comparison of study participants to non-respondents has been described (14). The Institutional Review Boards at each of the institutions involved approved the study, and all participants gave informed, written consent.

6.3.2 ECG methods

The ARIC Study used a standardized protocol for the acquisition of and processing of ECGs (15). All ECG recordings were carried out in a quiet, temperature-

controlled room. After participants rested in the supine position for fifteen minutes, trained and certified ECG technicians recorded ten-second, twelve-lead ECGs using Kendall Q-Trace 5400 Ag/AgCl electrodes (Ludlow Co, Chicopee, Mass). The E-V6 Halfpoint method (16) was used when recording ECGs using a MAC Personal Cardiographer (Marquette Electronics, Inc, Milwaukee, WI). The E-V6 Halfpoint method improves the precision and the repeatability of chest electrode positioning by placing the V_4 electrode at the horizontal level of the fifth intercostal space at the half-way point between the midsternal line and the left midaxillary line (V_6 location). ECGs were digitized and sent via modem after each recording session to the Epidemiological Cardiology Research (EPICARE) Center (Wake Forest University, Winston-Salem, North Carolina). The EPICARE Center, blinded to participant identity processed the ECGs using the 12SL version of the Marquette GE program.

The following ECG measures were generated at the EPICARE Center using methods previously described (11): spatial QRS/T angle, QT interval, Cornell voltage, Cornell product, LVM, T net amplitudes in leads V_5 and V_1, and ST depression. The QRS/T angle was defined as the angle between the net QRS and T wave vectors (17). The QRS/T angle was defined as the angle between the net QRS and T wave vectors (17). QRS/T angle was calculated using a simplified method from the net QRS amplitudes (R – absolute value of S or QS, whichever is larger, in leads V_6, aVF and V_2) and the net T wave amplitudes (signed T +signed T prime) in leads V_5, aVF and V_2. The QT interval, used to evaluate QT prolongation, is the sex- and race-specific QT adjusted for heart rate as a linear function of the RR interval (18). Cornell voltage (R wave amplitude in lead aVL + Q or QS wave amplitude in lead V_3) (19), Cornell product

(Cornell voltage x QRS duration) (20), and LVM predicted by a multivariate model (21) were used as measures of left ventricular hypertrophy. The LVM model adjusted for Cornell voltage and body weight. T waves were obtained by calculating mean and peak T wave values in lead V_5, whereas for T wave amplitude in lead V_1, only the mean value was used. ST depression was evaluated using ST amplitude in lead V_5 at 60 ms past the end of the QRS interval (the J-point) from the Marquette-GE program.

The following participant-specific linear regression model was used to derive the exposure variable, continuous change in the ECG measure (B_i): $y_{ij} = A_i + B_i t_{ij}$, where y = the ECG variable value, i = 1, 2, 3…n participants, j = 1, 2, 3 or 4 visits, and t was the time between ARIC Visit 1 and subsequent visits. The continuous change ECG variable is the average rate of change per year and summarizes the longitudinal information for each participant. To account for intra-individual variation (measurement error) in the continuous ECG variables, regression calibration techniques were used (22).

We additionally constructed categorical change ECG variables. To provide comparability with an earlier analysis in the ARIC Study, we used cut points for ECG variables shown to be associated with incident heart failure used by Rautaharju and colleagues (11). ECG variables were defined using the following cut points for men (M) and women (W): QRS/T angle (°): M ≥ 107, W ≥ 89; QT interval (ms): M ≥ 436, W ≥ 442; Cornell voltage (μV): M ≥ 2650, W ≥ 1673; Cornell product (μV.s): M ≥ 207, W ≥ 152; LVM (g): M ≥ 204, W ≥ 162; $T_{net}V_5$ amplitude (μV): M ≤ 122, W ≤ 107; $T_{net}V_1$ amplitude (μV): M ≥ 307, W ≥ 151; and $ST_{60}V_5$ (μV): M ≤ 5, W ≤ -7. For each ECG

variable, categorical change was defined as ever exceeding the cut point ("1") over ARIC visits, or else "0".

6.3.3 Heart failure

Documentation of heart failure at baseline was based on reported use of medication prescribed for heart failure, or stage 3 of the Gothenburg criteria for heart failure which requires specific cardiac, pulmonary and heart failure indicators to be present (23, 24). Incident heart failure was defined as the first hospital discharge associated with a diagnosis of heart failure (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM code 428 or 518.4) or death certificates with an underlying cause of death coded as heart failure (ICD-9-CM code 428 or ICD-10 code I50). All cohort hospitalizations that occurred before January 1, 2005 were included.

6.3.4 Covariates

The covariates selected for the analysis were age (years), sex (male or female), self-reported race/ethnicity (black or white). Additional covariates selected for the analysis include coronary heart disease (yes or no), diabetes (yes or no), hypertension (yes or no), smoking status (current or not current), use of cholesterol-lowering medication (yes or no), and body mass index (continuous) at the Visit 4 examination and physical activity (continuous) at the Visit 3 examination. If participants were missing covariate information for Visit 4, then Visit 3 covariates were used. Likewise, if

participants were missing Visit 3 covariates, then covariate information for Visit 2 was used. Each participant was asked to indicate whether they were white, black/African American, American Indian or Asian. Coronary heart disease at baseline was defined from a reported history of physician-diagnosed myocardial infarction, coronary artery bypass surgery, coronary angioplasty, or evidence of a previous myocardial infarction on an ECG. Blood pressure, lipids and glucose were measured according to standard ARIC procedures (15). Participants were asked to fast twelve hours before blood draw and actual fasting times were recorded. Blood was drawn from an antecubital vein of seated participants, serum was centrifuged, and frozen samples were shipped to central laboratories for analysis (16). The mean of the last two of three systolic and diastolic sitting blood pressure measurements obtained from a random-zero sphygmomanometer was used for measures of blood pressure. Hypertension was defined as a systolic blood pressure value equal to or greater than 140 mmHg, a diastolic blood pressure value equal to or greater than 90 mmHg, or use of blood pressure lowering medications in the past two weeks (25). Use of cholesterol-lowering medications was self-reported. Type II diabetes mellitus was defined as a fasting serum glucose level of 7.0 mmol/L or more (126 mg/dL) (26), nonfasting glucose level of 11.1 mmol/L or more (200 mg/dL), participant report of a physician diagnosis of diabetes, or current use of diabetes medication. Body mass index was calculated as measured weight (kg) divided by height (m^2). Physical activity was measured using the sport during leisure time activity index (range 1-5) of Baecke's questionnaire (27).

6.3.5 Statistical analysis

We excluded participants with fewer than two ECGs (n = 1340), with a QRS interval greater than or equal to 120 ms (n = 574), with a race/ethnicity other than black or white (n = 48), black participants in Minneapolis, MN or Washington County, MD (n = 55), those with prevalent heart failure at baseline (n = 752), with missing information on heart failure at the baseline examination (n = 287) and those who were censored prior to ARIC Visit 4 (n = 4486). The final sample size for a cohort so defined ("cohort 1") was 10313. Analyses evaluating the continuous change of ECG variables utilized cohort 1 data, whereas analyses evaluating categorical ECG change variables required the exclusion of participants with missing ECGs at baseline (n range = 228 – 287) and whose measurements parameters at baseline exceeded the established cut points mentioned above (cohorts 2 – 9; n range = 1287 – 4148). Cohorts 2 through 9 excluded those whose ECG measures at baseline exceeded the established cut point because they already had a higher risk for incident heart failure at baseline. The final sample sizes for cohorts 2, 3, 4, 5, 6, 7, 8 and 9 were 7812, 9637, 9554, 9205, 9152, 9110, 9086 and 9044, respectively.

Baseline characteristics and ECG measures were described as means and proportions in cohort 1, by incident heart failure status. For all survival analyses of time to heart failure the follow-up time was defined as the period from the third re-examination (Visit 4) to the first hospitalization for heart failure, heart failure death, December 31, 2004, or the last date of contact if lost-to-follow-up. In order to assess the associations between ECG change variables and incident heart failure, Cox proportional hazards regression modeling was used and confidence limit ratios were used to assess the precision of these estimates. We incorporated variance estimates derived from the ECG Repeatability Study(18, 28) to adjust for intra-individual variation (measurement error) in

continuous ECG change variables using regression calibration methods (22). The transformed ECG measure and its corresponding baseline ECG measure were jointly corrected for intra-individual variation. To minimize confounding, covariates were included based on clinical and demographic measures shown to be associated with both ECG abnormalities and incident heart failure. Effect measure modification by race/ethnicity, sex, hypertension, diabetes, coronary heart disease and baseline ECG measure was assessed by constructing ECG change variable-covariate interaction terms and were retained in the model if the *p*-value was < 0.15. A two-tailed *p*-value <0.05 was required for all other tests for statistical significance. The assumption of proportional hazard over time was verified by Cox tests and visual inspection of log(-log) plots. All analyses were performed with SAS 9.1 (SAS Institute, Inc., Cary, NC).

6.4 Results

During a mean follow-up of 7 years, 670 participants developed heart failure in cohort 1. Table 1 presents selected characteristics of cohort 1 at Visit 4 by incident heart failure status. When compared with participants without heart failure, persons with heart failure in cohort 1 were more likely to be older, men, black, smokers, less physically active, were more likely to have coronary heart disease, diabetes, hypertension, and a higher body mass index, and were more likely to use cholesterol-lowering medications. As expected, the mean rate of change in spatial QRS/T angle, QT interval, Cornell voltage, Cornell product, LVM, and T net amplitude in lead V_1 were higher and mean rates of change in T net amplitude in leads V_5 and ST depression were lower in

participants with incident heart failure, compared to participants without heart failure in cohort 1 (Table 2). Furthermore, a higher proportion of ECG change was present in participants with incident heart failure in cohort 1 as shown in Table 3.

Covariate and baseline-ECG adjusted Cox proportional hazards regression models for the associations between longitudinal change in continuous and categorical ECG variables and incident heart failure are presented in Table 4. Mean rates of annual change in QRS/T angle, Cornell voltage, Cornell product, LVM, and T net amplitude in lead V_5 were statistically significantly associated with new onset heart failure. The most precise predictor of incident heart failure was mean rate of annual in Cornell voltage (hazard ratio [HR] = 1.18; 95% confidence interval [CI] = 1.09, 1.27; confidence limit ratio [CLR] = 1.17), suggesting that a 1 standard deviation increase in mean rate of annual change in Cornell voltage was associated with 1.18 times the average hazard for heart failure over time. The strongest predictor of incident heart failure was mean rate of annual change in Cornell product (HR = 1.26; 95% CI = 1.13, 1.43; CLR = 1.27).

All covariate and baseline-ECG-adjusted hazard ratios for longitudinal change in categorical ECG variables were well above 1 (HR range = 1.32 – 2.86) (See Table 4). All categorical ECG change variables were statistically significantly associated with new onset heart failure, with the exception of QT interval and Cornell voltage. The most precise predictors of incident heart failure were categorical changes in QRS/T angle (HR = 1.97; 95% CI = 1.57, 2.48; CLR: 1.58) and T net amplitude in lead V_1 (HR = 1.33; 95% CI = 1.06, 1.68; CLR: 1.58). Although the least precise predictor of new onset heart failure, LVM had the greatest impact on incident heart failure (HR = 2.86; 95% CI =

1.89, 4.33; CLR: 2.29), and our results suggest that participants with LVM values ≥ 204g for men or ≥ 162g for women at any ARIC Visit (2, 3 or 4) had 2.86 times the average hazard for heart failure over time compared to participants with lower values.

6.5 Discussion

Mean rates of annual change of spatial QRS/T angle, Cornell voltage, Cornell product, LVM, and T net amplitude in lead V_5, and categorical changes in spatial QRS/T angle, Cornell product, LVM, T net amplitude in leads V_5 and V_1 and ST depression were associated with new onset heart failure, independently of covariates and the baseline value of the pertinent ECG measurement. In contrast, mean annual rates of change in QT interval, T net amplitude in lead V_1 and ST depression and categorical changes in QT interval and Cornell voltage were not associated with incident heart failure. This is the first study, to our knowledge, to examine the associations between continuous and categorical longitudinal changes in a wide variety of ECG measures and incident heart failure in a relatively healthy, population-based cohort.

Based on a single measurement, higher values of QRS/T angle, QT interval, Cornell voltage, Cornell product, LVM and T net amplitude in lead V_1, and lower values for T net amplitude in lead V_5 and ST depression have been shown to be associated with increased risk for heart failure in the ARIC Study, the Women's Health Initiative and the Strong Heart Study (9-11). The mechanisms linking these ECG variables with incident heart failure are unclear. It has been posited that the ECG measures studied may be markers of ventricular remodeling and evolving coronary heart disease (9-12), an

interpretation that would benefit from consideration of repeat measures of these ECG parameters. ECG variables are known to vary over time due to both biologic and methodologic variability (13). Furthermore, the short-term variability or measurement error in such ECG measures was not accounted for in previous analyses. Biased regression coefficients may result from modeling the association between ECG variables and the onset of heart failure if short-term repeatability is not accounted for in the analyses (29).

Two studies have reported on the effect of QRS interval, measured at one point in time, on heart failure incidence and found conflicting results. While Dhingra and colleagues found that both continuous and categorical measures of QRS interval were associated with incident heart failure in the Framingham Heart Study (12), Rautaharju and colleagues did not find the QRS interval to be a statistically significant predictor of heart failure (11). When we conducted additional analyses using the longitudinal change in QRS interval (< 120 ms), both continuous and categorical, as an additional exposure of interest, we found that a 1 standard deviation increase in mean rate of change in QRS interval was associated with 1.18 (95% CI = 1.12, 1.24; CLR = 1.11) times the average hazard for heart failure over time. However, this finding should be interpreted with caution since the short-term reliability of the QRS interval is not known, and thus was not adjusted for in this analysis. The association of its categorical counterpart with incident heart failure was weaker and less precise. Participants with a QRS interval ≥ 108 for men and ≥ 100 for women at any ARIC Visit (2, 3 or 4) had 3.6 (95% CI = 2.44, 5.32; CLR = 2.18) times the average hazard for heart failure over time compared to participants below these values.

To the best of our knowledge, there are only two studies that have examined the association between changes in ECG variables and new-onset heart failure, and the results are conflicting (30, 31). In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, Okin and colleagues found that both categorical and continuous measures of a temporal reduction in ECG-defined left ventricular hypertrophy were associated with lower likelihood of new-onset heart failure over an average of 4.7 years of follow-up (31). Categorical and continuous measures of reduction in LVH were defined as a Cornell product LVH reduction ≥ 236 mm per ms compared with lesser reductions, and as an 817 mm per ms (1 standard deviation of the mean) lower Cornell product, respectively. In contrast, Fagard and colleagues found that change, defined as a continuous time-varying measure of LVM (sum of 3 voltages, RaVL, SV_1 and RV_5), updated yearly during an average of 6.1 years, was not associated with incident heart failure in 4507 elderly patients (30). These two studies were limited to hypertensive patients receiving anti-hypertensive medications in clinical trials.

In contrast to previous studies of the long-term changes in ECG measures and incident heart failure, our study is the first to quantify the long-term changes in a wide array of ECG measures, inclusive of categorical and continuous measures, in a relatively healthy, population-based cohort. The repeat visits in the ARIC Study allowed us to construct measures of long-term ECG change variables over a mean of nine years. Over the course of this extended follow-up of this cohort, standardization was maintained in the acquisition and quantification of the ECG measures, as well as in risk factor assessment of men and women from four communities in the U.S. Further, we were able

to correct for the measurement error in the continuous ECG change measures using regression calibration methods (22).

There are limitations to this study for the readers to consider. The yearly rates of change were estimated from triennial re-examination points. However, the magnitude of average change was small (data not shown), and our inability to measure change in intervals smaller than three years does not represent a significant shortcoming, although estimated from middle-aged persons who survived from one ARIC visit to the next. As another limitation, changes in ECG measures were assessed in populations that tended to be healthier than the original cohort. As a result, the long-term changes in ECG measures were probably underestimated. Also, classification of incident heart failure depended on ICD-9 and ICD-10 diagnostic codes, which were not corroborated by a physician review and were obtained from death certificate data. Both ICD codes (32) and death certificate data (33) have been known to vary in validity. It is also possible that participants' ECG changes occurred post-ARIC Visit 4, but before their development of heart failure. Lastly, fixed sex-specific cut point values were used to classify the ECG measures in our analysis, while it is possible that the appropriateness of these cut points may not generalize to other population groups.

In conclusion, longitudinal changes in ECG measures are associated with incident heart failure in a relatively healthy, population-based cohort of middle-aged adults. The long-term changes of specific ECG measures might be especially useful for continuous monitoring of heart failure in the clinical setting, and based upon our results, these select ECG measures show promise. Further research to ascertain whether these select ECGs

predict incident heart failure above and beyond traditional risk factors for heart failure is warranted and may provide insight into avenues for the prevention of heart failure.

ACKNOWLEDGEMENTS

K.L.C was supported by a University of North Carolina at Chapel Hill, Royster Society of Fellows Dissertation Fellowship. The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by contracts from the National Heart, Lung, and Blood Institute (N01-55015, N01-55016, N01-55018, N01-55019, N01-55020, N01-55021, N01-55022, and R01-HL064142). The authors thank the staff and participants of the ARIC study for their important contributions.

6.6 References

1. Graves EJ, Owings MF. 1996 Summary: National Hospital Discharge Survey. Adv Data 1998:1-12.

2. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart Disease and Stroke Statistics--2008 Update: A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117:e25-146.

3. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart Disease and Stroke Statistics--2009 Update: A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:e21-181.

4. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-Term Trends in the Incidence of and Survival with Heart Failure. N Engl J Med 2002;347:1397-402.

5. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, et al. Trends in Heart Failure Incidence and Survival in a Community-Based Population. JAMA 2004;292:344-50.

6. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, et al. Congestive Heart Failure in the Community: Trends in Incidence and Survival in a 10-Year Period. Arch Intern Med 1999;159:29-34.

7. From AM, Leibson CL, Bursi F, Redfield MM, Weston SA, Jacobsen SJ, et al. Diabetes in Heart Failure: Prevalence and Impact on Outcome in the Population. Am J Med 2006;119:591-9.

8. Baker DW. Prevention of Heart Failure. J Card Fail 2002;8:333-46.

9. Okin PM, Roman MJ, Lee ET, Galloway JM, Best LG, Howard BV, et al. Usefulness of Quantitative Assessment of Electrocardiographic St Depression for Predicting New-Onset Heart Failure in American Indians (from the Strong Heart Study). Am J Cardiol 2007;100:94-8.

10. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic Predictors of Incident Congestive Heart Failure and All-Cause Mortality in Postmenopausal Women: The Women's Health Initiative. Circulation 2006;113:481-9.

11. Rautaharju PM, Prineas RJ, Wood J, Zhang ZM, Crow R, Heiss G. Electrocardiographic Predictors of New-Onset Heart Failure in Men and in Women Free of Coronary Heart Disease (from the Atherosclerosis in Communities [Aric] Study). Am J Cardiol 2007;100:1437-41.

12. Dhingra R, Pencina MJ, Wang TJ, Nam BH, Benjamin EJ, Levy D, et al. Electrocardiographic Qrs Duration and the Risk of Congestive Heart Failure: The Framingham Heart Study. Hypertension 2006;47:861-7.

13. de Bruyne MC, Kors JA, Visentin S, van Herpen G, Hoes AW, Grobbee DE, et al. Reproducibility of Computerized Ecg Measurements and Coding in a Nonhospitalized Elderly Population. J Electrocardiol 1998;31:189-95.

14. Jackson R, Chambless LE, Yang K, Byrne T, Watson R, Folsom A, et al. Differences between Respondents and Nonrespondents in a Multicenter Community-Based Study Vary by Gender Ethnicity. The Atherosclerosis Risk in Communities (Aric) Study Investigators. J Clin Epidemiol 1996;49:1441-46.

15. The Atherosclerosis Risk in Communities (Aric) Study: Manual of Procedures.

16. Rautaharju PM, Wolf HK, Eifler WJ, Blackburn H. A Simple Procedure for Positioning Precordial Ecg and Vcg Electrodes Using an Electrode Locator. J Electrocardiol 1976;9:35-40.

17. Rautaharju PM, Prineas RJ, Zhang ZM. A Simple Procedure for Estimation of the Spatial Qrs/T Angle from the Standard 12-Lead Electrocardiogram. J Electrocardiol 2007;40:300-4.

18. Vaidean GD, Schroeder EB, Whitsel EA, Prineas RJ, Chambless LE, Perhac JS, et al. Short-Term Repeatability of Electrocardiographic Spatial T-Wave Axis and Qt Interval. J Electrocardiol 2005;38:139-47.

19. Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, et al. Electrocardiographic Detection of Left Ventricular Hypertrophy: Development and Prospective Validation of Improved Criteria. J Am Coll Cardiol 1985;6:572-80.

20. Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic Detection of Left Ventricular Hypertrophy by the Simple Qrs Voltage-Duration Product. J Am Coll Cardiol 1992;20:1180-6.

21. Rautaharju PM, Park LP, Gottdiener JS, Siscovick D, Boineau R, Smith V, et al. Race- and Sex-Specific Ecg Models for Left Ventricular Mass in Older Populations. Factors Influencing Overestimation of Left Ventricular Hypertrophy Prevalence by Ecg Criteria in African-Americans. J Electrocardiol 2000;33:205-18.

22. Chambless LE, Davis V. Analysis of Associations with Change in a Multivariate Outcome Variable When Baseline Is Subject to Measurement Error. Stat Med 2003;22:1041-67.

23. Eriksson H, Caidahl K, Larsson B, Ohlson LO, Welin L, Wilhelmsen L, et al. Cardiac and Pulmonary Causes of Dyspnoea--Validation of a Scoring Test for

Clinical-Epidemiological Use: The Study of Men Born in 1913. Eur Heart J 1987;8:1007-14.

24. Fonseca C, Oliveira AG, Mota T, Matias F, Morais H, Costa C, et al. Evaluation of the Performance and Concordance of Clinical Questionnaires for the Diagnosis of Heart Failure in Primary Care. Eur J Heart Fail 2004;6:813-20, 21-2.

25. Verdecchia P, Angeli F. [the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure: The Weapons Are Ready]. Rev Esp Cardiol 2003;56:843-7.

26. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2003;26 Suppl 1:S5-20.

27. Baecke JA, Burema J, Frijters JE. A Short Questionnaire for the Measurement of Habitual Physical Activity in Epidemiological Studies. Am J Clin Nutr 1982;36:936-42.

28. Schroeder EB, Whitsel EA, Evans GW, Prineas RJ, Chambless LE, Heiss G. Repeatability of Heart Rate Variability Measures. J Electrocardiol 2004;37:163-72.

29. Armstrong BK WE, Saracci R. Principles of Exposure Measurement in Epidemiology. New York: Oxford University Press; 1992.

30. Fagard RH, Staessen JA, Thijs L, Celis H, Birkenhager WH, Bulpitt CJ, et al. Prognostic Significance of Electrocardiographic Voltages and Their Serial Changes in Elderly with Systolic Hypertension. Hypertension 2004;44:459-64.

31. Okin PM, Devereux RB, Harris KE, Jern S, Kjeldsen SE, Julius S, et al. Regression of Electrocardiographic Left Ventricular Hypertrophy Is Associated with Less Hospitalization for Heart Failure in Hypertensive Patients. Ann Intern Med 2007;147:311-9.

32. Goff DC, Jr., Pandey DK, Chan FA, Ortiz C, Nichaman MZ. Congestive Heart Failure in the United States: Is There More Than Meets the I(Cd Code)? The Corpus Christi Heart Project. Arch Intern Med 2000;160:197-202.

33. Coady SA, Sorlie PD, Cooper LS, Folsom AR, Rosamond WD, Conwill DE. Validation of Death Certificate Diagnosis for Coronary Heart Disease: The Atherosclerosis Risk in Communities (Aric) Study. J Clin Epidemiol 2001;54:40-50.

Table 22. (MS III: Table 1) Means (standard deviations) and proportions of participants' characteristics at Visit 4 (1996-1998), the Atherosclerosis Risk in Communities (ARIC) Study (n=10313)

Characteristic	Cohort 1		
	N(%) or mean (standard deviation)		*p* value
	No heart failure (n=9643)	Incident heart failure (n=670)	
Age (years)	62.5 (5.6)	65.5 (5.3)	<0.0001
Women	5542 (57.5%)	324 (48.4%)	<0.0001
Black	2115 (21.9%)	190 (28.4%)	0.0001
Coronary heart disease	411 (4.3%)	111 (16.8%)	<0.0001
Diabetes	1360 (14.3%)	239 (36.3%)	<0.0001
Hypertension	4269 (44.4%)	452 (68.0%)	<0.0001
Current smoker of cigarettes	1383 (14.5%)	138 (20.9%)	<0.0001
Current user of cholesterol-lowering medications	1191 (12.4%)	138 (20.9%)	<0.0001
Body mass index (kg/m^2)	28.5 (5.4)	30.6 (6.5)	<0.0001
Physical activity	2.5 (0.8)	2.4 (0.8)	<0.0001

Definitions: Cohort 1, participants with no missing ECG data at baseline, with more than one ECG, with a QRS interval < 120 ms, with a black or white race and without administrative censoring before Visit 4; heart failure, hospitalized heart failure using international classification codes $9^{th}/10^{th}$ Revision 428/I50; coronary heart disease, history of myocardial infarction, coronary artery bypass surgery or coronary angioplasty; diabetes, fasting blood glucose level ≥ 126 mg/dL, a nonfasting blood glucose level ≥ 200 mg/dL, use of hypoglycemic medications, or self-reported physician diagnosis; hypertension, systolic blood pressure >140 mm Hg, or diastolic blood pressure > 90 mm Hg, and/or use of anti-hypertension medications; physical activity, sport during leisure time index used.

Table 23. (MS III: Table 2) Mean rate of change per year in ECG measures over a mean follow-up of 9 years, the Atherosclerosis Risk in Communities (ARIC) Study (n=10313)*

Characteristic	Cohort 1		
	Mean (standard deviation)		*p* value
	No heart failure (n=9643)	Incident heart failure (n=670)	
QRS/T angle (°):			
Mean rate of change per year	0.0010 (0.0032)	0.0025 (0.0044)	<0.0001
QTrr interval (ms):			
Mean rate of change per year	0.0020 (0.0019)	0.0022 (0.0027)	0.0030
Cornell voltage (μV):			
Mean rate of change per year	0.0401 (0.0786)	0.0658 (0.1576)	<0.0001
Cornell product (μV.s):			
Mean rate of change per year	0.0043 (0.0092)	0.0097 (0.0243)	<0.0001
Left ventricular mass (g):			
Mean rate of change per year	0.0018 (0.0031)	0.0022 (0.0050)	0.0031
$T_{net}V_5$ amplitude (μV):			
Mean rate of change per year	-0.0027 (0.0280)	-0.0154 (0.0423)	<0.0001
$T_{net}V_1$ amplitude (μV):			
Mean rate of change per year	0.0007 (0.0172)	0.0036 (0.0240)	<0.0001
$ST_{60}V_5$ (μV):			
Mean rate of change per year	-0.0023 (0.0040)	-0.0044 (0.0065)	<0.0001

Abbreviation: ECG, electrocardiograph.

Definitions: *N presented is derived from Cohort 1; failure, hospitalized heart failure using international classification codes $9^{th}/10^{th}$ Revision 428/I50; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QT interval is the sex- and race-specific QT interval adjusted for heart rate as a linear function of the RR interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1;$ST_{60}V_5$,ST segment amplitude at time point 60 ms past end of QRS in lead V_5; mean rate of change per year, function of 2 or more ECG measures over visits 1-4 and time from baseline.

Table 24. (MS III: Table 3) Categorical change in ECG measures as proportions of participants that exceed thresholds for risk of heart failure over a mean follow-up of 9 years, the Atherosclerosis Risk in Communities (ARIC) Study

Characteristic	Mean (standard deviation)		*p* value
	No heart failure (n=9643)*	Incident heart failure (n=670)*	
QRS/T angle (°):			
Male ≥ 107, female ≥ 89 over any ARIC visit (2-4)	864 (17.3%)	75 (33.5%)	<0.0001
QTrr interval (ms):			
Male ≥ 436, female ≥ 442 over any ARIC visit (2-4)	659 (13.2%)	63 (28.1%)	<0.0001
Cornell voltage (μV):			
Male ≥ 2650, female ≥ 1673 over any ARIC visit (2-4)	248 (5.0%)	27 (12.1%)	<0.0001
Cornell product (μV.s):			
Male ≥ 207, female ≥ 152 over any ARIC visit (2-4)	352 (7.0%)	33 (14.7%)	<0.0001
Left ventricular mass (g):			
Male ≥ 204, female ≥ 162 over any ARIC visit (2-4)	404 (8.1%)	44 (19.6%)	<0.0001
$T_{net}V_5$ amplitude (μV):			
Male ≤ 122, female ≤ 107 over any ARIC visit (2-4)	490 (9.8%)	52 (23.2%)	<0.0001
$T_{net}V_1$ amplitude (μV):			
Male ≥ 307, female ≥ 151 over any ARIC visit (2-4)	597 (11.9%)	44 (19.6%)	0.0006
$ST_{60}V_5$ (μV):			
Male ≤ 5, female ≤ -7 over any ARIC visit (2-4)	634 (12.7%)	61 (27.2%)	<0.0001

Abbreviation: ECG, electrocardiograph.

Definitions: *N presented is derived from cohort 1, however cohorts 2-9 were used for calculations per each ECG measure; failure, hospitalized heart failure using international classification codes $9^{th}/10^{th}$ Revision 428/I50; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QT interval is the sex- and race-specific QT interval adjusted for heart rate as a linear function of the RR interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1;$ST_{60}V_5$,ST segment amplitude at time point 60 ms past end of QRS in lead V_5; categorical change, crossing the threshold cut point at visits 2, 3 or 4, indicating increased risk for heart failure.

Table 25. (MS III: Table 4) The adjusted hazard ratios for the associations between change in ECG variables, categorical and continuous, and incident heart failure over a mean of 7 years of follow-up, the Atherosclerosis Risk in Communities (ARIC) Study

ECG measure	Mean rate of change per year			Categorical change		
	HR	95% CI	CLR	HR	95% CI	CLR
QRS/T angle (°)	0.88†	(0.81, 0.96)	1.19	1.97*	(1.57, 2.48)	1.58
QT interval (ms)	0.68‡	(0.41, 1.13)	2.76	1.32†	(1.00, 1.74)	1.74
Cornell voltage (μV)	1.18§	(1.09, 1.27)	1.17	1.45§	(0.99, 2.12)	2.14
Cornell product (μV/s)	1.26#	(1.13, 1.43)	1.27	1.87†	(1.37, 2.55)	1.86
Left ventricular mass (g)	1.18**	(1.07, 1.31)	1.22	2.86**	(1.89, 4.33)	2.29
$T_{net}V_5$ amplitude (μV)	0.69††	(0.61, 0.79)	1.30	1.87§§	(1.47, 2.37)	1.61
$T_{net}V_1$ amplitude (μV)	1.10‡	(1.00, 1.21)	1.21	1.33*	(1.06, 1.68)	1.58
$ST_{60}V_5$ (μV)	1.02‡‡	(0.94, 1.10)	1.17	2.15‡‡	(1.63, 2.85)	1.75

Abbreviations: ECG, electrocardiogram; HR, hazard ratio; CI, confidence interval; CLR, confidence limit ratio.

Definitions: ECGxSEX, ECG change variable and sex interaction; ECGxRACE, ECG change variable and race; ECGxCHD, ECG change variable and coronary heart disease interaction; ECGxDIAB, ECG change variable and diabetes interaction; ECGxHTN, ECG change variable and hypertension interaction; ECGxBASE, ECG change variable and baseline ECG measure interaction.

*Model 1: Adjusted for age, body mass index, coronary heart disease, hypertension, diabetes, smoking status, physical activity, cholesterol-lowering medication and baseline ECG.

†Model 1 + ECGxSEX

‡Model 1 + ECGxCHD and ECGxBASE

§Model 1 + ECGxDIAB and ECGxSEX

#Model 1 + ECGxHTN, ECGxSEX and ECGxBASE

** Model 1 + ECGxHTN

††Model 1 + ECGxSEX and ECGxRACE

‡‡Model 1 + ECGxDIAB and ECGxBASE

§§Model 1 + ECGxBASE

CHAPTER 7: DISCUSSION

7.1 Overview and findings

This dissertation aimed to answer the question of whether electrocardiogram (ECG) variables are highly repeatable in the short-term, whether the magnitude of the long-term changes of ECG variables is associated with characteristics predictive of heart failure and whether the long-term changes of ECG variables are associated with incident heart failure, while considering their short-term repeatability when appropriate.

7.1.1 The ECG variables were highly repeatable in the short-term

Nested random effects models were employed to partition the total variance of each selected ECG variable into between-participant, between-visit and within-visit components of variance. Our measure of short-term repeatability, the intra-class correlation (ICC) coefficient represents the between-participant component of variation over the total variance (sum of between-participant, between-visit and within-visit variance) and can be interpreted as the correlation between ECG measures at different visits. Our results indicate that ECG-left ventricular mass (LVM) had the highest value of short-term repeatability (ICC coefficient = 0.99), and thus was highly repeatable between ECG Repeatability Study visits (mean of two weeks). In fact, all measures of

left ventricular hypertrophy were comparable with respect to short-term repeatability; Cornell voltage (ICC coefficient = 0.97) and Cornell product (ICC coefficient = 0.96). Although the short-term repeatability estimates were lower in the remaining ECG variables, spatial QRS/T angle, T net amplitudes in leads V_1 and V_5 and ST depression, short-term repeatability was excellent (ICC coefficients ≥ 0.86).

The greatest strength of this study is the quantification of the short-term repeatability of several ECG variables that have been show to be associated with subsequent cardiovascular morbidity and mortality (1-3). To the authors' knowledge, this is the first study to quantify the short-term repeatability of these ECG measures. Another strength of this study includes the application of strict quality control approaches and adherence to a standardized measurement protocol for data acquisition and processing of ECGs by trained and certified technicians. Based on our results in this study, we can conclude that estimation of their predicted effect on cardiovascular outcomes may not be subject to substantial bias due to short-term variability if measurements are obtained under standardized conditions. Under such circumstances, analytic adjustment for short-term measurement variability may not be essential. Since several other population-based studies have employed the data collecting and processing protocols used by the ARIC Study (4), generalizability of our estimates to other comparable populations is maximized.

7.1.2 The magnitude of the long-term changes of ECG variables is associated with coronary heart disease, diabetes and hypertension status

Linear and logistic regression modeling was used to evaluate the long-term changes of ECG measures, as continuous and categorical variables, over a mean of 9 years, adjusting for age, race/center, sex and baseline ECG. We found that higher mean values of the annual rate of change in QRS/T angle, QT interval, Cornell voltage, Cornell product, LVM, and T net amplitude in lead V_1, and lower mean values of the annual rate of change in T net amplitude in lead V_5 and ST depression, were observed in persons with coronary heart disease, diabetes and hypertension compared to participants without these conditions. As a result, a higher proportion of ECG change was present in persons with these conditions compared to those without.

Since few have described the long-term changes in ECG variables in population samples, or in individuals with coronary heart disease, diabetes or hypertension status, our study contributes to the literature. Furthermore, the ARIC Study is well suited to describe the long-term changes of ECG variables, and to examine these changes by clinical characteristics. Our study was based on an extended follow-up of a large cohort, with standardized risk factor assessment of men and women from diverse communities in the US population. Another important strength of this study is its reliance on a strict and standardized protocol for data collection and processing of ECGs throughout the study.

7.1.3 the long-term changes of ECG variables were associated with incident heart failure

We employed Cox proportional hazards regression modeling to assess the association between ECG change variables, continuous and categorical, and incident heart failure, while adjusting for covariates, pertinent baseline ECG and considering

measurement error in the continuous ECG change variable. Our findings show that over a mean of 7 years, mean rates of annual change of spatial QRS/T angle, Cornell voltage, Cornell product, LVM, and T net amplitude in lead V_5, and categorical changes in spatial QRS/T angle, Cornell product, LVM, T net amplitude in leads V_5 and V_1 and ST depression were associated with new onset heart failure, independently of covariates and the baseline value of the pertinent ECG measurement. The most precise predictor of incident heart failure was mean rate of annual in Cornell voltage (hazard ratio [HR] = 1.18; 95% confidence interval [CI] = 1.09, 1.27; confidence limit ratio [CLR] = 1.17), whereas the most precise predictors of incident heart failure were categorical changes in QRS/T angle (HR = 1.97; 95% CI = 1.57, 2.48; CLR: 1.58) and T net amplitude in lead V_1 (HR = 1.33; 95% CI = 1.06, 1.68; CLR: 1.58).

To the authors' knowledge, this is the first study to examine the effect of the changes of multiple ECGs, both continuous and categorical, on incident heart failure in a relatively healthy, population-based study. Moreover, we examined the effect of long-term changes in continuous ECG variables on incident heart failure, while considering its short-term reliability. However, the indirect calibration of ECG variables using data from the ECG Repeatability Study may have resulted in some inaccuracy in the regression calibration methods. Given that the ECG Repeatability Study followed the standardized protocol used in the ARIC Study for placing electrodes, room condition and data collection (5) and was similar to the ARIC cohort with respect to demographic factors (See Table 5), an inappropriate incorporation of the short-term repeatability estimates obtained from ECG measures in the ECG Repeatability Study into our analyses in the ARIC Study seems unlikely.

A major strength of this study is the construction of the long-term continuous ECG change variable since it maximizes the use of available information for each participant. Participant-specific linear regression modeling was used to derive the mean rate of annual change in ECG variable by summarizing longitudinal information, specifically the number of ECG measures per person and its corresponding time from baseline. However, the benefits of the long-term continuous ECG change variable did come with some costs; mean rate of change per year cannot be directly estimated in clinical settings nor is it easily interpretable. In order to address these limitations, we constructed a categorical change variable using clinically meaningful cut points for ECG variables shown to be associated with incident heart failure (3). However, it is possible that the appropriateness of the sex-specific cut point values chosen may not generalize to other population groups.

7.2 Overall discussion

Although ECG variables, either measured at one point in time (1, 3, 6) or entered in a model as a time-varying covariate (7), have been shown to be predictive of incident heart failure, little work has focused on the changes in these parameters long-term and their relation to new-onset heart failure. We hypothesized that changes in ECG variables over time may predict incident heart failure in a relatively healthy population-based cohort. However, without understanding the short-term variability in the measurement of ECG change variables, interpretation of change in ECG variables longer-term is limited. Our results suggest that select ECG variables, measured at one point in time and

employed for prediction in clinical and epidemiologic settings were highly reliable in the short-term. Since by design the participants in the ECG Repeatability Study were comparable to persons in the ARIC Study cohort (See Table 5), we were able to validly incorporate the short-term repeatability estimates obtained from ECG measures in the ECG Repeatability Study into our analyses in the ARIC Study. We extended regression calibration techniques that typically correct for measurement error in a variable at one point in time, to the case where an exposure variable, specifically continuous ECG change, incorporates repeat measures of ECG variables and several time points. As demonstrated in Table 40, the reliability coefficients for mean rate of change in ECG variables in the ARIC Study tended to be lower (range = 0.26 – 0.86) than the original reliability coefficients (range = 0.66 – 0.99) for ECG measures estimated in the ECG Repeatability Study. These results suggest that analytic adjustment for short-term measurement variability in ECG variables measured at one point in time may not be indicated. However, analytic adjustment for continuous ECG change measures may be desirable, since the ECG variable is likely to have bias associated with its estimate of effect on incident heart failure due to its low short-term repeatability (8).

Since a number of ECG measurements are predictive of downstream cardiovascular and cerebrovascular diseases, their change over time is of clinical and public health interest. We found that the long-term changes of ECG measures associated with cardiovascular risk were greater in magnitude in persons with coronary heart disease, diabetes or hypertension, compared with persons without these conditions. Taking into account these findings, we would expect that coronary heart disease, diabetes and hypertension status would modify the associations between the long term ECG

changes and incident heart failure. In support of this hypothesis, we found that coronary heart disease, diabetes or hypertension modified the association between several continuous and categorical measures of longitudinal changes in ECG measures and incident heart failure (See Table 25). It is important to note that Rautaharju and colleagues (3) observed modification of ECG abnormality-incident heart failure associations by sex in the ARIC Study when assessing ECG variables measured at one point in time. Our results indicate that sex modified the association between mean rates of annual change in QRS/Tangle, Cornell voltage, Cornell product and T net amplitude in lead V_5 or categorical measures of change in QT interval, Cornell voltage, Cornell product and ST depression and new-onset heart failure. Although Rautaharju and colleagues (3) did not observe effect measure modification of the associations between ECG variables measured at one point in time and incident heart failure by race/ethnicity, we found that the association between mean rate of change in T net amplitude and new onset heart failure was modified by race/ethnicity.

Taking results from Rautaharju and colleagues (3) into consideration, several conclusions about the effect of the long-term changes of ECG variables on incident heart failure can be drawn from this study. The most persuasive conclusion, based on our findings, is that longitudinal changes in ECG measures are predictive of incident heart failure, independent of clinical and demographic risk factors for heart failure and baseline ECG. On the other hand, the associations between baseline ECG abnormalities and incident heart failure presented by Rautaharju and colleagues (3) may suffice to capture the predictive association with heart failure, given the low degree of measurement error associated with the ECG variables and the minimal amount of change long-term.

However, our results tended to be more precise as indicated by the confidence limit ratios presented in Table 26. It is important to note that direct comparison between the two studies is limited since the exposure variables were not conceptually similar, sample populations of the ARIC cohort were not the same, covariate and effect measure modifier adjustment varied between the studies, and start of follow-up were at different ARIC visits.

Table 26. The adjusted hazard ratios for the effect of ECG variables, measured at one point and time or long-term ECG change variables, on incident heart failure, the Atherosclerosis Risk in Communities (ARIC) Study

	Rautaharju and colleagues[3]				Chichlowska and colleagues			
	Men		Women		Mean rate of change		+ Categorical change	
ECG measure	HR (95% CI)	CLR	HR (95% CI)	CLR	HR (95% CI)	CLR	HR (95% CI)	CLR
QRS/T angle (°)	2.04 (1.53, 2.72)	1.78	2.33 (1.63, 2.78)	1.71	0.88 (0.81, 0.96)	1.19	1.97 (1.57, 2.48)	1.58
QTrr interval (ms)	2.08 (1.55, 2.78)	1.79	1.08 (0.80, 1.46)	1.83	0.68 (0.41, 1.13)	2.76	1.32 (1.00, 1.74)	1.74
Cornell voltage (μV)	1.57 (1.11, 2.22)	2.00	1.50 (1.13, 2.01)	1.78	1.18 (1.09, 1.27)	1.17	1.45 (0.99, 2.12)	2.14
Cornell product (μV.s)	1.68 (1.21, 2.33)	1.93	1.62 (1.22, 2.15)	1.76	1.26 (1.13, 1.43)	1.27	1.87 (1.37, 2.55)	1.86
Left ventricular mass (g)	2.35 (1.66, 3.33)	2.01	1.34 (0.95, 1.90)	2.00	1.18 (1.07, 1.31)	1.22	2.86 (1.89, 4.33)	2.29
$T_{net}V_5$ amplitude (μV)	1.78 (1.32, 2.39)	1.81	1.32 (0.99, 1.77)	1.79	0.69 (0.61, 0.79)	1.30	1.87 (1.47, 2.37)	1.61
$T_{net}V_1$ amplitude (μV)	1.77 (1.28, 2.44)	1.90	1.59 (1.19, 2.12)	1.78	1.10 (1.00, 1.21)	1.21	1.33 (1.06, 1.68)	1.58
$ST_{60}V_5$ (μV)	2.11 (1.58, 2.82	1.78	1.38 (1.01, 1.88)	1.83	1.02 (0.94, 1.10)	1.17	2.15 (1.63, 2.85)	1.75

Abbreviations: ECG, electrocardiogram; HR, hazard ratio; CI, confidence interval; CLR, confidence limit ratio.

7.3 Conclusions

Because the long-term changes of specific ECG measures might be especially useful for continuous monitoring of heart failure in the clinical setting, it is important that physiological and methodological variations in ECG measures be readily distinguishable from variations that are likely to be pathological. Our results suggest that the short-term repeatability of ECG measures was excellent, and thus, intra-individual variation (measurement error) was minimal. Therefore, we have confidence in our ability to ascertain the long-term changes of ECG measures, representing physiological changes, and to assess their impact on new-onset heart failure. We also observed that the longitudinal changes in ECG measures were higher in magnitude in persons with coronary heart disease, diabetes and hypertension. Moreover, longitudinal changes in ECG measures were predictive of incident heart failure, independent of clinical and demographic risk factors for heart failure, pertinent baseline ECG measure and while considering their short-term variability, and thus these ECG measures show promise to be useful in the identification of persons at increased risk for heart failure in clinical settings. ECGs are relatively inexpensive and easy to obtain. On the other hand, these ECG measures were measured by a computer-ECG software, which can measure ECG variables with a greater degree of precision than visual coding methods used in clinical settings (9). Nonetheless, ascertainment of whether these select ECGs predict incident heart failure above and beyond traditional risk factors for heart failure is warranted before suggesting their use in clinical settings for the prevention of heart failure.

7.4 References

1. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic Predictors of Incident Congestive Heart Failure and All-Cause Mortality in Postmenopausal Women: The Women's Health Initiative. Circulation 2006;113:481-9.

2. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic Abnormalities That Predict Coronary Heart Disease Events and Mortality in Postmenopausal Women: The Women's Health Initiative. Circulation 2006;113:473-80.

3. Rautaharju PM, Prineas RJ, Wood J, Zhang ZM, Crow R, Heiss G. Electrocardiographic Predictors of New-Onset Heart Failure in Men and in Women Free of Coronary Heart Disease (from the Atherosclerosis in Communities [Aric] Study). Am J Cardiol 2007;100:1437-41.

4. Atherosclerosis Risk in Communities Study, Manual 5, Electrocardiography. 1987, p. http://www.cscc.unc.edu/aric/visit/Electrocardiography.1_5.pdf

5. The Atherosclerosis Risk in Communities (Aric) Study: Manual of Procedures.

6. Okin PM, Roman MJ, Lee ET, Galloway JM, Best LG, Howard BV, et al. Usefulness of Quantitative Assessment of Electrocardiographic St Depression for Predicting New-Onset Heart Failure in American Indians (from the Strong Heart Study). Am J Cardiol 2007;100:94-8.

7. Dhingra R, Pencina MJ, Wang TJ, Nam BH, Benjamin EJ, Levy D, et al. Electrocardiographic Qrs Duration and the Risk of Congestive Heart Failure: The Framingham Heart Study. Hypertension 2006;47:861-7.

8. Armstrong BK WE, Saracci R. Principles of Exposure Measurement in Epidemiology. New York: Oxford University Press; 1992.

9. Kors JA, Crow RS, Hannan PJ, Rautaharju PM, Folsom AR. Comparison of Computer-Assigned Minnesota Codes with the Visual Standard Method for New Coronary Heart Disease Events. Am J Epidemiol 2000;151:790-7.

APPENDIX A: SUPPLEMENTAL RESULTS FOR MANUSCRIPT II

Construction of the cohort sample used to address Aim 2, Tables 27 – 33

We excluded participants in the Atherosclerosis Risk in Communities (ARIC) Study with fewer than two electrocardiograms (ECGs) (n = 1340), with a QRS interval greater than or equal to 120 ms (n = 574), with a race/ethnicity other than black or white (n = 48), and black participants in Minneapolis, Minnesota (MN) or Washington County, Maryland (MD) (n = 55). The final sample size for a cohort so defined (cohort 1) was 13,901. Analyses evaluating the continuous change of ECG variables utilized cohort 1 data, whereas analyses evaluating categorical ECG change variables required the exclusion of participants with missing ECGs at baseline (n range = 228 – 287) and whose measurements parameters at baseline exceeded the established cut points for heart failure detailed in Chapter 3, Section 4 (n range = 1287 – 4148; cohorts 2 – 9). The final sample sizes for cohorts 2, 3, 4, 5, 6, 7, 8 and 9 were 10239, 12870, 10239, 12230, 12142, 12033, 12126 and 12004, respectively. Cohorts 1 through 9 were used to address Aim 2.

Table 27. (MS II supplemental results) Means (standard deviations) and proportions of participants' characteristics at the baseline examination (1987-1989) by number of ECGs, the Atherosclerosis Risk in Communities (ARIC) Study

Covariate	Mean (Standard deviation) or n (percent)		
	Full cohort (n=15792)	Participants with 1 ECG	Participants with 2 or more ECGs (n=13901)*
Age (years)			
< 50	4235 (26.8%)	279 (22.5%)	3827 (27.5%)
50-54	4097 (25.9%)	265 (21.3%)	3681 (26.5%)
55-59	3852 (24.4%)	300 (24.1%)	3372 (24.3%)
≥ 60	3608 (22.9%)	399 (32.1%)	3021 (21.7%)
Mean	54.2 (5.8)	55.4 (6.1%)	54.0 (5.7)
Sex			
Women	8710 (55.2%)	631 (50.8%)	7829 (56.3%)
Men	7082 (44.9%)	612 (49.2%)	6072 (43.7%)
Race/ethnicity			
White	11478 (72.7%)	600 (53.1%)	10420 (75.0%)
Black	4266 (27.0%)	583 (46.9%)	3481 (25.0%)
Race/Center			
White/Minneapolis, MN	4009 (25.4%)	159 (12.8%)	3662 (26.3%)
White/Washington County, MD	4020 (25.5%)	250 (20.1%)	3581 (25.8%)
Black/Jackson, MS	3728 (23.6%)	495 (39.8%)	3103 (22.3%)
White/Foryth County, NC	3531 (22.4%)	251 (20.2%)	3177 (22.9%)
Black/Forsyth County, NC	483 (3.1%)	88 (7.1%)	378 (2.7%)
Coronary heart disease			
No	14682 (95.0%)	1092 (90.0%)	13072 (96.0%)
Yes	766 (5.0%)	121 (10.0%)	551 (4.0%)
Diabetes			
No	13774 (88.1%)	929 (76.3%)	12302 (89.2%)
Yes	1870 (12.0%)	289 (23.7%)	1486 (10.8%)
Hypertension			
No	10208 (65.0%)	613 (49.5%)	9229 (66.7%)
Yes	5504 (35.0%)	625 (50.5%)	4605 (33.3%)

Definitions: *Cohort 1, black or white participants with at least two electrocardiograms (ECGs) between visits 1-4, with a QRS interval < 120 ms; coronary heart disease, history of myocardial infarction, coronary artery bypass surgery or coronary angioplasty; diabetes, fasting blood glucose level ≥ 126 mg/dL, a nonfasting blood glucose level ≥ 200 mg/dL, use of hypoglycemic medications, or self-reported physician diagnosis; hypertensives, systolic blood pressure >140 mm Hg, or diastolic blood pressure > 90 mm Hg, and/or use of anti-hypertension medications.

Table 28. (MS II supplemental results) Means (standard deviations) and proportions of participants' characteristics for cohorts 2-5 at the baseline examination (1987-1989), the Atherosclerosis Risk in Communities (ARIC) Study

Covariate	Mean (Standard deviation) or n (percent)			
	Cohort 2* (n=10239)	Cohort 3† (n=12870)	Cohort 4‡ (n=12735)	Cohort 5§ (n=12230)
Age (years)	53.9 (5.7)	53.9 (5.7)	53.9 (5.7)	53.9 (5.7)
Sex				
Women	5686 (55.5%)	7274 (56.5%)	6872 (54.0%)	6874 (56.2%)
Men	4553 (44.5%)	5596 (43.5%)	5863 (46.0%)	5356 (43.8%)
Race/ethnicity				
White	7865 (76.8%)	9701 (75.4%)	9919 (77.9%)	9577 (78.3%)
Black	2374 (23.2%)	3169 (24.6%)	2816 (22.1%)	2653 (21.7%)
Race/Center				
White/Minneapolis, MN	2790 (27.3%)	3408 (26.5%)	3492 (27.4%)	3368 (27.5%)
White/Washington County, MD	2741 (26.8%)	3329 (25.9%)	3391 (26.6%)	3260 (26.7%)
Black/Jackson, MS	2116 (20.7%)	2824 (21.9%)	2494 (19.6%)	2346 (19.2%)
White/Foryth County, NC	2334 (22.8%)	2964 (23.0%)	3036 (23.8%)	2949 (24.1%)
Black/Forsyth County, NC	258 (2.5%)	345 (2.7%)	322 (2.5%)	307 (2.5%)
Coronary heart disease				
No	9770 (97.0%)	12190 (96.3%)	12034 (96.0%)	11595 (96.3%)
Yes	306 (3.0%)	475 (3.8%)	501 (4.0%)	445 (3.7%)
Non-diabetic	8105 (79.8%)	10073 (78.9%)	10043 (79.4%)	9679 (79.7%)
Prediabetic	1100 (10.8%)	1379 (10.8%)	1352 (10.7%)	1287 (10.6%)
Diabetic	947 (9.3%)	1323 (10.4%)	1248 (9.9%)	1174 (9.7%)
Normotensive	4556 (44.7%)	5601 (43.7%)	5678 (44.8%)	5547 (45.6%)
Pre-hypertensive	2519 (24.7%)	3108 (24.3%)	3103 (24.5%)	2975 (24.5%)
Hypertensive	3117 (30.6%)	4100 (32.0%)	3893 (30.7%)	3648 (30.0%)

Definitions: *Cohort 2, participants excluded if exceeding cut point for QRS/T angle at baseline; †cohort 3, participants excluded if exceeding cut point for QT interval at baseline; ‡cohort4, participants excluded if exceeding cut point for Cornell voltage at baseline; §cohort 5, participants excluded if exceeding cut point for Cornell product at baseline; coronary heart disease, history of myocardial infarction, coronary artery bypass surgery or coronary angioplasty; non-diabetics, fasting blood glucose < 110 mg/dL; pre-diabetics, fasting blood glucose 110-125 mg/dL; diabetics, fasting blood glucose level ≥ 126 mg/dL, a nonfasting blood glucose level ≥ 200 mg/dL, use of hypoglycemic medications, or self-reported physician diagnosis; normotensives, systolic blood pressure < 120 mm Hg or diastolic blood pressure < 80 mm Hg; pre-hypertensives, systolic blood pressure 120-140 mm Hg or diastolic blood pressure 80-90 mm Hg; hypertensives, systolic blood pressure >140 mm Hg, or diastolic blood pressure > 90 mm Hg, and/or use of anti hypertension medications.

Table 29. (MS II supplemental results) Means (standard deviations) and proportions of participants' characteristics for cohorts 6-9 at the baseline examination (1987-1989), the Atherosclerosis Risk in Communities (ARIC) Study

Covariate	Mean (Standard deviation) or n (percent)			
	Cohort 6* (n=12142)	Cohort 7† (n=12033)	Cohort 8‡ (n=12126)	Cohort 9§ (n=12004)
Age (years)	54.0 (5.7)	53.8 (5.7)	54.0 (5.7)	53.6 (5.7)
Sex				
Women	6808 (56.1%)	6817 (56.7%)	6803 (56.1%)	6820 (56.8%)
Men	5334 (43.9%)	5216 (43.4%)	5323 (43.9%)	5184 (43.2%)
Race/ethnicity				
White	9256 (76.2%)	9213 (76.6%)	9283 (76.6%)	8815 (73.4%)
Black	2886 (23.8%)	2820 (23.4%)	2843 (23.5%)	3189 (26.6%)
Race/Center				
White/Minneapolis, MN	3252 (26.8%)	3219 (26.8%)	3256 (26.9%)	3054 (25.4%)
White/Washington County, MD	3092 (25.5%)	3176 (26.4%)	3114 (25.7%)	3104 (25.9%)
Black/Jackson, MS	2550 (21.0%)	2526 (21.0%)	2500 (20.6%)	2844 (23.7%)
White/Foryth County, NC	2912 (24.0%)	2818 (23.4%)	2913 (24.0%)	2657 (22.1%)
Black/Forsyth County, NC	336 (2.8%)	294 (2.4%)	343 (2.8%)	345 (2.9%)
Coronary heart disease				
No	11504 (96.2%)	11510 (97.2%)	11514 (96.3%)	11473 (97.1%)
Yes	454 (3.8%)	334 (2.8%)	438 (3.7%)	347 (2.9%)
Non-diabetic	9740 (80.8%)	9543 (80.4%)	9505 (79.0%)	9456 (79.4%)
Prediabetic	1227 (10.2%)	1240 (10.4%)	1300 (10.8%)	1243 (10.4%)
Diabetic	1087 (9.0%)	1158 (9.7%)	1230 (10.2%)	1211 (10.2%)
Normotensive	5552 (45.9%)	5385 (45.0%)	5251 (43.5%)	5318 (44.5%)
Pre-hypertensive	2937 (24.3%)	2900 (24.2%)	2941 (24.4%)	2910 (24.4%)
Hypertensive	3596 (29.8%)	3690 (30.8%)	3878 (32.1%)	3723 (31.2%)

Definitions: *Cohort 6, participants excluded if exceeding cut point for left ventricular mass at baseline; †cohort 7, participants excluded if exceeding cut point for TV_5 at baseline; ‡cohort 8, participants excluded if exceeding cut point for TV_1 at baseline; §cohort 9, participants excluded if exceeding cut point for ST depression at baseline; coronary heart disease, history of myocardial infarction, coronary artery bypass surgery or coronary angioplasty; non-diabetics, fasting blood glucose < 110 mg/dL; pre-diabetics, fasting blood glucose 110-125 mg/dL; diabetics, fasting blood glucose level ≥ 126 mg/dL, a nonfasting blood glucose level ≥ 200 mg/dL, use of hypoglycemic medications, or self-reported physician diagnosis; normotensives, systolic blood pressure < 120 mm Hg or diastolic blood pressure < 80 mm Hg; pre-hypertensives, systolic blood pressure 120-140 mm Hg or diastolic blood pressure 80-90 mm Hg; hypertensives, systolic blood pressure >140 mm Hg, or diastolic blood pressure > 90 mm Hg, and/or use of anti-hypertension medications.

Table 30. (MS II supplemental results) Proportion of participants with specific patterns of ECGs available by visit over a mean follow-up of 9 years, by ECG measure, the Atherosclerosis Risk on Communities (ARIC) Study (n=13901)*

	ARIC Visit, n (percent)										
	1 & 2	**1 & 3**	**1 &4**	**2 & 3**	**2 &4**	**3 & 4**	**1,2 &3**	**1,2 &4**	**1,3 &4**	**2,3 &4**	**1,2,3 &4**
QRS/T angle (°)	1195 (8.6%)	154 (1.1%)	110 (7.9%)	19 (0.1%)	11 (0.0%)	8 (0.0%)	1397 (10.0%)	360 (2.6%)	278 (20.0%)	152 (1.1%)	10217 (73.5%)
QTrr interval (ms)	1190 (8.6%)	152 (1.1%)	107 (7.7%)	17 (0.1%)	11 (0.0%)	6 (0.0%)	1397 (10.0%)	350 (2.5%)	272 (19.6%)	142 (1.0%)	10257 (73.8%)
Cornell voltage (μV)	1190 (8.6%)	152 (1.1%)	107 (7.7%)	17 (0.1%)	11 (0.0%)	6 (0.0%)	1397 (10.0%)	350 (2.5%)	272 (19.6%)	142 (1.0%)	10257 (73.8%)
Cornell product (μV.s)	1190 (8.6%)	152 (1.1%)	107 (7.7%)	17 (0.1%)	11 (0.0%)	6 (0.0%)	1397 (10.0%)	350 (2.5%)	272 (19.6%)	142 (1.0%)	10257 (73.8%)
Left ventricular mass (g)	1197 (8.6%)	154 (1.1%)	108 (7.8%)	17 (0.1%)	11 (0.0%)	8 (0.0%)	1404 (10.1%)	348 (2.5%)	273 (19.6%)	143 (1.0%)	10238 (73.8%)
$T_{net}V_5$ amplitude (μV)	1190 (8.6%)	152 (1.1%)	107 (7.7%)	17 (0.1%)	11 (0.0%)	6 (0.0%)	1397 (10.0%)	350 (2.5%)	272 (19.6%)	142 (1.0%)	10257 (73.8%)
$T_{net}V_1$ amplitude (μV)	1190 (8.6%)	152 (1.1%)	107 (7.7%)	17 (0.1%)	11 (0.0%)	6 (0.0%)	1397 (10.0%)	350 (2.5%)	272 (19.6%)	142 (1.0%)	10257 (73.8%)
$ST_{60}V_5$ (μV)	1190 (8.6%)	152 (1.1%)	107 (7.7%)	17 (0.1%)	11 (0.0%)	6 (0.0%)	1397 (10.0%)	350 (2.5%)	272 (19.6%)	142 (1.0%)	10257 (73.8%)

* Cohort 1, black or white participants with at least one electrocardiogram (ECG) beyond baseline, with a QRS interval < 120 ms; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QTrr, used to evaluate QT prolongation, is the sex- and race-specific QT adjusted for heart rate as a linear function of the RR-interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1; $ST_{60}V_5$, ST segment amplitude at time point 60 ms past end of QRS in lead V_5.

Table 31. (MS II supplemental results) Proportion of participants with 2, 3 or 4 visits over a mean follow-up of 9 years, by ECG measure, the Atherosclerosis Risk in Communities (ARIC) Study (n=13901)*

	ARIC Visit, n (percent)		
	2	**3**	**4**
QRS/T angle (°)	1497 (10.8%)	2187 (15.7%)	10217 (73.5%)
QTrr interval (ms)	1483 (10.7%)	2161 (15.5%)	10257 (73.8%)
Cornell voltage (μV)	1483 (10.7%)	2161 (15.5%)	10257 (73.8%)
Cornell product (μV.s)	1483 (10.7%)	2161 (15.5%)	10257 (73.8%)
Left ventricular mass (g)	1495 (10.8%)	2168 (15.6%)	10238 (73.6%)
$T_{net}V_5$ amplitude (μV)	1483 (10.7%)	2161 (15.5%)	10257 (73.8%)
$T_{net}V_1$ amplitude (μV)	1483 (10.7%)	2161 (15.5%)	10257 (73.8%)
$ST_{60}V_5$ (μV)	1483 (10.7%)	2161 (15.5%)	10257 (73.8%)

* Cohort 1, black or white participants with at least one electrocardiogram (ECG) beyond baseline, with a QRS interval < 120 ms; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QTrr, used to evaluate QT prolongation, is the sex- and race-specific QT adjusted for heart rate as a linear function of the RR-interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1; $ST_{60}V_5$, ST segment amplitude at time point 60 ms past end of QRS in lead V_5.

Table 32. (MS II supplemental results) Means (standard deviations) for ECG measures per visit, the Atherosclerosis Risk in Communities (ARIC) Study (n=13901)*

ECG Measure	Mean (Standard deviation)			
	Visit 1 (n = 13725)	Visit 2 (n = 13364)	Visit 3 (n = 12243)	Visit 4 (n = 11145)
QRS duration (ms)	90.8 (9.6)	91.3 (10.4)	92.1 (11.8)	92.6 (13.2)
Missing	176	537	1676	2765
QRS/T angle (°)	77.0 (30.2)	78.2 (31.6)	80.3 (33.1)	79.7 (33.1)
Missing	190	550	1658	2756
QTrr interval (ms)	415.2 (15.7)	416.6 (16.5)	419.4 (19.1)	421.3 (19.1)
Mising	176	537	1658	2756
Cornell voltage (μV)	1220.6 (524.6)	1253.0 (537.7)	1260.6 (544.2)	1353.4 (561.0)
Missing	176	537	1658	2756
Cornell product (μV.s)	112.7 (54.8)	116.4 (577.2)	118.3 (61.5)	128.0 (67.0)
Missing	176	537	1658	2756
Left ventricular mass (g)	152.8 (29.6)	154.4 (29.6)	155.9 (29.9)	158.5 (30.5)
Missing	179	543	1664	2772
$T_{net}V_5$ amplitude (μV)	287.5 (178.3)	272.1 (181.7)	241.0 (181.0)	287.6 (196.7)
Missing	176	537	1658	2756
$T_{net}V_1$ amplitude (μV)	67.4 (146.6)	82.3 (147.5)	65.4 (143.8)	74.3 (151.9)
Missing	176	537	1858	2756
$ST_{60}V_5$ (μV)	33.9 (35.9)	30.8 (36.3)	26.1 (36.6)	26.3 (37.0)
Missing	176	537	1658	2756

* Cohort 1, black or white participants with at least one electrocardiogram (ECG) beyond baseline, with a QRS interval < 120 ms; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QTrr, used to evaluate QT prolongation, is the sex- and race-specific QT adjusted for heart rate as a linear function of the RR-interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1; $ST_{60}V_5$, ST segment amplitude at time point 60 ms past end of QRS in lead V_5.

Table 33. (MS II supplemental results) Mean rate of change per year for ECG measures, the Atherosclerosis Risk in Communities (ARIC) Study (n=13901)*

ECG Measure	Mean					
	Minimum	Quartile 1	Median	Quartile 3	Maximum	Mean rate of change per year (standard deviation)
QRS duration (ms)	-0.02064	-0.00093	0.00009	0.00138	0.06186	0.00062 (0.00363)
QRS/T angle (°)	-0.09930	-0.00300	0.00097	0.00542	0.11925	0.00155 (0.00971)
QTrr interval (ms)	-0.10263	-0.00113	0.00175	0.00475	0.11173	0.00200 (0.00775)
Cornell voltage (μV)	-1.52300	-0.01896	0.03687	0.09408	2.36022	0.04040 (0.14135)
Cornell product (μV.s)	-0.12856	-0.00181	0.00354	0.00919	0.37982	0.00478 (0.01689)
Left ventricular mass (g)	-0.06551	-0.00066	0.00170	0.00402	0.04729	0.00174 (0.00500)
$T_{net}V_5$ amplitude (μV)	-0.73810	-0.03191	-0.00403	0.02141	0.54277	-0.00863 (0.06013)
$T_{net}V_1$ amplitude (μV)	-0.59814	-0.01857	0.00152	0.02165	0.44881	0.00236 (0.04817)
$ST_{60}V_5$ (μV)	-0.27867	-0.00718	-0.00192	0.00247	0.15794	-0.00301 (0.01176)

* Cohort 1, black or white participants with at least one ECG beyond baseline, with a QRS interval < 120 ms.

† Abbreviations: ECG, electrocardiogram; °, degree; μV, micro-volts; g, gram; s, seconds.

‡ Definitions: QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QTrr, used to evaluate QT prolongation, is the sex- and race-specific QT adjusted for heart rate as a linear function of the RR interval; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1; left ventricular mass, estimated by a multivariate ECG model; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell Voltage (μV) x QRS (s)); $ST_{60}V_5$, ST segment amplitude at time point 60 ms past end of QRS in lead V_5; mean rate of change per year, function of 2 or more ECG measures over visits 1-4 and time from baseline.

Construction of the cohort sample used to assess QRS duration

We described the long-term changes of QRS interval over ARIC Study visits (Table 34). Categorical change for the QRS interval was defined as ever exceeding the cut point ("1") over ARIC visits, or else "0". The categorical QRS interval variable was defined using the following cut point for men and women: men ≥ 112 ms, women ≥ 100 ms. Analyses evaluating the continuous change of the QRS interval variable utilized cohort 1 data, whereas analyses evaluating the categorical change of the QRS interval variable required the exclusion of participants with a missing ECG at baseline (n = 228) and whose QRS interval exceeded the cut points mentioned above at baseline (n = 1596). The final sample size was 12751.

Table 34. (MS II supplemental results) Race/center-, sex-, age and baseline ECG-adjusted means (standard deviations) of change in QRS interval and proportions of participants that exceed threshold for risk of heart failure over a mean follow-up of 9 years, by CHD, diabetes and hypertension status at baseline, the Atherosclerosis Risk in Communities (ARIC) Study (n=13901)*

	Mean (Standard deviation) or percent (95% confidence interval)		
QRS Interval (ms)	**No CHD (n=13072)**	**CHD (n=551)**	
Mean rate of change per year	0.0006 (0.0005, 0.0006)	0.0019 (0.0017, 0.0021)†	
+ change across threshold of risk	9% (8%, 9%)	20% (18%, 23%)†	
	Non-diabetics (n=10871)	**Pre-diabetics (n=1452)**	**Diabetics (n=1486)**
Mean rate of change per year	0.0006 (0.0005, 0.0006)	0.0006 (0.0005, 0.0007)	0.0011 (0.0010, 0.0012)†
+ change across threshold of risk	9% (9%, 9%)	11% (10%, 12%)†	13% (11%, 14%)†
	Normotensives (n=5880)	**Pre-hypertensives (n=3349)**	**Hypertensives (n=4605)**
Mean rate of change per year	0.0004 (0.0004, 0.0005)	0.0006 (0.0006, 0.0007)†	0.0008 (0.0008, 0.0009)†
+ change across threshold of risk	7% (7%, 8%)	10% (9%, 11%)†	12% (11%, 13%)†

* Cohort 1, black or white participants with at least one ECG beyond baseline, with a QRS interval < 120 ms.

Definitions: Observations that exceeded the threshold ("1") for categorical QRS interval were determined using the following cut points for men and women: men ≥ 112, women ≥ 100; CHD, coronary heart disease; CHD, history of myocardial infarction, coronary artery bypass surgery or coronary angioplasty; non-diabetics, fasting blood glucose < 110 mg/dL; pre-diabetics, fasting blood glucose 110-125 mg/dL; diabetics, fasting blood glucose level ≥ 126 mg/dL, a nonfasting blood glucose level ≥ 200 mg/dL, use of hypoglycemic medications, or self-reported physician diagnosis; normotensives, systolic blood pressure < 120 mm Hg or diastolic blood pressure < 80 mm Hg; pre-hypertensives, systolic blood pressure 120-140 mm Hg or diastolic blood pressure 80-90 mm Hg; hypertensives, systolic blood pressure >140 mm Hg, or diastolic blood pressure > 90 mm Hg, and/or use of anti-hypertension medications; †$p < 0.05$ compared with no CHD, non-diabetics or normotensives.

We described observations that exceeded the threshold ("1") for categorical ECG variables and remained in that category versus those that went back to "0" status over ARIC visits (Tables 35 – 37).

Table 35. (MS II supplemental results) Race/center-, sex-, age- and baseline ECG variable-adjusted* proportions of participants that exceed thresholds for risk of heart failure and stay, over a mean follow-up of 9 years, by CHD status at baseline, the Atherosclerosis Risk in Communities (ARIC) Study (n=13901)†

Measures of ECG change	Percent (95% confidence interval)	
	No CHD (n=13072)	CHD (n=551)
QRS/T angle (°)		
+ change across threshold of risk	15% (15%, 16%)	30% (27%, 33%)‡
QT interval (ms)		
+ change across threshold of risk	11% (11%, 12%)	14% (13%, 16%)‡
Cornell voltage (μV)		
+ change across threshold of risk	8% (7%, 9%)	14% (12%, 17%)‡
Cornell product (μV.s)		
+ change across threshold of risk	8% (8%, 9%)	17% (15%, 19%)‡
Left ventricular mass (g)		
+ change across threshold of risk	8% (8%, 9%)	9% (8%, 11%)
$T_{net}V_5$ amplitude (μV)		
+ change across threshold of risk	9% (9%, 9%)	20% (17%, 22%)‡
$T_{net}V_1$ amplitude (μV)		
+ change across threshold of risk	8% (8%, 9%)	17% (15%, 20%)‡
$ST_{60}V_5$ (μV)		
+ change across threshold of risk	11% (11%, 12%)	20% (17%, 22%)‡

Abbreviations: ECG, electrocardiograph; CHD, coronary heart disease

Definitions: *QT interval and left ventricular mass were adjusted for age and baseline ECG only; †the N presented is derived from Cohort 1; CHD, history of myocardial infarction, coronary artery bypass surgery or coronary angioplasty; ‡$p < 0.05$ compared with no CHD; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QT interval is the sex- and race-specific QT interval adjusted for heart rate as a linear function of the RR interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1;$ST_{60}V_5$,ST segment amplitude at time point 60 ms past end of QRS in lead V_5; + change across threshold of risk, crossing the threshold cut point at visits 2, 3 or 4, indicating increased risk for heart failure.

Table 36. (MS II supplemental results) Race/center-, sex-, age- and baseline ECG variable-adjusted* proportions of participants that exceed thresholds for risk of heart failure and stay, over a mean follow-up of 9 years, by diabetes status at baseline, the Atherosclerosis Risk in Communities (ARIC) Study (n=13901)†

Measures of ECG change	Percent (95 % confidence interval)		
	Non-diabetics (n=10871)	Pre-diabetics (n=1452)	Diabetics (n=1486)
QRS/T angle (°)			
+ change across threshold of risk	14% (14%, 15%)	19% (17%, 20%)‡	28% (26%, 30%)‡
QT interval (ms)			
+ change across threshold of risk	11% (11%, 11%)	13% (12%, 14%)‡	12% (11%, 13%)‡
Cornell voltage (μV)			
+ change across threshold of risk	6% (6%, 7%)	6% (5%, 7%)	8% (7%, 9%)‡
Cornell product (μV.s)			
+ change across threshold of risk	9% (9%, 10%)	8% (7%, 8%)‡	10% (9%, 12%)‡
Left ventricular mass (g)			
+ change across threshold of risk	9% (8%, 9%)	9% (8%, 10%)	13% (12%, 14%)‡
$T_{net}V_5$ amplitude (μV)			
+ change across threshold of risk	8% (8%, 9%)	10% (9%, 11%)‡	16% (14%, 17%)‡
$T_{net}V_1$ amplitude (μV)			
+ change across threshold of risk	8% (7%, 8%)	9% (8%, 10%)	13% (12%, 14%)‡
$ST_{60}V_5$ (μV)			
+ change across threshold of risk	11% (10%, 11%)	10% (9%, 11%)	17% (16%, 19%)‡

Abbreviation: ECG, electrocardiograph.

Definitions: *QT interval and left ventricular mass were adjusted for age and baseline ECG only; †the N presented is derived from Cohort 1; non-diabetics, fasting blood glucose < 110 mg/dL; pre-diabetics, fasting blood glucose 110-125 mg/dL; diabetics, fasting blood glucose level ≥ 126 mg/dL, a nonfasting blood glucose level ≥ 200 mg/dL, use of hypoglycemic medications, or self-reported physician diagnosis; ‡$p < 0.05$ compared with non-diabetics; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QT interval is the sex- and race-specific QT interval adjusted for heart rate as a linear function of the RR interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1;$ST_{60}V_5$,ST segment amplitude at time point 60 ms past end of QRS in lead V_5; + change across threshold of risk, crossing the threshold cut point at visits 2, 3 or 4, indicating increased risk for heart failure.

Table 37. (MS II supplemental results) Race/center-, sex-, age- and baseline ECG-adjusted* proportions of participants that exceed thresholds for risk of heart failure and stay, over a mean follow-up of 9 years, by hypertension status at baseline, the Atherosclerosis Risk in Communities (ARIC) Study (n=13901)†

Measures of ECG change	Percent (95 % confidence interval)		
	Normotensives (n=5880)	Pre-hypertensive (n=3349)	Hypertensivess (n=4605)
QRS/T angle (°)			
+ change across threshold of risk	13% (12%, 13%)	16% (15%, 17%)‡	21% (20%, 22%)‡
QT interval (ms)			
+ change across threshold of risk	13% (12%, 13%)	15% (15%, 16%)‡	19% (19%, 20%)‡
Cornell voltage (μV)			
+ change across threshold of risk	7% (6%, 7%)	9% (8%,10%)‡	10% (9%, 11%)‡
Cornell product (μV.s)			
+ change across threshold of risk	7% (7%, 8%)	9% (9%, 10%)‡	10% (9%, 11%)‡
Left ventricular mass (g)			
+ change across threshold of risk	7% (7%, 7%)	8% (7%, 8%)‡	12% (11%, 12%)‡
$T_{net}V_5$ amplitude (μV)			
+ change across threshold of risk	7% (7%, 8%)	10% (9%, 10%)‡	12% (12%, 13%)‡
$T_{net}V_1$ amplitude (μV)			
+ change across threshold of risk	7% (6%, 7%)	9% (8%, 9%)‡	10% (10%, 11%)‡
$ST_{60}V_5$ (μV)			
+ change across threshold of risk	9% (8%, 9%)	11% (11%, 12%)‡	15% (14%, 16%)‡

Abbreviation: ECG, electrocardiograph

Definitions: *QT interval and left ventricular mass were adjusted for age and baseline ECG only; †the N presented is derived from Cohort 1; normotensives, systolic blood pressure < 120 mm Hg or diastolic blood pressure < 80 mm Hg; pre-hypertensives, systolic blood pressure 120-140 mm Hg or diastolic blood pressure 80-90 mm Hg; hypertensives, systolic blood pressure >140 mm Hg, or diastolic blood pressure > 90 mm Hg, and/or use of anti-hypertension medications; ‡$p < 0.05$ compared with non-hypertensives; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QT interval is the sex- and race-specific QT interval adjusted for heart rate as a linear function of the RR interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1;$ST_{60}V_5$,ST segment amplitude at time point 60 ms past end of QRS in lead V_5; + change across threshold of risk, crossing the threshold cut point at visits 2, 3 or 4, indicating increased risk for heart failure.

We described the long-term changes in ECG measures over ARIC visits in participants with coronary heart disease, diabetes and hypertension status compared to participants without these conditions (Table 38).

Table 38. (MS II supplemental results) Race/center-, sex-, age- and baseline ECG-adjusted* mean rate of change per year (standard deviations) in ECG measures and proportions of participants that exceed thresholds for risk of heart failure over a mean follow-up of 9 years, by CHD, diabetes and hypertension status at baseline, the Atherosclerosis Risk in Communities (ARIC) Study (n=13901)†

Measures of ECG change	Mean (95% confidence interval) or percent (95 % confidence interval)	
	No CHD, diabetes and hypertension (n=13819)	CHD, diabetes and hypertension (n=81)
QRS/T angle (°)		
Mean rate of change per year	0.0015 (0.0014, 0.0016)	0.0080 (0.0070, 0.0090)‡
+ change across threshold of risk	23% (22%, 24%)	46% (37%, 57%)‡
QT interval (ms)		
Mean rate of change per year	0.0020 (0.0019, 0.0020)	0.0042 (0.0034, 0.0050)‡
+ change across threshold of risk	17% (17%, 18%)	19% (15%, 25%)
Cornell voltage (μV)		
Mean rate of change per year	0.0403 (0.0392, 0.0415)	0.0736 (0.0585, 0.0888)‡
+ change across threshold of risk	8% (8%, 9%)	22% (15%, 32%)‡
Cornell product (μV.s)		
Mean rate of change per year	0.0047 (0.0046, 0.0049)	0.0115 (0.0096, 0.0133)‡
+ change across threshold of risk	11% (11%, 12%)	19% (13%, 26%)‡
Left ventricular mass (g)		
Mean rate of change per year	0.0017 (0.0017, 0.0018)	0.0017 (0.0012, 0.0022)
+ change across threshold of risk	11% (11%, 11%)	10% (7%, 14%)
$T_{net}V_5$ amplitude (μV)		
Mean rate of change per year	-0.0085 (-0.0089, -0.0080)	-0.0366 (-0.0429, -0.0303)‡
+ change across threshold of risk	17% (16%, 17%)	32% (24%, 42%)‡
$T_{net}V_1$ amplitude (μV)		
Mean rate of change per year	0.0023 (0.0019, 0.0027)	0.0149 (0.0099, 0.0198)‡
+ change across threshold of risk	14% (13%, 14%)	26% (20%, 33%)‡
$ST_{60}V_5$ (μV)		
Mean rate of change per year	-0.0030 (-0.0031, -0.0029)	-0.0058 (-0.0070, -0.0046)‡
+ change across threshold of risk	16% (16%, 17%)	45% (34%, 59%)‡

Abbreviations: ECG, electrocardiograph; CHD, coronary heart disease

Definitions: *QT interval and left ventricular mass were adjusted for age and baseline ECG only; †the N presented is derived from Cohort 1; CHD, history of myocardial infarction, coronary artery bypass surgery or coronary angioplasty; non-diabetics, fasting blood glucose < 110 mg/dL; pre-diabetics, fasting blood glucose 100-125 mg/dL;

diabetics, fasting blood glucose level ≥ 126 mg/dL, a nonfasting blood glucose level ≥ 200 mg/dL, use of hypoglycemic medications, or self-reported physician diagnosis; normotensives, systolic blood pressure < 120 mm Hg or diastolic blood pressure < 80 mm Hg; pre-hypertensives, systolic blood pressure 120-140 mm Hg or diastolic blood pressure 80-90 mm Hg; hypertensives, systolic blood pressure >140 mm Hg, or diastolic blood pressure > 90 mm Hg, and/or use of anti-hypertension medications; ‡$p < 0.05$ compared with no CHD, diabetes and hypertension; QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QT interval is the sex- and race-specific QT interval adjusted for heart rate as a linear function of the RR interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1; $ST_{60}V_5$,ST segment amplitude at time point 60 ms past end of QRS in lead V_5; mean rate of change per year, function of 2 or more ECG measures over visits 1-4 and time from baseline; + change across threshold of risk, crossing the threshold cut point at visits 2, 3 or 4, indicating increased risk for heart failure.

We additionally described the long-term changes of ST amplitude, above and below 0 μV, over ARIC visits in participants with coronary heart disease, diabetes or hypertension status compared to participants without these conditions (Table 39).

Table 39. (MS II supplemental results) Race/center-, sex-, age- and baseline ECG-adjusted* mean rate of change per year (standard deviations) in ST amplitude over a mean follow-up of 9 years, by CHD, diabetes or hypertension status at baseline, the Atherosclerosis Risk in Communities (ARIC) Study (n=13901)*

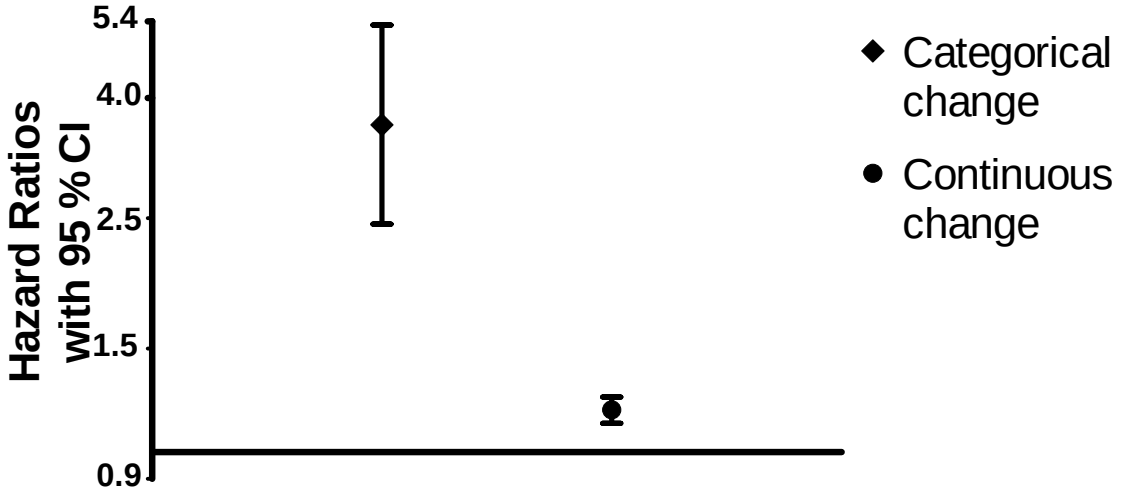
	Mean rate of change per year (Standard deviation)		
ST amplitude	**No CHD (n=13072)**	**CHD (n=551)**	
Above 0 μV	0.0058 (0.0057, 0.0059)	0.0076 (0.0070, 0.0081)‡	
Below 0 μV	-0.0084 (-0.0085, -0.0083)	-0.0124 (-0.0129, -0.0118)‡	
	Non diabetics (n=10871)	**Pre-Diabetics (n=1452)**	**Diabetics (n=1486)**
Above 0 μV	0.0056 (0.0055, 0.0057)	0.0058 (0.0055, 0.0061)	0.0078 (0.0075, 0.0081)‡
Below 0 μV	-0.0081 (-0.0082, -0.0080)	-0.0087 (-0.0091, -0.0084) ‡	-0.0117 (-0.0120, -0.0114)‡
	Normotensives (n=5880)	**Pre-Hypertensives (n=3349)**	**Hypertensives (n=4605)**
Above 0 μV	0.0055 (0.0054, 00057)	0.0054 (0.0052, 0.0057)	0.0065 (0.0064, 0.0067)‡
Bwlow 0 μV	-0.0077 (-0.0079, -0.0075)	-0.0082 (-0.0084, -0.0080)‡	-0.0101 (-0.0103, -0.0099)‡

Abbreviations: ECG, electrocardiograph; CHD, coronary heart disease

Definitions: The N presented is derived from Cohort 1; CHD, history of myocardial infarction, coronary artery bypass surgery or coronary angioplasty; non-diabetics, fasting blood glucose < 110 mg/dL; pre-diabetics, fasting blood glucose 110-125 mg/dL; diabetics, fasting blood glucose level ≥ 126 mg/dL, a nonfasting blood glucose level ≥ 200 mg/dL, use of hypoglycemic medications, or self-reported physician diagnosis; normotensives, systolic blood pressure < 120 mm Hg or diastolic blood pressure < 80 mm Hg; pre-hypertensives, systolic blood pressure 120-140 mm Hg or diastolic blood pressure 80-90 mm Hg; hypertensives, systolic blood pressure >140 mm Hg, or diastolic blood pressure > 90 mm Hg, and/or use of anti-hypertension medications; ‡$p < 0.05$ compared with no CHD, diabetes or hypertension;$ST_{60}V_5$,ST segment amplitude at time point 60 ms past end of QRS in lead V_5; mean rate of change per year, function of 2 or more ECG measures over visits 1-4 and time from baseline.

APPENDIX B: SUPPLEMENTAL RESULTS FOR MANUSCRIPT III

Figure 1. The adjusted hazard ratios for the association between change in QRS interval, categorical (n=9847) and continuous (n=10313), and incident heart failure over a mean of 7 years of follow-up, the Atherosclerosis Risk in Communities (ARIC) Study.



Definition: The QRS categorical variable was defined using the following cut points for men (M) and women (W): M ≥ 108, W ≥ 100. Note: Hazard ratios for categorical change in QRS interval were adjusted for age, sex, race/ethnicity, body mass index, physical activity, hypertension, cholesterol-lowering medications, diabetes, smoking status, coronary heart disease, and interactions between the ECG change variable with baseline QRS interval, coronary heart disease, sex and hypertension. Hazard ratios for continuous change in QRS interval were adjusted for age, sex,race/ethnicity, body mass index, physical activity, hypertension, cholesterol-lowering medications, diabetes, smoking status, coronary heart disease, and interactions between the ECG change variable with coronary heart disease and diabetes.

Table 40. (MS III supplemental results) Short-term reliability estimates (R) for the ECG measures in the ECG Repeatability Study and for the long-term continuous ECG change variable (mean rate of change per year) in the Atherosclerosis Risk in Communities (ARIC) Study

	ECG Repeatability Study	The ARIC Study
ECG measure	R for ECG measure	R for the mean rate of annual change in the ECG measure
QRS/T angle (°)	0.87	0.47
QT interval	0.66	0.34
Cornell voltage (μV)	0.97	0.83
Cornell product (μV.s)	0.96	0.83
Left ventricular mass (g)	0.99	0.88
$T_{net}V_5$ amplitude (μV)	0.90	0.65
$T_{net}V_1$ amplitude (μV)	0.86	0.49
$ST_{60}V_5$ (μV)	0.86	0.45

Abbreviations: R, intra-class correlation coefficient; ECG, electrocardiogram
Definitions: QRS/T angle, calculated using QRS_{net} amplitudes from leads V_6, aVF and V_2 and T_{net} amplitudes from leads V_5, aVF and V_2; QT interval is the sex- and race-specific QT interval adjusted for heart rate as a linear function of the RR interval; Cornell voltage, (RaVL + SV3); Cornell product, (Cornell voltage (μV) x QRS (s)); left ventricular mass, estimated by a multivariate ECG model; $T_{net}V_5$, net T wave amplitude in lead V_5; $T_{net}V_1$, net T wave amplitude in lead V_1;$ST_{60}V_5$,ST segment amplitude at time point 60 ms past end of QRS in lead V_5mean rate of change per year, function of 2 or more ECG measures over visits 1-4 and time from baseline.

Construction of the cohort sample used to address Aim 3, Table 41

We excluded participants with fewer than two electrocardiograms (ECGs) (n = 1340), with a QRS interval greater than or equal to 120 ms (n = 574), with a race/ethnicity other than black or white (n = 48), black participants in Minneapolis, Minnesota (MN) or Washington County, Maryland (MD) (n = 55), those with prevalent heart failure at baseline (n = 752), with missing information on heart failure at the baseline examination (n = 287) and those who were censored prior to Atherosclerosis Risk in Communities (ARIC) Study Visit 4 (n = 4486). The final sample size for a cohort so defined (cohort 1) was 10,313.

Table 41. (MS III supplemental results) Means (standard deviations) and proportions of participants' characteristics at Visit 4 (1996-1998)*, the Atherosclerosis Risk in Communities (ARIC) Study

Covariate	Mean (Standard deviation) or N (%)	
	Full cohort (N=11656)	**Cohort 1† (N=10313)**
Age (years)	62.8 (5.7)	62.7 (5.7)
Women	6508 (55.8%)	5866 (56.9%)
Black race/ethnicity	2664 (22.9%)	2305 (22.4%)
Coronary heart disease	983 (8.6%)	522 (5.1%)
Diabetes	1943 (16.9 %)	1599 (15.7%)
Hypertension	5557 (47.9%)	4721 (46.0%)
Current smoker of cigarettes	1716 (14.9%)	1521 (14.9%)
Current user of cholesterol-lowering medications	1663 (14.3)	1329 (12.9%)
Body mass index (kg/m^2)	28.8 (5.6)	28.6 (5.5)
Physical activity	2.5 (0.8)	2.5 (0.8)

Definitions: *If if participants were missing covariate information for Visit 4, then Visit 3 covariates were used. Likewise, if participants were missing Visit 3 covariates, then covariate information for Visit 2 was used. †Cohort 1, black or white participants with at least one electrocardiogram (ECG) beyond baseline, with a QRS interval < 120 ms; coronary heart disease, history of myocardial infarction, coronary artery bypass surgery or coronary angioplasty; non-diabetics, fasting blood glucose < 110 mg/dL; pre-diabetics, fasting blood glucose 110-125 mg/dL; diabetics, fasting blood glucose level ≥ 126 mg/dL, a nonfasting blood glucose level ≥ 200 mg/dL, use of hypoglycemic medications, or self-reported physician diagnosis; normotensives, systolic blood pressure < 120 mm Hg or diastolic blood pressure < 80 mm Hg; pre-hypertensives, systolic blood pressure 120-140 mm Hg or diastolic blood pressure 80-90 mm Hg; hypertensives, systolic blood pressure >140 mm Hg, or diastolic blood pressure > 90 mm Hg, and/or use of anti hypertension medications.

Table 42. (MS III supplemental results) The adjusted hazard ratios for the association between mean rate of change per year in ST amplitude and incident heart failure over a mean of 7 years of follow-up, the Atherosclerosis Risk in Communities (ARIC) Study

	HR	95% CI	CLR
ST elevation (≥0 μV), n=4019	1.13	(1.03, 1.24)	1.20
ST depression (≤0 μV), n=6294	0.87	(0.85, 0.90)	1.06

Abbreviations: HR, hazard ratio; CI, confidence interval; CLR, confidence limit ratio.
*Adjusted for age, race/ethnicity, body mass index, coronary heart disease, hypertension, diabetes, smoking status, physical activity, cholesterol-lowering medication and interactions with coronary heart disease and baseline ECG.
† Adjusted for age, race/ethnicity, body mass index, coronary heart disease, hypertension, diabetes, smoking status, physical activity, cholesterol-lowering medication and interactions with coronary heart disease and hypertension.