Early Repolarization: A Marker of Increased Risk of Sudden Cardiac Death?

By

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Abstract

This Master’s Paper is composed of two principal parts. The first portion provides a brief introduction on the problem of sudden cardiac death and its possible association with the early repolarization pattern seen on electrocardiogram. This is followed by a systematic review of the existing literature on the topic. The second portion of the paper is an original research manuscript. Data from the Atherosclerosis Risk in Communities (ARIC) study was used to examine the association between J-point elevation on electrocardiogram and long term risk of sudden cardiac death and other adverse outcomes.
Early Repolarization: A Marker of Increased Risk of Ventricular Arrhythmia and Sudden Cardiac Death?

A Systematic Literature Review

INTRODUCTION

Sudden cardiac death (SCD) accounts for more than half of all deaths from cardiovascular disease in the United States.\(^1\)\(^-\)\(^3\) SCD is typically caused by sudden cardiac arrest from ventricular arrhythmia. Most individuals who suffer SCD have underlying coronary heart disease, but 5-10% of those dying of SCD have structurally normal but electrically abnormal hearts.\(^1\),\(^8\) In individuals who are at risk for SCD due to cardiac electrical abnormalities, the electrocardiogram (ECG) is one of the best tools that clinicians have at their disposal for detecting abnormal electrical patterns.

The electrocardiographic finding of early repolarization has traditionally been viewed as a benign finding. Its clinical significance has largely been limited to the need to differentiate between early repolarization and acute myocardial infarction. Early repolarization is a common ECG finding that affects 1-5% of people.\(^1\),\(^2\) It tends to be more prevalent among males, athletes, and young people.\(^1\)-\(^6\) Several studies indicate that it is also more prevalent in blacks.\(^1\),\(^3\),\(^7\),\(^8\)

Recent reports have sparked renewed debate over the phenomenon of early repolarization. Experts are now questioning the supposed benign nature of this finding. Initially, several case reports described patients with idiopathic ventricular fibrillation who had signs of early repolarization on ECG. Several case control studies, and most recently, a population-based study have supported this association.\(^3\),\(^9\)-\(^11\)
In electrocardiography, the J point is the common name for the junction between the QRS complex and the ST segment on ECG. Early repolarization is characterized by elevation of the J-point above baseline. J point elevation (JPE) itself is the consequence of a transmural voltage gradient. Differential distribution of ion channels throughout the various layers of the ventricular wall leads to differing action potential duration and morphology. This in turn leads to a voltage gradient across the wall, which causes an upward deflection on the ECG at the J point. Experts postulate that these same transmural differences in action potential duration create a substrate for ventricular arrhythmias and sudden cardiac death in some individuals.4,13

Our ability to treat sudden cardiac arrest in many settings is limited and outcomes are poor.14 We must therefore endeavor to identify individuals who are at risk for arrhythmia before an event occurs in hopes that an intervention can effectively reduce their risk. Therefore, the objective of this review is to systematically examine the literature to assess whether early repolarization is a risk factor for ventricular arrhythmia and sudden cardiac death in adult patients.

METHODS
Selection of Articles
In order to select original research articles for review, PubMed was used to conduct a MEDLINE search for studies that examined the relationship between early repolarization and ventricular fibrillation or sudden cardiac death. The MeSH terms “electrocardiography” and “death, sudden cardiac” or “ventricular fibrillation” were used. The “limits” function was employed to limit to human subjects and English language, and to exclude meta-analyses and review articles. The search was then narrowed by using (Death, sudden, cardiac OR Ventricular fibrillation) AND
("j-point elevation" OR "j point elevation" OR "early repolarization" OR "j-point amplitude" OR "j point amplitude" OR "j-wave" OR "j wave") as the search item. Abstracts obtained via this search strategy were then reviewed in order to determine whether the articles contained data relevant to the review. Case reports and editorials were excluded. Hand searches of the references of several pertinent articles were also performed in order to identify studies that the initial search missed. Articles included after abstract review were then subjected to a full text review to determine whether they met eligibility criteria. In order to be eligible, studies had to examine early repolarization as the exposure and either idiopathic ventricular fibrillation or death from arrhythmia as outcomes. From the eligible articles, three were selected that had been cited extensively in the literature on the topic, and that had the largest sample sizes and most complete reporting of methods.

Data Abstraction

A standardized evidence table template was used by the author to abstract relevant study information. The abstracted data included information about study design, research question, source population, study population, selection and maintenance of study groups, measurement of exposure and outcomes, analysis strategy, study quality, and study results.

Quality Assessment

For each study, quality was assessed using a standardized template for critical appraisal. This process included assessment of the following elements: research design, source population, study population, initial comparability of groups, adherence and drop outs, measurement of exposure, outcome, and potential confounders, and clinical importance. In addition, the potential for selection bias, measurement bias, and confounding was assessed for each study and quantified as low, moderate, or high potential for bias. Overall internal validity of individual studies was
graded as good, fair, or poor. Description of the source population, study population representativeness of source population, and statistical analysis were also graded as good, fair, or poor.

RESULTS

The literature search yielded 89 publications for abstract review. After abstract review, six articles were found suitable for full text review. Two of these articles were excluded due to incomplete reporting of methods,\textsuperscript{10,15} and one was excluded because it failed to meet exposure criteria (Merchant).\textsuperscript{16} The search resulted in 3 articles that examined early repolarization as the exposure and either idiopathic ventricular fibrillation or death from arrhythmia as outcomes (Table 1). One article employed a cohort design, and two utilized a case-control design. Table 2 presents quality ratings for each of the included articles.
Table 1. Selected Observational Studies of the Association between Early Repolarization and Cardiac Outcomes.

<table>
<thead>
<tr>
<th>Study Authors, Year</th>
<th>Study Design</th>
<th>Source Population</th>
<th>Study Population</th>
<th>Measurements</th>
<th>Significant Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tikkanen, Anttonen, Juntilla et al., 2009</td>
<td>Retrospective Cohort Study</td>
<td>All adults ages 30-59 who resided in one of the 35 geographic areas of Finland chosen for the study. (a random sample was used in some of the geographic areas to obtain the invited study population)</td>
<td>10,864 subjects in the Finnish Social Insurance Institution’s Coronary Heart Disease (CHD) Study who underwent baseline exam between 1966 and 1972. Age: mean 44.0 y at baseline Sex: 52.4% male</td>
<td>Exposure: baseline ECGs were analyzed independently by five physicians for the presence of early repolarization and for amplitude of J-point elevation. Outcome: Death from cardiac causes assessed by cardiologists blinded to ECG findings using death certificates and hospital records based on predetermined definitions.</td>
<td>JPE of ≥0.1 mm found in 5.8%, those with JPE more often men and smokers, lower resting HR, lower BP, lower BMI, shorter QTc, longer QRS, more LVH. Death from arrhythmia when JPE was present in inferior leads: ≥0.1 mm JPE: HR (95% CI) 1.43 (1.06-1.94) ≥0.2 mm JPE: HR (95% CI) 2.92 (1.45-5.89) Borderline significance when JPE present in lateral leads</td>
</tr>
<tr>
<td>Haissaguerre, Derval, Sacher et al., 2008</td>
<td>Case-Control</td>
<td>Study base: individuals under 60 y living in the catchment/referral areas of the 22 centers who would have been treated at the study centers if they had had IVF. Exclusions: QTc &lt;340 or &gt;440, Brugada syndrome, catecholaminergic arrhythmia</td>
<td>Cases (n=206) enrolled at 22 international tertiary care arrhythmia centers resuscitated after cardiac arrest due to IVF. Controls (n=412) without prevalent CHD who were matched for age, sex, race, and physical activity level. Age: mean 36 y Sex: 65.5% male Race: 92.2% white 6.6% Asian 1.2% black</td>
<td>Exposure: baseline ECGs were evaluated for the presence of early repolarization, defined based on explicitly stated criteria. Does not state that exposure assessment was blinded to outcome status. Outcome: IVF classification based on IVF registry of U.S. and UCR of Europe guidelines. (based on ECHO, angiography, exercise testing, and no known repolarization abnormalities)</td>
<td>Prevalence of early repolarization 31% in cases vs. 5% in controls (P &lt; .001) OR (95% CI): 10.9 (6.3-18.9) after adjusting for age, sex, race, and physical activity level. Magnitude of early repolarization was 2.0 +/- 0.4 mm in cases vs. 1.2 +/- 0.4 mm in controls (p &lt; .001). Among cases, those with early repolarization were more likely to be male and to have a history of unexplained syncope and SCA during sleep, and a shorter QTc</td>
</tr>
<tr>
<td>Rosso, Kogan, Belhassen et al., 2008</td>
<td>Case-Control</td>
<td>Study base: uncertain; origin of cases is not disclosed. Matched controls were individuals enrolled in the Tel Aviv Medical Screening program. Inclusion: 1) no h/o syncope or heart disease 2) normal ECG 3) no heart disease on screening</td>
<td>Cases: 45 patients aged 14-69 diagnosed with IVF. Age: mean 38 y Sex: 71% male Race: NR Control group 1 (matched): n=124; 3 controls matched for age and gender for each case. Control group 2 (athletes): 121 non-competitive athletes aged 17-19 who were selected from a pre-participation medical screening program, 50% male</td>
<td>Exposure: ECGs were reviewed for presence of JPE, QRS slurring, and ST elevation by 3 investigators in random order, blinded to patient group. JPE and ST elevation were explicitly defined. Grading was by consensus. Outcome: IVF diagnosed based on criteria from “Electrical Diseases of the Heart” text, Gussak and Antzelvich editors (negative workup for all alternative etiologies and classic IVF characteristics)</td>
<td>Overall prevalence of any JPE was 42% in cases and 13% in matched controls, OR (95% CI) 3.2 (1.7-6.3) OR (95% CI) for presence of JPE &gt;1.0 mm was 3.4 (1.5-7.5) ORs for QRS slurring and ST segment elevation: NS* VF patients most commonly had JPE in the inferior leads and I &amp; aVL, whereas healthy subjects had it most often in V4-V6 Prevalence of JPE in athletes was ~22%</td>
</tr>
</tbody>
</table>

*NR: not reported
†NS: not significant
Table 2. Quality Ratings for Studies in Systematic Review.

<table>
<thead>
<tr>
<th>Study Authors, Year</th>
<th>Source population adequately described?*</th>
<th>Study population representative of source population?*</th>
<th>Potential for selection bias†</th>
<th>Potential for measurement bias†</th>
<th>Potential for confounding†</th>
<th>Statistical analysis*</th>
<th>Overall internal validity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tikkanen, Anttonen, Junttila et al., 2009</td>
<td>good</td>
<td>good</td>
<td>low</td>
<td>low-moderate</td>
<td>low</td>
<td>good</td>
<td>good</td>
</tr>
<tr>
<td>Haissaguerre, Derval, Sacher et al., 2008</td>
<td>fair</td>
<td>fair</td>
<td>high</td>
<td>moderate</td>
<td>high</td>
<td>fair</td>
<td>fair</td>
</tr>
<tr>
<td>Rosso, Kogan, Belhassen et al., 2008</td>
<td>poor</td>
<td>uncertain</td>
<td>high</td>
<td>moderate</td>
<td>high</td>
<td>fair</td>
<td>poor</td>
</tr>
</tbody>
</table>

*Graded as good, fair, or poor
†Graded as low, moderate, or high potential for bias

Tikkanen Study

The Tikkanen study was a retrospective cohort study that examined the prevalence of early repolarization and its association with death from cardiac causes, death from all causes, and death from arrhythmia in Finnish subjects aged 30-59. The study population consisted of 10,864 subjects originally recruited for the Finnish Social Insurance Institution’s Coronary Heart Disease (CHD) Study who underwent baseline exam between 1966 and 1972. Subjects were followed for a mean of 30±11 years for the purposes of this study. The presence of early repolarization was determined by visual review of ECGs. Early repolarization patterns were stratified according to degree of J-point elevation (≥0.1mV or >0.2mV) and according to lead location as inferior (II, III, aVF) or lateral (I, aVL, V₄-V₆). Mortality causes and rates were ascertained using death certificates from Statistics Finland, and death from arrhythmia was determined by cardiologists using death certificates and hospital records, according to the Cardiac Arrhythmia Pilot Study definition.

The overall prevalence of early repolarization ≥0.1mV was 5.8%. Adjusted hazard ratios (HRs) of associations of death from cardiac causes with early repolarization in the inferior leads
were 1.28 (95% CI 1.04 to 1.59) for JPE ≥0.1 mV, and 2.98 (95% CI 1.85-4.92) for JPE ≥0.2 mV. For all cause mortality adjusted HRs were 1.10 (95%CI .97-1.26) for JPE ≥0.1 mV and 1.54 (95% CI 1.06-2.24) for JPE ≥0.2 mV. For death from arrhythmia, adjusted HRs were 1.43 (95% CI 1.06-1.94) for JPE ≥0.1 mV and 2.92 (95% CI 1.45-5.89) for JPE ≥0.2 mV. In the lateral leads, statistical significance was borderline for all cause mortality and death from cardiac causes, and results were not significant for death from arrhythmia.

Study Design

The study’s population-based cohort design is a strength, as is the large sample size. This is an appropriate research design because cohort studies are useful for identifying exposures that increase or decrease the risk of disease. For a research question such as this, a randomized controlled trial is obviously not feasible. The data used in this study are from a prospective cohort study, which means that ECG data were collected at baseline, and subjects were followed longitudinally. This clear temporality is another strength of the study. However, we must remember that this study was indeed a retrospective cohort study, meaning that the data pertinent to this research question were identified from past records. The design is thus not as strong as that of a true prospective cohort study, which would have precise and predefined definitions of cause of death and other variables.

Selection of Study Population

An examination of baseline characteristics shows several baseline differences between groups. This is to be expected since this is a cohort study and the groups were not randomized. Those with J point elevation were more often men and smokers, had lower resting resting heart rates, lower blood pressure, lower BMI, shorter QTc intervals, longer QRS duration, more left ventricular hypertrophy, and more evidence of coronary heart disease on ECG. The study had
less than 2% loss to follow up, and even for these 2%, vital status could be ascertained for the majority. Initially there was moderate potential for selection bias given the differences in baseline characteristics, but the authors corrected for many covariates in regression analysis, and so overall potential for selection bias is low.

**Measurements**

Turning to measurement, the study has several strengths. ECG review procedures were standardized: ECGs were read for early repolarization by 5 five physicians, who examined inferior (II, III, aVF) and lateral (I, aVL, V4-V6) groups. Reading physicians chose not to examine leads V1-V3 in order to avoid including the highly arrhythmogenic Brugada syndrome.

For outcomes assessment, investigators used death data from Statistics Finland. Finland maintains an extensive death registry, and the reliability of this registry had been validated by previous studies. The criteria used by study physicians to ascertain death from arrhythmia were well explained and based on published guidelines. Lastly, but importantly, outcomes were assessed by cardiologists blinded to ECG findings.

There were several weaknesses related to measurement. Study authors do not clearly define their criteria for diagnosis of early repolarization; they state only that they “stratified by degree of JPE, that was either notched or slurred in 2 consecutive leads.” There is no explicit mention of what criteria were used to make the initial diagnosis of early repolarization. Thus it is not clear whether they took ST segment shape or T wave characteristics into account. Authors also did not specifically define what types of deaths constituted death from cardiac causes. Finally, there is a limited ability using retrospective analysis of death certificates to determine whether death is definitively associated with arrhythmia. This is an inherent limitation of the study design, and could only be remedied by utilizing a prospective design with precise
definitions of arrhythmia death. Possible lack of accuracy in death classification could lead to nondifferential measurement bias; it would affect both the exposed and unexposed groups, producing bias towards the null. Potential for measurement bias in this study is low to moderate.

Confounding

There are a few possible sources of confounding that deserve mention. The authors state that they measured CV risk factors, but they do not explicitly list all of the variables measured, which leads one to wonder whether they included all the pertinent risk factors. For example, there was no mention of diabetes, claudication, or high density lipoprotein measurement. Since these are established cardiovascular risk factors, we would hope that they were at least examined as potential covariates. Similarly, the authors state that the use of medications that affect cardiac repolarization was rare at the time of baseline exam. Though that may be true, it would be useful to see data on the prevalence of use of these medications between groups to assure that they could not have acted as confounders. It is not clear whether use of antiarrhythmics was measured. Measurement of use of these drugs is important because they affect cardiac repolarization and are also likely to be associated with death from cardiac causes. Aside from these factors, other possible sources of confounding appear to be well addressed. Outcomes assessors were blinded. The study was retrospective, so differential treatment of patients by physicians would not be an issue. Overall potential for confounding was low after statistical adjustment.

Statistical Analysis

The Tikkanen study was strong from a statistical standpoint. They had a large number of events (n=6133 deaths), including 1969 deaths from cardiac causes. Due to the large sample size and large number of events, there is robust statistical power to detect a difference and less chance
of type II error. Results were precise, as shown by the generally narrow confidence intervals, indicating that the results of the study are likely to be reproducible. Authors used Cox proportional hazards models to examine death outcomes between groups. They controlled well for confounders, and listed all of the covariates included in the model, though it would have been helpful to list all of the variables that were initially examined as possible confounders. Another strong feature of the analysis was the stratification by degree of J point elevation as ≥0.1mV or >0.2mV. This allows for examination for a dose-response effect, which was present in the results and strengthens the argument for causality.

*Overall Quality*

Overall, the Tikkanen study had good internal validity. Apart from a few measurement issues, the study was sound. The population-based nature of this study enhances its generalizability. No information on race was provided, but there were likely few non-whites included in the sample. The study was done in Finland, so there is uncertainty as to whether it generalizes to the U.S. or to nonwhite racial groups. The prevalence of JPE has been shown to differ between ethnic groups, and most experts suspect that there is a genetic basis for JPE, which would lead to differing prevalence in various racial groups. Lastly, it is unclear whether JPE represents a single pathophysiology or is merely the phenotypic expression of a range of underlying processes. If the latter case proves true, then differential geographic (and ethnic) distribution of the various underlying processes could mean than the prognosis associated with JPE varies widely between groups.

One final point on this study is related to clarity of terminology. The authors use the terms J point elevation and early repolarization interchangeably, even when discussing their results. While JPE is a central feature of the early repolarization pattern, JPE and early
repolarization are not synonymous. J point elevation can be seen in a variety of other conditions, such as Brugada syndrome, pericarditis, acute MI, bundle-branch block, and hyperkalemia. Since the authors did not list any ECG exclusion criteria with which would have excluded other potential causes of JPE, referring to these terms interchangeably could be misleading. This study examines the association of death with early repolarization, not with J-point elevation from any cause. This lack of clarity is not a threat to the validity of the study, but it is a threat to its interpretability by readers, especially when published in a journal that is read by a wide audience, not exclusively by electrocardiologists.

**Haissaguerre Study**

The Haissaguerre study was a case control study that investigated the prevalence of early repolarization and its association with idiopathic ventricular fibrillation (IVF). Study cases consisted of 206 individuals enrolled at 22 international tertiary care arrhythmia centers who were under age 60 and were resuscitated after cardiac arrest due to IVF. Controls (n=412) without prevalent CHD were matched for age, sex, race, and physical activity level. Early repolarization was defined as “elevation of the QRS-ST junction of ≥0.1 mV in the inferior (II, III, aVF) or lateral (I, aVL, V, V) leads, manifested as QRS notching or slurring” at the time of ICD placement. IVF classification was based on guidelines from the Joint Steering Committees of the Unexplained Cardiac Registry of Europe and IVF registry of United States.

Comparing cases to controls, the prevalence of early repolarization was 31% vs. 5% (p<.001). After adjustment for age, sex, race, and physical activity, the odds ratio (OR) for the presence of JPE was 10.9 (95% CI 6.3-18.9). Magnitude of JPE when early repolarization was present was 2.0±0.9 in cases and 1.2±0.4 in controls (p<.001).
**Study Design**

The case control study design does not have quite the same ability as a population-based cohort study to definitively answer the clinical question. That being said, the role of initial clinical studies on a topic often is to see whether the hypotheses generated in experimental studies or observed in case reports is supported by clinical evidence. Case control studies are often less expensive and logistically easier to do. In fact, it was the results of the Haissaguerre study that helped generate greater interest in the topic and likely lead to the Tikkanen study discussed earlier.

**Selection of Study Population**

In a case-control study, the main issues with selection bias often center on the selection of controls; controls must reflect the exposure prevalence in the study base for the study to be valid. In this study, the study base would be people under age 60 living in the catchment/referral areas of the 22 tertiary care centers who would have been treated at the centers if they had had IVF. Location of the centers is not reported. The question then is whether the controls chosen for this study are likely to represent the exposure prevalence in the study base. The control group in this study was made up of health care professionals. We do not know where they were from or how they were selected. Therefore it is difficult to say whether this group represents the study base well, though it is likely that this is not a representative control group. This group of professionals may differ from the study base on variables such as age and race, which are closely linked to JPE. If that were the case, the exposure prevalence in this group would not accurately represent that of the study case. The ideal control group in a case control study is a random sample of the population that produced the cases.
It is essential that cases and controls meet the same criteria for inclusion in the study, otherwise other systematic differences between them could account for observed results. In this study, controls were required to have a normal echocardiogram, no prevalent heart disease and no history of syncope. This was a prudent decision by investigators because the cases, in order to be included as IVF cases, also had to meet similar criteria.

Typically an important part of the assessment of selection bias in case control studies involves review of the table comparing baseline characteristics of cases to those of controls. The table given in this study compares only the cases stratified by exposure status; it does not compare case vs. control baseline characteristics. Therefore, it cannot determine whether the baseline characteristics between groups show the expected known exposure-disease associations. Normally the table should include an examination of differences in terms of risk characteristics between cases and controls. Bearing that in mind, this may be less of an issue in this study, because for IVF we do not know as much about its risk factors as we do about the risk factors of many other diseases. On the positive side, no loss to follow-up was reported, and the authors state no cases were lost to follow-up. This reassures the reader than there is less likely to be selection bias introduced from differential loss to follow-up.

On the issue of matching, controls were matched for age, sex, race, and physical activity level using global frequency matching. Matching can be useful because it reduces the differences between groups on determinants of disease other than the exposure being considered. However, matching changes the exposure prevalence in the controls if the exposure is related to the matching variables. In this study matching selects for controls that look more like IVF cases. This can produce bias toward the null, as it likely leads to higher exposure prevalence than the true study base. Matching should be reserved for strong confounders and strong risk factors.
There is potential for overmatching in this study, which would diminish the ability of the study to detect an effect. The study did still find significant results, so there is a possibility that the relationship is even stronger than what is indicated by the results. Overall, there is high potential for selection bias in this study.

**Measurements**

Turning now to measurement issues, the Haissaguerre study had several positive traits. The definition of early repolarization was explicitly defined as quoted above. Thus, it is clear exactly what criteria ECG readers were looking for in order to identify early repolarization. In addition, IVF classification was based on international guidelines. These facts are reassuring in terms of valid and reliable assessment of exposure and outcome.

The authors do not disclose who read the ECGs, how many readers there were, or whether coding was double-checked. Additionally, they do not indicate that exposure assessment was blinded to case/control status. This could easily produce bias away from the null if the unblinded reader believed in a positive association between early repolarization and IVF, because due to its nature, some subjectivity remains in the interpretation of the early repolarization pattern. Finally, the authors admit that data collection was not uniform between centers. This means that measurement may have been unequal between cases at different centers. Because it is not likely that the controls were distributed equally between the various centers, it is also likely that measurement was unequal between cases and controls. This would constitute differential measurement bias, and could produce bias either toward or away from the null hypothesis depending on the exact nature of measurement differences. Potential for measurement bias in this study was moderate.

**Confounding**
Several other possible confounding factors in this study must be discussed. The first is the possibility of survival bias. Survival bias is possible if early repolarization somehow provides a survival advantage in IVF patients. In any study, using prevalent cases or using living cases may introduce bias if exposure is related to duration of disease or prognosis. If survival bias were operating, it could produce study findings that were the exact opposite of the truth. This may be a theoretical concern, but since we still do not fully understand the complex interplay between early repolarization and arrhythmogenesis, survival bias should at the very least be considered.

A related issue is that of temporality. One must consider the expected temporal relationship when investigating an association. Ideally, we would look for the presence of early repolarization on ECGs recorded before IVF occurred. In this study they read ECGs that were recorded after the event. Therefore, the theoretical possibility exists that the IVF event somehow caused the finding of early repolarization. When the exposure is influenced by the disease, it is referred to as protopathic bias. This is by no means a certainty in this situation, but the possibility needs to be considered. Could the outcome have caused or influenced the exposure?

Several other variables deserved mention in the study to assuage concerns about confounding. No mention was made of the prevalence of use of antiarrhythmics or other drugs that might affect cardiac repolarization such as beta-blockers. Similarly, other risk factors for early repolarization, namely heart rate, were not mentioned. It may be that these variables were not related to IVF, but they deserved comment.

Statistical Analysis

From an analysis standpoint, the main concern was that there was no discussion about adjustment during analysis for factors other than those on which controls were matched. The
authors used logistic regression to compare the odds of early repolarization between cases and controls, and controlled for age, race, sex, and physical activity. They do not mention considering any other possible covariates. This raises the concern that control for confounding was incomplete, especially in the absence of a table comparing baseline characteristics between groups.

Statistical analysis was otherwise sound. Investigators used traditional exclusive sampling for controls. This method can sometimes overestimate the OR because it utilizes the rare disease assumption. However, it is acceptable in this case because the outcome in question is rare and incident cases were used. Since the authors used global frequency matching, they did not need to do a matched analysis. The authors used 2:1 ratio of controls to cases. This is a good way to increase the power of the study if the number of cases is limited, or if there is a low prevalence of the exposure among controls, as is true in this study. Finally, the authors excluded $V_1$-$V_3$ from the analysis to avoid Brugada syndrome, as it is highly arrhythmogenic and could confound the results.

Overall Quality

Overall, the internal validity of the Haissaguerre study was fair. There were significant issues with selection bias and measurement. However, some of the concerns are more theoretical and not necessarily major threats to the study’s validity. In terms of generalizability, the study contained few athletes or blacks, which are populations with a higher prevalence of early repolarization, so results may not be generalizable to these populations. The fact that the study was not population-based also limits its generalizability to some extent.

Rosso Study
The Rosso study was a case control study that assessed the association between J point elevation and IVF. Cases consisted of 45 patients aged 14-69 who had been diagnosed with IVF after sudden cardiac arrest. There were 2 control groups. The main control group consisted of 124 controls aged 24-70 years who were matched for age and gender, 3 controls per case. A second control group included 121 non-competitive athletes aged 17-19 years. JPE was defined as a positive “humplike deflection” at the J-point. The authors evaluated “QRS slurring” as a separate entity in this study, and defined it as an R wave gradually slurring into the ST segment with upright concavity. IVF diagnosis was based on criteria described in a prominent cardiac electrophysiology text.

Overall prevalence of any JPE was 42% in cases and 13% in matched controls (p=.001). The OR for the overall presence of any JPE was 3.2 (95%CI 1.7-6.3). Stratified by lead groupings, ORs for the presence of JPE were 3.2 (95%CI 1.4-7.5) in the inferior leads, 16.9 (95%CI 2.0-140.3) in leads I and aVL, and 0.9 (95%CI 0.2-3.3) in leads V4-V6. Authors found that the OR for presence of JPE >1.0mm was 3.4 (95%CI 1.5-7.5). The OR for QRS slurring was 1.3 (95%CI 0.7-2.4), and for ST segment elevation the OR was 1.3 (95%CI 0.7-2.5). Neither of these measurements added diagnostic value when combined with JPE, and no significant relationships were found when stratified by lead groupings. IVF patients most commonly had JPE in the inferior leads and I & aVL, whereas healthy subjects had it most often in leads V4-V6. The prevalence of JPE in athletes was intermediate, at ~22%.

Selection of Study Population

Similar to the Haissaguerre study discussed above, the Rosso study was a case-control study. Therefore, one of the main points that must be assessed is whether the choice of controls was appropriate, that is whether the controls accurately represent the exposure prevalence in the
study base. In this study, the authors do not disclose where the cases came from. It is impossible to surmise the study base, and therefore difficult to determine whether the controls used were an accurate representation of the source population. We know that the matched controls were selected from among 3,500 adults who participated in the Tel Aviv Medical Screening program in 2007. Controls were individually matched for age and sex. The exact source of these individuals is not stated, and we do not know how they were recruited for screening, their reasons for enrolling, or even whether they represent the same geographic area as the controls. The issue here, as previously stated, is that there is not sufficient information given to determine whether these controls are an appropriate choice to represent the study base. It is possible that participants in the Tel Aviv Medical Screening Program do represent the study base well, but there is no way of knowing. To obtain controls for younger cases, investigators used “medical personnel and their offspring.” This is a vague, somewhat suspect source of controls. For the second control group, investigators selected non-competitive athletes aged 17-19 from a pre-participation medical screening program, 50% of whom were male. No mention is made of how the participants were chosen from among those who participated in the medical screening program. As with the previous study, these groups may differ from the study base on variables that are closely linked to JPE. If this were true, the exposure prevalence in these groups would not accurately represent that of the study base.

It is also important that cases and controls meet the same criteria for inclusion in the study, such that if one of the controls had the outcome in question, he or she would have been included as a case. This means that not only should controls be part of the study base, but that they also should meet any other inclusion criteria imposed on the cases. A strength of this study related to control selection was that inclusion criteria for controls included 1) no history of
syncope or heart disease 2) a normal ECG, and 3) no heart disease uncovered on screening exam. Again, this is similar to the criteria that sudden cardiac arrest survivors had to meet in order to be classified as IVF, so this was a good decision by the investigators.

The authors did not include a table of baseline characteristics, so one cannot compare the cases and controls on a range of characteristics. Typically we want to make sure that cases differ from controls in ways that we would expect. The failure to provide this information prevents us from assessing differences between groups and therefore from deciding whether confounding was adequately addressed in the study design and analysis.

The issues surrounding matching in general were discussed above. In this study, the matched control subjects were individually matched based on age and sex. This may seem appropriate, because age and sex are strong risk factors for IVF, and thus could lead to confounding. However, age and sex are also strongly related to JPE, so matching on these variables will lead to an artificially high exposure prevalence in the control group and to a greater chance that cases and controls have the same exposure history. Again, this would produce bias towards the null. In contrast, athletes were not age or sex matched. Many epidemiologists prefer this avoidance of matching, provided that other measures are taken to account for confounding by these important variables. Matching interferes with the fundamental goal of having controls approximate the exposure prevalence in the source population.

A strength of this study, and indeed of all case-control studies, is that there is no loss to follow up. Investigators excluded 11 matched controls and 11 athlete controls after selection mainly due to poor ECG quality. This is not likely to be a large problem because this is not a randomized trial, in which case we would be very worried about post-randomization exclusions.
Still, considering all of the aforementioned issues, there is high potential for selection bias in this study.

Measurements

From a measurement standpoint, the Rosso study did several things well. JPE was explicitly defined as a positive “humplike deflection” immediately after the QRS at the onset of the ST segment. Similarly, QRS slurring was defined when the R wave gradually became the ST segment with upright concavity, and ST height was measured at most horizontal portion with electronic calipers. This indicates that exposure measurement is at least somewhat reproducible. ECGs were reviewed by 3 investigators in random order. Another strength of the study was that ECG interpretation was blinded to case/control status, thereby helping eliminate the chance of a bias on the part of ECG readers toward finding more JPE in the case group. Blinding helps prevent this bias away from the null. Lastly, IVF diagnosis was based on published rigorous criteria that included negative workup for all alternative etiologies, a compatible history, and all of the unique IVF characteristics. The only glaring deficiency in terms of measurements was the fact that there was no discussion of the measurement of possible covariates and other cardiovascular risk factors. It is unclear whether this was done. The overall potential for measurement bias is therefore moderate.

Confounding

Apart from issues with selection bias, only one other possible confounding issue stands out. The authors mention in passing that some of the ECG tracings were old. This brings up an issue that is related to the use of historical controls in case control studies. Generally, historical control groups are a poor choice in case control studies because disease diagnosis patterns, disease management, and even the characteristics of the patient population can and do change
over time, thereby introducing many opportunities for confounding if historical controls are used. Even though in this situation it is some of the cases that are old, not the controls, some of the same bias could still be operating. However, in this situation the potential for problems with this issue is less because diagnosis and treatment of IVF have not changed a great deal, and the occurrence of IVF is not intimately related to deficiencies in treatment or diagnosis. In any case, we are studying survivors of IVF. This of course also means that survivor bias is again an issue to consider. Overall potential for confounding is high, largely due to the contribution of selection bias.

Statistical Analysis

In their analysis, the authors compared continuous variables with blocked analysis of variance, and compared dichotomous variables with conditional logistic regression. Since the investigators used individual matching to match cases and controls, this must be accounted for during the statistical analysis. The above measures are appropriate ways in which to account for matching during analysis. Like the other studies, the Rosso study excluded lead V₁-V₃ to avoid events possibly caused by Brugada syndrome. Two patients included as cases were eventually diagnosed with Brugada syndrome. Authors did a sensitivity analysis excluding the two Brugada patients that did not change the results.

As discussed earlier, investigators can justify a decision to forgo matching if they account for covariates by another method. While the control group made up of young athletes was not matched on any characteristics, it appears that no effort was made to control for any covariates during analysis. Therefore, differences in prevalence between the athletes and the cases could be explained by other factors. For example, the mean age of cases was 38 years, whereas the athlete controls were aged 17-19 years. JPE is strongly associated with age, so age must be accounted
for, or the results are not interpretable. Similarly, in the matched controls it does not seem that any additional covariates were adjusted for during analysis. Controls were matched on sex and age, but analysis appeared to be strictly bivariate. The direction of bias produced by this type of issue is difficult to predict because it depends on a complex interplay between various levels of different confounders, the baseline levels of which are not available to us.

**Overall Quality**

The results of the Rosso study results are consistent with other studies, finding a positive association between JPE and IVF. It is also important to note that while the two previous studies defined early repolarization as slurring or notching at the J point, the Rosso study separates notching from slurring. Interestingly, J point notching was found to be significantly associated with IVF, but QRS slurring was not. Overall, the internal validity of this study was poor. It is difficult to interpret the results given that there was great potential for selection bias based on ambiguity in control selection and that little was done to account for selection bias in the study design and analysis. It is inappropriate to generalize the findings of the study to other populations because its internal validity is suspect.

**DISCUSSION**

The Haissaguerre and Rosso studies had difficulty controlling for selection bias. My greatest concerns were the authors’ failure to fully disclose the source of cases and the comparability of cases and controls, coupled with inadequate measures to address several potential sources of confounding. However, these studies laid the foundation for stronger, population-based studies such as the Tikkanen study.
These studies highlight the presence of more general issues with the measurement of early repolarization. Definitions and descriptions of early repolarization differ between articles, and varying criteria for diagnosis of early repolarization are used from study to study. This may lead to questionable reproducibility and comparability of findings. Furthermore, in these studies the definitions of visually coded ECGs were limited; they used a “broad definition of early repolarization, with no regard for t-wave amplitude or specification of the shape of the ST segment.”\textsuperscript{18} Consensus criteria for the diagnosis of early repolarization on ECG are needed.

The differences in the prevalence of early repolarization between groups were large in the case control studies, and the effect sizes for the relationship between early repolarization in the inferior leads and death from arrhythmia were significant and dose-dependent in the cohort study. The large effects are unlikely to be accounted for completely by the aforementioned biases. In general, although there were some potential issues with internal validity, they are not likely to be sufficient to account for the results obtained in these three studies, especially since some of potential biases actually would have produced bias toward the null hypothesis of no effect.

Despite various threats to internal validity in these studies, their overall similar findings increase the likelihood of a true association. Relative consistency of results across several types of study designs makes it less likely that some unmeasured confounder is operating to cause the observed association. A trend toward increased risk from early repolarization in the inferior leads deserves further investigation. All of the studies also had limits in terms of generalizability. However, the consistency of these findings in a variety of different populations is meaningful. Though these studies were individually flawed, there is sufficient evidence to merit the further investigation of the relationship between early repolarization and ventricular
arrhythmia in future population-based studies. This research should be actively pursued, as prevention of sudden cardiac death from ventricular arrhythmia is an important public health issue.
REFERENCES


ABSTRACT

BACKGROUND
Sudden cardiac death accounts for greater than half of all cardiovascular disease deaths. Ventricular arrhythmia is the most common cause of sudden cardiac death. Several studies have demonstrated an association between ventricular fibrillation and early repolarization, an electrocardiogram finding characterized by elevation of the QRS-ST junction (J-point elevation). A recent population-based study found that early repolarization was associated with increased risk of sudden death from arrhythmia. Further study of this association in more diverse populations is needed.

METHODS
We assessed the long-term prognosis associated with J-point elevation on electrocardiogram in a biracial cohort of 15,141 subjects. These subjects, aged 45-64, were participants in the Atherosclerosis Risk in Communities (ARIC) study. The primary endpoint was adjudicated sudden cardiac death, and secondary endpoints were fatal/nonfatal coronary heart disease events and all-cause mortality. Mean follow-up time was 17±4 years, and J-point elevation was considered to be present if J-point amplitude was ≥ 0.1mV in any lead.

RESULTS
J-point elevation was present in 1,866 subjects (12.3%). After adjustment for demographic, clinical, lifestyle, and laboratory data, J-point elevation was not significantly related to adjudicated SCD in the overall sample (adjusted hazard ratio, 1.23; 95% CI, 0.87-1.75). There was a significant interaction between race and J-point elevation for adjudicated SCD. Whites with J-point elevation had a higher risk of death from adjudicated SCD (adjusted HR, 2.03; 95% CI, 1.28-3.21) than did whites without J-point elevation. However, blacks with J-point elevation did not have an increased risk of death from adjudicated SCD (adjusted HR, 0.82; 95% CI, 0.52-1.30) compared to blacks without the finding. There was also a significant interaction between sex and J-point elevation. J-point elevation significantly increased risk of adjudicated SCD in females (adjusted HR, 2.54; 95% CI, 1.34-4.82). However, the finding of J-point elevation did not similarly increase risk of adjudicated SCD in males (adjusted HR, 1.02; 95% CI, 0.69-1.50).

CONCLUSIONS
The finding of J-point elevation on electrocardiogram is associated with an increased risk of sudden cardiac death in white individuals and in females. This association was not observed among black individuals or among males.
INTRODUCTION

Sudden cardiac death (SCD) is an important public health problem that accounts for more than half of all deaths from cardiovascular disease.\textsuperscript{1-3} The incidence of SCD is estimated to be between 300,000 and 450,000 annually in the United States (U.S.).\textsuperscript{1,4} In most cases, SCD is thought to be caused by cardiac arrest from ventricular arrhythmia. Despite advances in treatment in many areas of medicine, outcomes for cardiac arrest remain poor, with overall survival rates of 5-10%.\textsuperscript{5} Prompt defibrillation offers the greatest chance of survival in individuals who have suffered a cardiac arrest. However, approximately 70-80% of cardiac arrests occur in the home, with no timely access to defibrillation.\textsuperscript{6,7}

In light of the difficulty of treating cardiac arrest, efforts must focus on prevention. One preventive strategy is to identify and ameliorate risk factors for SCD. Most individuals who suffer SCD have underlying coronary heart disease (CHD), and attention must continue to be paid to major modifiable risk factors for CHD (such as hypertension and hyperlipidemia). However, 5-10% of those who succumb to SCD do not have CHD. Such patients’ hearts, while structurally normal, are believed to have an underlying electrical abnormality.\textsuperscript{1,8} These patients, in the absence of evidence of a primary arrhythmogenic disorder, are labeled as having idiopathic ventricular fibrillation (IVF).\textsuperscript{1,2} Identification of people at increased risk of IVF may allow targeted prevention strategies that could ultimately decrease the burden of SCD.

Although traditionally viewed as benign (especially in young healthy adults), several case-control studies have suggested that one electrocardiogram (ECG) finding that may be associated with the development of IVF is the early repolarization pattern.\textsuperscript{9-11} Early repolarization is a common ECG finding that is seen in 1-6% of people.\textsuperscript{12-14} It is characterized by elevation of the QRS-ST junction (the J point) above baseline on ECG. Recently, a Finnish...
population-based cohort study showed that early repolarization was associated with increased risk of death from cardiac causes and with increased risk of death from arrhythmia.\textsuperscript{14} Though it is the only population-based study on the topic that we are aware of, its findings may not be generalizable to other populations. For example, the Finnish cohort likely had few blacks in the sample, though this was not discussed explicitly. Importantly though, blacks have a higher prevalence of the early repolarization pattern, and are more likely to experience SCD.\textsuperscript{1, 9, 12, 15, 16} Research regarding the implications of early repolarization for cardiovascular outcomes in this high risk population is lacking, and experts have called for investigation into the significance of these junctional changes in the groups that are at higher risk for them.\textsuperscript{16}

The early repolarization pattern has many morphologic variants.\textsuperscript{17} A considerable degree of subjectivity is involved in the diagnosis of early repolarization, and no consensus criteria currently exist for the diagnosis of early repolarization. Each study on the topic has used a slightly different definition for the identification of early repolarization, making it difficult to directly compare results. J-point elevation is not only a central feature of the early repolarization pattern, but is also a critical component in the diagnosis of other arrhythmogenic ECG patterns such as Brugada syndrome.\textsuperscript{9, 16, 18} Like the early repolarization pattern, J point elevation has been found in some studies to be more common in blacks.\textsuperscript{19, 20} An examination specifically of J point elevation has several advantages. It can be determined from computerized ECG coding programs, and is therefore useful in large epidemiologic studies. J point measurements provide a quantitative, unambiguous, and objective measurement of ST segment deviation.

The goals of this study were therefore to (1) estimate the prevalence of J-point elevation in a large biracial cohort of U.S. adults, and (2) examine the association of J-point elevation with risk of cardiac events and whether prognostic significance of the finding varies by race or gender.
Specifically, we investigated the association of J-point elevation with sudden cardiac death, fatal/nonfatal coronary heart disease (CHD) events, and all-cause mortality in a large biracial cohort.

METHODS

Study Population
The Atherosclerosis Risk in Communities (ARIC) study\textsuperscript{21} is a prospective, population-based cohort study designed to investigate the etiology and natural history of cardiovascular disease. From 1987 to 1989, ARIC investigators used probability sampling to enroll 15,792 men and women aged 45-64 residing in four U.S. communities: Jackson, Mississippi, Washington County, Maryland, Forsyth County, North Carolina, and the northwestern suburbs of Minneapolis, Minnesota.

For the present analysis, we excluded 202 subjects for whom J-point amplitude data were missing or incomplete. We also excluded 604 subjects with QRS complex duration >120 milliseconds in order to remove cases of bundle branch block, Wolf-Parkinson-White syndrome, and idioventricular rhythm. Additionally, 48 subjects were excluded for race other than black or white. Finally, we excluded three individuals who were large positive outliers on the J-point amplitude variable. After the above exclusions, 15,141 subjects remained for analysis.

Baseline Measurements

At the baseline examination, a standard, resting, supine 12-lead ECG was obtained for each participant a minimum of 1 hour after any smoking or caffeine ingestion. An electrode
locator was used to determine and standardize the positioning of chest electrodes V₃-V₆. Each ECG tracing consisted of 10 seconds of each of the 12 leads recorded simultaneously. Tracings were sent via phone modem to be computer coded at the ARIC ECG Reading Center. Computer analysis included measurement of the voltage and duration of ECG waves and segments, as well as ECG classification according to Minnesota Code. All records with significant Minnesota code findings as determined by the computer, as well as a random sample of tracings, were sent to the ECG coding center to be visually coded. Discrepancies between the computer code and visual code were adjudicated by a senior coder. A rhythm strip consisting of 2 minutes of lead V1, II, and V5 was taken immediately following the 12-lead ECG and sent to the ECG coding center for coding of arrhythmias. Later processing of the ECGs took place at EPICARE (Epidemiological Cardiology Research Center at Wake Forest University, Winston-Salem, NC), where the 2001 version of the GE Marquette 12-SL program was used to obtain ST amplitude at the J-point in relation to the isoelectric line (thus giving both negative and positive values). Each tracing was checked visually to confirm accuracy of readings.

J-point elevation was defined as a J-point amplitude ≥1.0 mm in any lead. Cornell Voltage (|S V₃| + R in aVL), a measure of ECG-defined left ventricular hypertrophy (LVH), was also calculated. LVH was considered to be present if the Cornell Voltage was >28mm in males and >22mm in females.

Anthropometric measurements were taken with subjects wearing scrub suits and no shoes. Height, measured to the nearest centimeter, and weight measured to the nearest pound were used to calculate body mass index (BMI) in kg/m². Three seated blood pressures were taken using a random-zero sphygmomanometer, and the average of the last two was used. Participants were asked to fast for 12 hours before the baseline examination. Phlebotomy was
performed on the antecubital vein of seated subjects, and blood samples were analyzed for lipid levels and chemistry. Diabetes was defined as a fasting glucose level of ≥126 mg/dl, a nonfasting level of ≥200 mg/dl, self-reported physician diagnosis of diabetes, or pharmacologic treatment for diabetes. Information regarding race, smoking history, physical activity, family health history, and educational attainment was obtained through interviews. Education was categorized as basic (less than high school), intermediate (high school diploma and/or vocational school), or advanced (some college, graduate school, or professional school). Physical activity was based on reported level of sport activity using the Baecke physical activity questionnaire.²⁴

Follow-up

Follow-up procedures are described in detail elsewhere.²¹ The primary outcome was adjudicated sudden cardiac death. All cases of fatal CHD in ARIC were reviewed by a committee of physicians. Reviewed cardiovascular deaths were coded as Definite SCD, Possible SCD, or non-sudden CHD death. For the outcome SCD by 1 hour definition, SCD was defined as sudden and unexpected death within 1 hour of symptom onset. For the outcome SCD by 24 hour definition, the subject had to have been observed alive with 24 hours of death if the event was unwitnessed.⁴ Individuals meeting the criteria for SCD by 1 hour definition were also included in the SCD by 24 hour group. Secondary outcomes included fatal/nonfatal CHD events and all-cause mortality. Fatal/nonfatal CHD event was defined as definite or probable myocardial infarction, or definite CHD death.²¹ Myocardial infarction was classified using standardized criteria.²¹ Events occurring between the baseline examination and December 31ˢᵗ, 2007 were included in analysis of all outcomes with the exception of adjudicated sudden cardiac death, for which the end of follow-up was December 31ˢᵗ, 2002.
Statistical Analysis

Continuous variables are presented as means (±SD), and categorical variables are presented as overall percentages and as percentages for those with and without J point elevation. We examined the relationships between J point elevation and subject characteristics using 2-sample t-tests for continuous characteristics and Pearson’s chi square tests for categorical characteristics. We then examined associations of subject characteristics with sudden cardiac death, again using 2-sample t-tests for continuous variables and Pearson’s chi square tests for categorical variables.

Cox proportional hazards models were used to obtain multivariate-adjusted hazard ratios for SCD by all three definitions, CHD events, and all-cause mortality for those with versus without J-point elevation. ECG leads were grouped into anterior (V₁-V₅), inferior (II, III, aVL), and lateral (I, aVL,V₆) leads, as well as into an overall measure of J-point elevation in any lead. Results are reported as hazard ratios with 95% confidence intervals. Censoring occurred at the time of an event, death, loss to follow up, or at the end of follow-up (December 31st, 2007).

Potential covariates included in the initial model were: age, sex, race, BMI, heart rate, systolic blood pressure, smoking status, high-density lipoprotein level, low-density lipoprotein level, diabetes, level of physical activity, family history of premature CHD, education level, Cornell voltage for LVH, electrolyte levels, and presence of major ECG abnormality on Minnesota Code. We also examined data on prevalent CHD (including myocardial infarction determined by self-report or ECG, self report of heart or arterial surgery, coronary bypass, balloon angioplasty, coronary artery angioplasty) and on physician-diagnosed stroke, angina, and intermittent claudication as ascertained by the Rose questionnaire. The following cardiac
medications were also studied: digitalis, selective and non-selective beta-blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, and antiarrhythmic drugs.

Variables found not to be related to J point amplitude in bivariate analysis were dropped from the full model in a stepwise fashion, and the resulting reduced models were tested against the full model using the likelihood ratio test. Tested variables that did not significantly affect results were dropped from the model. Using this method, we created a set of reduced models fit to J-point elevation in any lead as the main exposure and adjudicated sudden cardiac death as the outcome. This same set of covariates was then employed across all exposures and all outcomes in order to enhance comparability and reproducibility. Given the uncertain nature of the relationship between LVH and J-point elevation, we conducted a sensitivity analysis by removing Cornell voltage from the models, which produced no meaningful change in the results.

Model 1 adjusts for demographic factors. Model 2 adjusts for demographic and clinical data. Model 3 adjusts for demographic, clinical, lifestyle, and laboratory data.

The proportional hazards assumption was tested for each model using the test of Schoenfeld residuals. We used stratified Cox models to stratify on any variables that violated the proportional hazards assumption, and this produced no meaningful change in the results. Violations of the proportional hazards assumption by J-point elevation were checked graphically and judged to be trivial. We also undertook pre-specified subgroup analyses by race, sex, heart rate, and prevalent CHD in order to assess whether effect modification was present. We tested for the presence of these interactions individually using the likelihood ratio test. When a significant interaction was present, we calculated hazard ratios for the subgroups individually using coefficients from models with the pertinent interaction term included.
For the lead groupings in which significant results were consistently observed, we examined the individual component leads, both as continuous measures of J-point amplitude and as a dichotomized measure of J-point elevation. For continuous variables, the linearity assumption was tested using a test for linear trend.

Statistical analyses were performed using STATA 11.0 (Stata Corp., College Station, Texas). All reported p values are 2-sided, with a p-value of less than 0.05 considered to indicate statistical significance.

This secondary analysis was exempted from full review by the Office of Human Research Ethics of the University of North Carolina at Chapel Hill.

RESULTS

Sample Characteristics

Baseline characteristics of the overall sample and of subjects with and without J-point elevation are shown in Table 1. Overall, the sample was 44.3% male and 26.9% black. However, among subjects with J-point elevation, 76.1% were male and 53.3% were black. Subjects with J-point elevation also had lower BMI, lower heart rate, and higher blood pressure. They were more likely to be smokers (34.1% vs. 25.0%, p<0.001), to have LVH (6.0% vs 1.3%, p<0.001), and were more likely to have a major Minnesota Code abnormality on ECG (14.5 vs. 8.6%, p<0.001). Finally, those with J-point elevation were more likely to have a history of CHD or other vascular disease, but were less likely to have a family history of premature CHD.

Prevalence of J-Point Elevation
J-point elevation was present in 1,866 of 15,141 subjects (12.3%) (Table 2). Elevation in the anterior leads (V₁-V₅) was found in 1,767 subjects (11.7%). Elevation in the inferior leads (II, III, aVL) was found in 119 subjects (0.8%), and 92 subjects (0.6%) had elevation in the lateral leads (I, aVL, V₆). Males were more likely than females to have J-point elevation in at least one lead (21.2% vs. 5.3%, p<0.001). Among blacks, there was a 24.4% prevalence of J-point elevation; prevalence among whites was 7.9%. J-point elevation was significantly more common among younger subjects (13.1%) than among older subjects (11.5%).

Overall Risk of Death and Cardiac Outcomes

After a mean follow-up of 17±4 years, 3,555 subjects (23.5%) died. Of these deaths, 237 were due to adjudicated SCD, representing 6.6% of all deaths. Using the 1 hour definition of SCD, 244 SCDs occurred, representing 6.9% of all deaths. When this group is expanded to include SCD by 24 hour definition in addition to SCD by 1 hour definition, 482 deaths are attributed to SCD. This figure represents 13.6% of all deaths during follow-up. During follow-up, 1,764 subjects experienced confirmed fatal or nonfatal CHD events. Of these events, 339 were fatal CHD, 105 were fatal MI, and 1,320 were nonfatal MI.

In unadjusted analysis, those with J-point elevation in any lead were approximately 2.3 times more likely to suffer adjudicated SCD (adjusted HR, 2.28; 95%CI, 1.69-3.07, Table 3). Statistically significant relationships were also present between J-point elevation and all other outcomes in unadjusted analysis. After adjustment for race, sex, and age, J-point elevation was no longer significantly related to adjudicated SCD (adjusted HR, 1.31; 95% CI, 0.94-1.82), and hazard ratios for secondary outcomes approached one. Upon further adjustment for clinical,
lifestyle, and laboratory data in addition to demographic factors, these relationships remained nonsignificant. Hazard ratios for leads V_{1}-V_{5} individually are shown in supplemental table 1.

Among subjects with J-point elevation in any lead, there was a significant interaction between race and J-point elevation for the primary outcome adjudicated SCD (Table 4). Whites with J-point elevation had a higher risk of death from adjudicated SCD (adjusted HR, 2.03; 95% CI, 1.28-3.21) than did whites without J-point elevation. However, blacks with J-point elevation did not have an increased risk of death from adjudicated SCD (adjusted HR, 0.82; 95% CI, 0.52-1.30) compared to blacks without the finding. The ratio of hazard ratios for whites compared to blacks was 2.46, indicating a large difference between these groups in the risk associated with J-point elevation.

A significant interaction was also present between sex and J-point elevation. J-point elevation significantly increased risk of adjudicated SCD in females (adjusted HR, 2.54; 95% CI, 1.34-4.82). However, the finding of J-point elevation did not similarly increase risk of adjudicated SCD in males (adjusted HR, 1.02; 95% CI, 0.69-1.50). The ratio of hazard ratios for females compared to males for adjudicated RSCD was 2.50, indicating that J-point elevation connotes a much greater risk of SCD in females than it does in males. The ratios of hazard ratios are nearly universally above one, indicating that the trend of increased risk associated with J-point elevation in whites and females is consistent across outcomes.

**DISCUSSION**

Our study suggests that the finding of J-point elevation in white individuals is associated with an increased risk of SCD. This association was not shown to be present among black individuals. Our results also showed that J-point elevation in females is associated with greater risk of SCD,
but J-point elevation in males does not appear to be a marker of increased risk. A similar trend toward increased risk associated with J-point elevation in whites and females was observed across all outcomes, through the differences between groups were less pronounced. This trend has, to our knowledge, not been previously discussed the literature.

Several explanations could account for the observed difference in risk between groups. The possibility exists that subtle physiologic differences between these groups are responsible for the discrepancies in risk. Similarly, it is possible that the phenomenon of J-point elevation is a single phenotypic manifestation of a rather diverse array of genotypes. These genotypic variations may be differentially distributed between various groups. Some genotypes may increase risk of poor outcomes, whereas others may be completely benign while producing similar ECG findings. Alternatively, race and gender-based differences could be attributable to the use of a single ECG cutoff across both races and sexes. The normal distributions of various ECG findings were originally obtained from samples of white males. We have since become aware of the need to use different cutoffs for “abnormality” based on the characteristics of the individual patient. For example, clinicians now often use different cutoffs for defining LVH in males and females. Several studies have shown that the LVH criteria that are used clinically are of limited utility in blacks. It is therefore possible that we are seeing risk discrepancies not due to differences underlying pathophysiology, but because of a need for more accurate race and gender-based norms.

Consistent with past studies that examined the closely-related early repolarization pattern, our study found that J-point elevation was associated with male sex, black race, younger age, and lower heart rate. Several case-control studies have reported a higher incidence of early repolarization among survivors of idiopathic ventricular fibrillation.
control study found that J-point elevation was more common among survivors of primary ventricular fibrillation. More recently, a population-based study by Tikkanen et al. found that early repolarization in the inferior leads was a marker of increased risk of death from cardiac causes and of sudden death from arrhythmia.

In all of these studies, race was either not reported or predominantly white. No subgroup analyses based on sex were reported. The sex and race-based differences present in our study were not obvious upon examination of the overall hazard ratios, but during the pre-specified subgroup analysis by race and sex, these relationships became evident. Even though these interactions were not uniformly significant, one can see that there is a consistent trend towards increased risk amongst whites and females. The largely consistent directionality of these effects makes it less probable that these results were due to chance.

In this study we examined the ECG finding of J-point elevation. Although J-point elevation is closely related to early repolarization, they are not equivalent. J-point elevation can be present even when early repolarization is not, but early repolarization cannot be diagnosed without J-point elevation. This partially explains why the exposure prevalence in this study (12.3%) was higher than that observed in previous studies. Additionally, we included leads V₁-V₃, whereas these leads are omitted in studies of early repolarization.

In addition to differences in the studied exposure, differences in cohort characteristics between this study and the Tikkanen study may explain the discrepancies in results. The Tikkanen study had more events and thus more power to detect a difference in the individual lead groupings. However, the results may more compatible than they appear at first glance. If J-point elevation does indeed connote increased risk in whites but not in blacks, as our results suggest, then it is not surprising that the Finnish cohort, which was likely to be largely white,
showed a significant relationship. The fact that our cohort is 27% black is a strength of the study in terms of generalizability, but may mask an effect when analysis is not stratified by race.

A strength of our study is the use of multiple definitions of SCD as outcomes. The adjudicated SCD outcome was ascertained through a strict adjudication process, thus providing a more accurate definition of SCD than is often available in epidemiological studies. Limits to the retrospective adjudication process certainly exist, and prospective ascertainment of arrhythmic events would provide a more accurate outcome measure. Sudden cardiac death by 1 hour definition and by 24 hour definition provide alternate, more traditional definitions of SCD that, while possibly less accurate, allow for easier comparison across studies.

A further strength of this study is the integrity of the J-point amplitude data. The J-point amplitude measurement is based on a computer algorithm that produces highly precise measurements, allows for good reproducibility, and eliminates inter-reader variability. This contrasts with studies of early repolarization in which the subjective judgment of the ECG reader is a factor and varying definitions of early repolarization are used between studies.

Despite the large size of the cohort, there were relatively few SCD events in our study. In addition, there were few subjects who manifested J-point elevation in the inferior and lateral ECG leads. Therefore, very few events occurred in these groups for most of the outcomes. Estimates of the effects in these lead groupings are somewhat unstable, especially for the rarer SCD outcomes, and thus it is difficult to draw conclusions about patterns in these lead groupings.

Our study shows that J-point elevation may be an important marker of risk for SCD in some populations. Additional research is needed to further characterize the relationship between J-point elevation and long-term outcomes. Further population-based study is preferable in order to obtain an accurate estimate of the predictive value of this finding in the general population.
The trends found based on gender and race are important, and these relationships need further investigation. Ultimately we must understand why these differences exist in order to target strategies to prevent SCD in these high-risk patients.
REFERENCES


### Appendix 1: Manuscript Tables

#### Table 1: Baseline Patient Characteristics for Overall Sample, and Stratified by Presence vs. Absence of J-Point Elevation ≥ 0.1mV in Any Lead

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>Overall Mean(SD) or % (n=15,141)</th>
<th>J-point Elevation Mean(SD) or % (n=1,866)</th>
<th>No J-point Elevation Mean(SD) or % (n=13,275)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.1(5.8)</td>
<td>53.7(5.8)</td>
<td>54.1(5.7)</td>
<td>.005</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Male</td>
<td>44.3</td>
<td>76.1</td>
<td>39.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% Female</td>
<td>55.7</td>
<td>23.9</td>
<td>60.2</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% White</td>
<td>73.1</td>
<td>46.7</td>
<td>76.8</td>
<td></td>
</tr>
<tr>
<td>% Black</td>
<td>26.9</td>
<td>53.3</td>
<td>23.1</td>
<td></td>
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<tr>
<td>Body Mass Index</td>
<td>27.7(5.4)</td>
<td>26.6(4.7)</td>
<td>27.9(5.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>66.8(10.4)</td>
<td>64.7(10.7)</td>
<td>67.0(10.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>121.2(18.8)</td>
<td>125.1(21.9)</td>
<td>120.7(18.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>73.7(11.2)</td>
<td>76.9(12.9)</td>
<td>73.3(10.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>% Current Smoker</td>
<td>26.1</td>
<td>34.1</td>
<td>25.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% Former Smoker</td>
<td>32.1</td>
<td>33.5</td>
<td>31.9</td>
<td></td>
</tr>
<tr>
<td>% Never Smoker</td>
<td>41.8</td>
<td>32.4</td>
<td>43.1</td>
<td></td>
</tr>
<tr>
<td>% Diabetic</td>
<td>11.9</td>
<td>13.7</td>
<td>11.6</td>
<td>.008</td>
</tr>
<tr>
<td>% with LVH by Cornell criteria</td>
<td>1.9</td>
<td>6.0</td>
<td>1.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cornell Voltage (µV)</td>
<td>1216(531)</td>
<td>1388(717)</td>
<td>1192(494)</td>
<td>&lt;.001</td>
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<tr>
<td>Major Abnormality on ECG*(%)</td>
<td>9.5</td>
<td>14.5</td>
<td>8.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>High-Density Lipoprotein (mg/dL)</td>
<td>51.7(17.1)</td>
<td>51.4(17.2)</td>
<td>51.7(17.1)</td>
<td>.42</td>
</tr>
<tr>
<td>Low-Density Lipoprotein (mg/dL)</td>
<td>137.4(39.4)</td>
<td>136.8(40.6)</td>
<td>137.5(39.2)</td>
<td>.42</td>
</tr>
<tr>
<td>Physical Activity (unitless)</td>
<td>2.43(0.79)</td>
<td>2.44(0.83)</td>
<td>2.43(0.79)</td>
<td>.67</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Basic</td>
<td>23.6</td>
<td>31.7</td>
<td>22.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% Intermediate</td>
<td>40.9</td>
<td>32.7</td>
<td>42.0</td>
<td></td>
</tr>
<tr>
<td>% Advanced</td>
<td>35.6</td>
<td>35.6</td>
<td>35.6</td>
<td></td>
</tr>
<tr>
<td>Personal History of CHD (%)</td>
<td>4.6</td>
<td>7.1</td>
<td>4.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of Stroke (%)</td>
<td>1.7</td>
<td>2.6</td>
<td>1.6</td>
<td>.001</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>5.0</td>
<td>3.6</td>
<td>5.2</td>
<td>.004</td>
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<tr>
<td>Intermittent Claudication (%)</td>
<td>0.77</td>
<td>0.75</td>
<td>0.77</td>
<td>.93</td>
</tr>
<tr>
<td>Family History of Premature CHD (%)</td>
<td>10.3</td>
<td>7.6</td>
<td>10.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiac Medications (%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Beta-Blockers</td>
<td>10.67</td>
<td>10.09</td>
<td>10.75</td>
<td>.38</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>3.40</td>
<td>3.80</td>
<td>3.34</td>
<td>.31</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>-----</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>0.65</td>
<td>0.94</td>
<td>0.61</td>
<td>.11</td>
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<tr>
<td>Digitalis</td>
<td>1.46</td>
<td>1.49</td>
<td>1.45</td>
<td>.91</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>3.05</td>
<td>3.47</td>
<td>2.99</td>
<td>.26</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>4.42(0.48)</td>
<td>4.41(0.47)</td>
<td>4.42(0.48)</td>
<td>.55</td>
</tr>
<tr>
<td>Serum Sodium (mmol/L)</td>
<td>141.0(2.4)</td>
<td>140.9(2.5)</td>
<td>141.0(2.4)</td>
<td>.73</td>
</tr>
<tr>
<td>Serum Calcium (mg/dL)</td>
<td>9.79(0.43)</td>
<td>9.81(0.45)</td>
<td>9.78(0.43)</td>
<td>.003</td>
</tr>
<tr>
<td>Serum Magnesium (mEq/L)</td>
<td>1.63(0.16)</td>
<td>1.62(0.16)</td>
<td>1.63(0.16)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

1Significance tests for comparisons by J-point elevation status based on 2-sample t-test for continuous subject characteristics and Pearson’s chi square test for categorical subject characteristics

*Major ECG abnormality as defined by Minnesota Code

| Table 2: Overall Prevalence of J-Point Elevation and Prevalence in Various Subgroups |
|------------------------------------------|------|------|-----|
| Overall (n=15,141)                       | 1,866 | 12.3% | n/a |
| Sex                                      |      |      |     |
| Male (n=6,707)                           | 1,420 | 21.2% | <.001 |
| Female (n=8,434)                         | 446  | 5.3%  |     |
| Race                                     |      |      |     |
| White (n=11,068)                         | 871  | 7.9%  | <.001 |
| Black (n=4,073)                          | 995  | 24.4% |     |
| Age (years)                              |      |      |     |
| 45-54 (n=8,063)                          | 1,053 | 13.1% | .003 |
| 55-64 (n=7,078)                          | 813  | 11.5% |     |

3Significance tests based on Pearson’s chi square test
<table>
<thead>
<tr>
<th></th>
<th>Adjudicated Sudden Cardiac Death HR (95% CI)</th>
<th>Sudden Cardiac Death (1 hr) HR(95% CI)</th>
<th>Sudden Cardiac Death (24 hr) HR (95% CI)</th>
<th>Fatal/Nonfatal CHD HR (95% CI)</th>
<th>All-Cause Mortality HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted Model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JPE in any lead</td>
<td>2.28 (1.69-3.07)</td>
<td>1.68 (1.22-2.32)</td>
<td>1.85 (1.48-2.31)</td>
<td>1.46 (1.28-1.65)</td>
<td>1.40 (1.28-1.53)*</td>
</tr>
<tr>
<td>JPE in leads II,III,aVF</td>
<td>1.69 (0.54-5.27)</td>
<td>1.09 (0.27-4.40)</td>
<td>1.11 (0.41-2.96)</td>
<td>1.06 (0.63-1.79)</td>
<td>1.52 (1.11-2.08)</td>
</tr>
<tr>
<td>JPE in leads I,V₆, aVL</td>
<td>2.87 (1.06-7.70)</td>
<td>2.78 (1.04-7.48)</td>
<td>1.75 (0.72-4.22)</td>
<td>1.23 (0.71-2.12)</td>
<td>1.07 (0.71-1.62)</td>
</tr>
<tr>
<td>JPE in leads V₁-V₅</td>
<td>2.20 (1.62-2.99)</td>
<td>1.69 (1.22-2.35)</td>
<td>1.89 (1.51-2.37)</td>
<td>1.45 (1.28-1.65)</td>
<td>1.40 (1.27-1.53)*</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>JPE in any lead</td>
<td>1.31 (0.94-1.82)</td>
<td>1.01 (0.71-1.43)</td>
<td>1.09 (0.86-1.40)</td>
<td>1.06 (0.92-1.21)</td>
<td>1.05 (0.96-1.16)*</td>
</tr>
<tr>
<td>JPE in leads II,III,aVF</td>
<td>1.25 (0.40-3.92)</td>
<td>0.86 (0.21-3.46)</td>
<td>0.87 (0.32-2.33)</td>
<td>0.90 (0.53-1.52)</td>
<td>1.37 (1.00-1.87)*</td>
</tr>
<tr>
<td>JPE in leads I,V₆, aVL</td>
<td>1.88 (0.69-5.09)</td>
<td>2.06 (0.76-5.61)</td>
<td>1.20 (0.50-2.91)</td>
<td>1.06 (0.61-1.83)</td>
<td>0.90 (0.60-1.36)*</td>
</tr>
<tr>
<td>JPE in leads V₁-V₅</td>
<td>1.23 (0.88-1.73)</td>
<td>1.00 (0.70-1.43)</td>
<td>1.10 (0.86-1.41)</td>
<td>1.04 (0.91-1.20)</td>
<td>1.04 (0.94-1.15)*</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>JPE in any lead</td>
<td>1.28 (0.90-1.82)</td>
<td>1.09 (0.76-1.58)*</td>
<td>1.10 (0.85-1.43)</td>
<td>1.06 (0.92-1.23)</td>
<td>1.06 (0.96-1.18)*</td>
</tr>
<tr>
<td>JPE in leads II,III,aVF</td>
<td>1.85 (0.59-5.83)</td>
<td>1.20 (0.30-4.85)*</td>
<td>1.25 (0.46-3.35)</td>
<td>0.89 (0.49-1.62)</td>
<td>1.51 (1.07-2.12)*</td>
</tr>
<tr>
<td>JPE in leads I,V₆, aVL</td>
<td>3.00 (1.09-8.26)</td>
<td>2.87 (1.04-7.93)*</td>
<td>1.60 (0.65-3.91)</td>
<td>1.24 (0.70-2.20)</td>
<td>1.00 (0.64-1.55)*</td>
</tr>
<tr>
<td>JPE in leads V₁-V₅</td>
<td>1.19 (0.83-1.70)</td>
<td>1.08 (0.74-1.57)*</td>
<td>1.11 (0.85-1.45)</td>
<td>1.05 (0.90-1.22)</td>
<td>1.05 (0.94-1.17)*</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
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<td></td>
<td></td>
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<tr>
<td>JPE in any lead</td>
<td>1.23 (0.87-1.75)</td>
<td>1.06 (0.73-1.53)</td>
<td>1.06 (0.81-1.38)</td>
<td>1.03 (0.89-1.19)</td>
<td>1.02 (0.92-1.13)*</td>
</tr>
<tr>
<td>JPE in leads II,III,aVF</td>
<td>1.88 (0.60-5.91)</td>
<td>1.25 (0.31-5.05)*</td>
<td>1.32 (0.49-3.54)</td>
<td>0.94 (0.52-1.71)</td>
<td>1.57 (1.12-2.20)*</td>
</tr>
<tr>
<td>JPE in leads I,V₆, aVL</td>
<td>2.82 (1.02-7.79)</td>
<td>2.76 (1.00-7.64)*</td>
<td>1.58 (0.65-3.88)</td>
<td>1.28 (0.72-2.27)</td>
<td>1.08 (0.69-1.68)*</td>
</tr>
<tr>
<td>JPE in leads V₁-V₅</td>
<td>1.14 (0.79-1.63)</td>
<td>1.04 (0.72-1.52)</td>
<td>1.06 (0.81-1.38)</td>
<td>1.02 (0.88-1.18)</td>
<td>1.00 (0.90-1.11)*</td>
</tr>
</tbody>
</table>

*J-point elevation is present when J-point amplitude is ≥0.1mV
†Based on Cox proportional hazards model, adjusted for age, sex, and race
‡Based on Cox proportional hazards model, adjusted for age, sex, race, heart rate, systolic blood pressure, BMI, serum low-density lipoprotein, diabetes, presence of major ECG abnormality, Cornell voltage for LVH, previous CHD, history of angina or stroke
§Based on Cox proportional hazards model, adjusted for age, sex, race, heart rate, systolic blood pressure, BMI, serum low-density lipoprotein, diabetes, presence of major ECG abnormality, Cornell voltage for LVH, previous CHD, history of angina or stroke, smoking status, physical activity, and serum potassium
¶Proportional Hazards assumption violated for one or more covariates in the model. Stratification on violating covariates produced negligible change in the results
¥Heart rate interaction present
Table 4: Pre-specified Subgroup Analyses: Adjusted Hazard Ratios$^*$ for Primary and Secondary Outcomes Comparing Subjects with J-Point Elevation in Any Lead to Subjects without J-Point Elevation

<table>
<thead>
<tr>
<th></th>
<th>Adjudicated Sudden Cardiac Death HR(95%CI)</th>
<th>1 Hour Sudden Cardiac Death HR(95%CI)</th>
<th>24 Hour Sudden Cardiac Death HR(95%CI)</th>
<th>Fatal/Nonfatal CHD HR(95%CI)</th>
<th>All-Cause Mortality HR(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2.03(1.28-3.21)*</td>
<td>1.11(0.64-1.92)</td>
<td>1.25(0.84-1.86)</td>
<td>1.16(0.95-1.40)</td>
<td>1.10(0.95-1.28)</td>
</tr>
<tr>
<td>Black</td>
<td>0.82(0.52-1.30)*</td>
<td>1.02(0.63-1.65)</td>
<td>0.95(0.68-1.32)</td>
<td>0.91(0.74-1.12)</td>
<td>0.96(0.83-1.10)</td>
</tr>
<tr>
<td>Ratio of Hazard Ratios</td>
<td>2.46</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2.54(1.34-4.82)*</td>
<td>1.49(0.68-3.30)</td>
<td>1.48(0.88-2.51)</td>
<td>1.47(1.10-1.96)*</td>
<td>0.96(0.77-1.19)</td>
</tr>
<tr>
<td>Male</td>
<td>1.02(0.69-1.50)*</td>
<td>0.99(0.66-1.48)</td>
<td>0.97(0.72-1.30)</td>
<td>0.94(0.80-1.11)*</td>
<td>1.04(0.92-1.16)</td>
</tr>
<tr>
<td>Ratio of Hazard Ratios</td>
<td>2.50</td>
<td>1.51</td>
<td>1.53</td>
<td>1.55</td>
<td>0.92</td>
</tr>
</tbody>
</table>

$^*$Based on Cox proportional hazards model, adjusted for age, sex, race, heart rate, systolic blood pressure, BMI, serum low-density lipoprotein, diabetes, presence of major ECG abnormality, Cornell voltage for LVH, previous CHD, history of angina or stroke, smoking status, physical activity, and serum potassium

$^*$P value for interaction <.05
## Supplemental Table 1: Adjusted Hazard Ratios* for Adjudicated Sudden Cardiac Death in Leads V₁-V₅

<table>
<thead>
<tr>
<th>J-Point Amplitude (continuous)</th>
<th>Adjudicated Sudden Cardiac Death HR(95%CI)</th>
<th>J-Point Elevation ≥0.1mV (dichotomized)</th>
<th>Adjudicated Sudden Cardiac Death HR(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead V₁</td>
<td>Black 0.71(0.44-1.15) White 2.56(1.57-4.18)</td>
<td>Lead V₁ Black 0.66(0.40-1.09) White 1.90(1.15-3.15)</td>
<td></td>
</tr>
<tr>
<td>Lead V₂</td>
<td>Black 0.77(0.55-1.09) White 1.85(1.30-2.64)</td>
<td>Lead V₂ Black 0.64(0.36-1.12) White 2.86(1.59-5.16)</td>
<td></td>
</tr>
<tr>
<td>Lead V₃</td>
<td>Black 0.79(0.55-1.13) White 1.88(1.25-2.81)</td>
<td>Lead V₃ Black 0.64(0.36-1.12) White 2.86(1.59-5.16)</td>
<td></td>
</tr>
<tr>
<td>Lead V₄</td>
<td>0.99(0.72-1.36)</td>
<td>Lead V₄ Black 0.66(0.40-1.09) White 1.90(1.15-3.15)</td>
<td></td>
</tr>
<tr>
<td>Lead V₅</td>
<td>0.89(0.61-1.31)</td>
<td>Lead V₅ Black 0.64(0.36-1.12) White 2.86(1.59-5.16)</td>
<td></td>
</tr>
</tbody>
</table>

*Based on Cox proportional hazards model, adjusted for age, sex, race, heart rate, systolic blood pressure, BMI, serum low-density lipoprotein, diabetes, presence of major ECG abnormality, Cornell voltage for LVH, previous CHD, history of angina or stroke, smoking status, physical activity, and serum potassium

† Hazard ratios presented are for a 100µV increase in J-point amplitude