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Abayomi O. Bamgboje 07/30/2024

Approval Sheet

How do prolonged Tpe interval, T peak amplitude and QRS durations among individuals with coronary heart disease (CHD) in Atlanta associate with future non-fatal HF and fatal CVD outcomes?

By

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Degree to be awarded: MPH

Executive Master of Public Health

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Abstract Cover Page

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A thesis submitted to the faculty of the

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Abstract

Background:

Markers of ventricular depolarization and repolarization, such as T peak amplitude, Tpe interval, and QRS duration, have been recognized as significant predictors of prognosis in both heart failure patients and apparently healthy individuals. However, contemporary studies examining their prognostic significance in stable coronary heart disease, a common cause of mortality, are limited.

Method:

Data were sourced from the Mental Stress Ischemia Prognosis Study (MIPS) and Myocardial Infarction and Mental Stress Study 2 (MIMS2) conducted between June 2011 and March 2016. Participants were categorized into tall or short resting T-Peak amplitude measured with an electrocardiogram in limb lead 1. Baseline characteristics, including age, Body mass Index, QRS duration, Tpe interval, Systolic/diastolic blood pressure (SBP/DBP), heart rate, creatinine, potassium, hemoglobin, gender, and race, were analyzed using Cox Proportional Hazard regression models to assess associations with mortality and HF outcomes.

Result:

We analyzed baseline characteristics of 446 stable CHD patients based on their T-peak amplitude. The lower mean T-peak amplitude group (n=226) compared with the higher mean T-peak amplitude group (n=220) had a lower mean EF (66% vs. 73%), a higher percentage of Black participants, and more baseline HF cases, while other characteristics such as age, BMI, QRS duration, blood pressure, heart rate, creatinine, potassium, and hemoglobin levels showed

no significant differences. Of the 446 stable patients, 45 experienced incident non-fatal HF and 23 experienced cardiovascular mortality during a median follow up period of 1836 and 1862 days, respectively. T-Peak amplitude in limb lead 1 (<6mm vs. ≥6mm) emerged as a significant predictor of heart failure (HR 2.96, 95% CI: 1.64, 5.33) and cardiovascular mortality (HR 2.48, 95% CI: 1.08, 5.66). T-Peak to end in lead V2 and QRS duration did not predict incident heart failure or cardiovascular mortality.

Conclusion:

We found that T-Peak amplitude in limb lead 1 was a robust predictor of adverse CVD outcomes in CHD patients that was independent of sociodemographic and other CVD factors.

How do prolonged Tpe interval, T peak amplitude and QRS durations among individuals with coronary heart disease (CHD) in Atlanta associate with future non-fatal HF and fatal CVD outcomes?

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Chapter 1

Introduction

The significance of studying cardiac electrophysiology, specifically Tpe interval, T peak amplitude and QRS duration, in the context of HF and CVD.

Since the mid-1960s, there has been a consistent decline in heart disease deaths.[1] The factors contributing to this decline in cardiac deaths remain uncertain and we still have gaps in predicting and preventing CVD death, and ECG digital biomarkers are potentially important for early diagnosis and treatment. In the United States, coronary heart disease resulting from coronary atherosclerosis remains the primary cause of cardiac deaths, constituting 64% of all cardiac deaths in 2009.[2] CAD is the leading cause of Heart failure in the United states. [3] Surface electrocardiography (EKG) continues to be a key diagnostic tool for coronary artery disease (CAD), and its prognostic value is widely recognized and documented.[2]

The Tpe interval, which is the time from the peak to the end of the electrocardiographic T wave, may reflect the transmural dispersion of repolarization in the ventricles.[3] The Tpe/cTpe intervals are usually calculated with a computer program. The most clinically relevant Tpe and QTC intervals are usually measured in lead V2.[4] The end of the T wave is defined as the intersection of the tangent to the down-slope of the T wave and the isoelectric line and the peak is the maximum amplitude of T wave.[4] According to Koca et al normal mean and median Tpe intervals are 70.3 ± 12.3 ms, and 70 ms respectively.[3] Whereas Tpe-c mean and standard deviation, and median values were found to be 76.1 ± 14.6 ms, and 75 ms respectively[3]. A

prolonged Tpe interval has been associated with an increased risk of arrhythmias and sudden cardiac death. It is considered a non-invasive marker that could indicate the heterogeneity of ventricular repolarization, which is a risk factor for malignant ventricular arrhythmias.[4,5]

The amplitude of the T wave peak can provide insights into the electrical activity of the heart and help identify various cardiac conditions. According to Okuda et al[6] As the peak T-wave amplitude in lead aVR becomes less negative, there was a progressive increase in mortality.[6]

The results here are impressive but are limited by the fact that this study focused on HF patients, studied AVR (not lead 1) and excluded wide QRS. Wide QRS in fact may be an important effect modifier to explore. Abnormalities in T wave amplitude may suggest myocardial ischemia, electrolyte imbalances, or other pathologies.[7]

The QRS duration measures the time it takes for the ventricles to depolarize. A prolonged QRS duration can be indicative of ventricular dyssynchrony, which is when different parts of the ventricles contract at different times.[8] This dyssynchrony can lead to inefficient pumping of the heart, contributing to the progression of HF. Moreover, a wide QRS complex is often associated with structural heart disease and can be a predictor of CVD mortality.[8] In patients with a history of myocardial infarction and/or heart failure, QRS duration serves as a prognostic indicator.[8]

Over an average follow-up period of 4.2 ± 2.4 years, 280 patients (23%) experienced mortality, with 129 deaths attributed to cardiac causes, while 60 patients (5%) suffered a nonfatal infarction.[8] Patients with QRS duration <120 ms exhibited annualized cardiac death rates of 2.0%, whereas those with QRS duration ≥120 ms had rates of 4.4% ($p < 0.0001$).[8] Additionally, the annualized event rates for cardiac death or nonfatal infarction were 2.8% and 4.8% in

patients with QRS duration <120 ms and ≥120 ms, respectively (p = 0.0001).[8]

We analyzed the predictive capacity of Tpe interval, T peak amplitude and QRS duration in this study.

By studying these intervals in patients with stable coronary heart disease (CHD), we aim to identify those at higher risk for HF hospitalization and CVD mortality. This can lead to better risk stratification and potentially guide therapeutic interventions to improve patient outcomes. For instance, patients with a prolonged Tpe interval or QRS duration, short T peak amplitude may benefit from more aggressive management strategies to prevent HF or CVD events. The Tpe interval, T peak amplitude and QRS duration are valuable components of cardiac electrophysiology that can provide insights into the electrical stability and mechanical function of the heart. Their study is significant because it helps to identify individuals with CHD who are at an increased risk of HF hospitalization and CVD mortality, thereby offering opportunities for early intervention.

Definitions of coronary artery disease:

Stable coronary artery disease (SCAD) encompasses several patient groups: (i) individuals experiencing stable angina pectoris or other symptoms associated with coronary artery disease (CAD), such as dyspnea; (ii) previously symptomatic patients with known obstructive or non-obstructive CAD who have become asymptomatic with treatment and require regular monitoring; and (iii) individuals reporting symptoms for the first time but deemed to already be in a chronic stable state (e.g., based on historical evidence of similar symptoms persisting for

several months).[9] Therefore, SCAD delineates various stages of CAD evolution, excluding situations where coronary artery thrombosis predominates the clinical presentation (acute coronary syndromes).[9] Stable angina, previous myocardial infarctions, prior percutaneous revascularization, coronary artery bypass graft (CABG) procedures, confirmed coronary atherosclerosis via angiography, or reliable non-invasive indications of myocardial ischemia are all in the spectrum of SCAD.[10]

Phenotypic definitions of coronary artery disease:

Acute coronary syndromes (ACS phenotype), including MI (fatal and nonfatal) and unstable angina according to standard criteria (World Health Organization or universal definition criteria).[11]

Angiographically documented disease (angiographic phenotype) defined as presence of stenosis above a certain threshold on a major epicardial artery on angiography.

Broadly defined CAD (broad phenotype) on the basis of varying clinical criteria and history of disease, or not otherwise specified.[12]

Prevalence of HF Hospitalization and CVD Mortality in individuals with stable CAD:

In the CORONOR study of 4184 consecutive CAD outpatients who were free from any myocardial infarction (MI) or coronary revascularization for more than 1 year, there were 677 deaths, with cardiovascular causes identified in 269 patients (1.3% per year). Among these, 99 deaths were attributed to heart failure (HF), 91 to sudden events, and 65 to vascular causes

(including stroke, MI, limb or mesenteric ischemia, and aortic aneurysm). Predictors of cardiovascular disease (CVD) included age [subhazard ratio (SHR)=1.06 (1.04–1.07) per year increase], prior hospitalization for decompensated HF [SHR=3.10 (2.19–4.40)], left ventricular ejection fraction [SHR=0.97 (0.96–0.98) per percentage increase], previous aortic or peripheral intervention [SHR=1.61 (1.12–2.13)], and estimated glomerular filtration rate [SHR=0.99 (0.98–1.00) per ml/min/1.73m2 increase].[13]

HF affects more than 64 million people worldwide, and its prevalence is increasing, particularly due to the aging population and improved survival rates with ischemic heart disease. [14] The 2021 American Heart Association Heart Disease and Stroke Statistics used NHANES data from 2015 to 2018 to estimate the prevalence of heart failure (HF). It revealed that approximately 6.0 million Americans aged 20 years and older had HF, up from about 5.7 million reported in NHANES data from 2009 to 2012. In 2012, HF prevalence in the USA was 2.4%, and it is projected to increase to 3.0% by 2030.[15]

In the United States, CHD was the leading cause of deaths attributable to CVD, with HF accounting for 9.1% of these deaths as of 2021. In the same year, coronary heart disease (CHD) resulted in 375,476 deaths in the United States. Data from 2005 to 2014 revealed an estimated annual incidence of 605,000 new heart attacks and 200,000 recurrent attacks, with males experiencing their first heart attack at an average age of 65.6 years and females at 72.0 years. Approximately every 40 seconds, an individual in the United States suffers a myocardial infarction. Despite a 15.0% decrease in the annual death rate attributable to CHD from 2011 to 2021, the actual number of deaths increased by 0.05% during this period.[16]

Impact of HF Hospitalization:

Hospitalization for HF is associated with a high morbidity rate, significantly impacting patients' quality of life and functional capacity. The burden of HF hospitalizations is also a major economic concern, with substantial costs incurred for both acute care and long-term management. The financial impact of heart failure (HF) on healthcare expenses globally is worrisome. In 2012, HF incurred an estimated total cost of $30.7 billion in the USA. Projections indicate a staggering 127% rise in costs by 2030, reaching $69.8 billion, averaging around $244 for every US adult.[17]

Impact of CVD Mortality:

CVD, including CHD, remains a leading cause of mortality globally. The death rate from ischemic heart disease in the U.S. The number of deaths related to cardiovascular disease surged from 874,613 in 2019 to 928,741 in 2020, marking the most significant single-year increase since 2015, as reported in the 2023 update to the American Heart Association's heart disease and stroke statistics.[18] The continuous rise in heart failure death rates, from 2016 to 2020, highlights the growing impact of this condition on overall CVD mortality. [19]

Hospitalization Trends:

In 1995, IHD hospitalization was double that of HF, at 37.6 and 19.0 per 1000 adults with diabetes, respectively. From 1995 to 2015, IHD hospitalization decreased by 67.8%, while HF hospitalization decreased by 38.9%.[19] The data underscores the importance of effective management strategies for individuals with stable CHD to prevent HF hospitalization and reduce CVD mortality. It also highlights the need for ongoing research to better understand and

address the factors contributing to these trends.[19]

The rationale for selecting the MIPS and MIMS2 studies for this review.[20,21]

The rationale for selecting the Mental Stress Ischemia Prognosis Study (MIPS) and the Myocardial Infarction and Mental Stress Study 2 (MIMS2) as a data source on the prediction of heart failure (HF) hospitalization and cardiovascular disease (CVD) mortality among individuals with stable coronary heart disease (CHD):

The MIPS and MIMS2 focus on mental stress-induced myocardial ischemia, which is a significant but under-recognized factor in the prognosis of patients with CHD. [22]

These studies provide valuable insights into how psychological stress can trigger ischemic events that may not be evident during physical stress testing.

MIPS and MIMS2 included longitudinal follow-up of participants, which is crucial for evaluating the predictive value of Tpe interval T wave amplitude and QRS duration over time.[22] The duration of these studies ensures that the data captured reflects the long-term implications of mental stress on cardiac health. Additionally, these studies enrolled a diverse patient population from hospitals and clinics affiliated with Emory University, enhancing the generalizability of the findings. This diversity helps in understanding the impact of mental stress-induced ischemia across different demographics and clinical backgrounds. The selection of MIPS and MIMS2 for the data source is justified by its focus on mental stress-induced ischemia, comprehensive data collection, longitudinal follow-up, diverse patient population, significant findings, and innovative approach to studying CHD.[20,21]

These aspects make them highly relevant for investigating the predictive power of Tpe interval, T-amplitude and QRS duration in the context of HF hospitalization and CVD mortality among individuals with stable CHD. The findings from these studies have shown that patients with mental stress-induced ischemia had higher event rates for cardiovascular outcomes compared to those without, highlighting the importance of these parameters in predicting HF hospitalization and CVD mortality.

Chapter 2 Literature review

Background

Pathophysiology of CHD and its progression to HF and CVD.

The pathophysiology of coronary heart disease (CHD) and its progression to heart failure (HF) and cardiovascular disease (CVD) mortality involves a complex interplay of various factors: Remodeling refers to both structural and functional changes in the heart following injury. Remodeling encompasses changes in heart dimensions, mass, and shape in response to cardiac events, categorized as either physiologic or pathologic.[23] Physiologic remodeling, like "athlete's heart," occurs in response to physiological stimuli and differs from pathologic remodeling, which involves processes like fibrosis due to cardiac injury or overload.[23] Despite diverse causes, cardiac remodeling follows a common molecular pathway, involving various heart components like cardiomyocytes, fibroblasts, and endothelium.[23] Factors like neurohumoral activation and hemodynamic changes influence remodeling, leading to ventricular hypertrophy, dilation, and cellular alterations such as cardiomyocyte hypertrophy and fibrosis.[23] Progression from adaptive to maladaptive remodeling is influenced by event severity, compensatory mechanisms, and treatment efficacy, with no precise transition point identified.[24]

Many risk factors for atherosclerosis, such as LDL, affect endothelial cells uniformly throughout the circulatory system. However, atherosclerotic lesions tend to develop segmentally, especially at arterial branch points.[23] In normal arterial regions, laminar shear stress induces a protective response from endothelial cells that mitigates the effects of risk factors like LDL and counteracts vasoconstriction by releasing nitric oxide, an endothelial-derived relaxing factor.

This protective response includes the suppression of vasoconstrictor, inflammatory, and prothrombotic gene expression through well-understood molecular mechanisms. [23]At flow dividers, disturbed flow hinders these atheroprotective functions, activating the proinflammatory transcription factor nuclear factor κB, which recruits inflammatory cells and impairs vasodilation.[23] This leads to the accumulation of leukocytes, primarily mononuclear phagocytes, in the arterial intima, setting the stage for foam-cell formation as these cells engulf modified lipoproteins that accumulate in the intima exposed to excess LDL.[23] Foam cells generate mediators that enhance and sustain the local inflammatory response, which leads to the progression and thrombotic complications of atherosclerosis. These signals from foam cells also induce smooth muscle cells to migrate from the tunica media to the arterial intima, where they produce extracellular matrix macromolecules that form fibrous lesions.[23] These lesions can cause arterial stenosis, restricting blood flow and leading to ischemic conditions like angina pectoris, intermittent claudication, and cerebrovascular disease. Additionally, the loss of arterial elasticity increases pulse pressure, a condition associated with aging and an increased risk of cardiovascular events. While arterioles generally resist plaque formation seen in larger arteries, they can develop medial hypertrophy and intimal thickening, a type of remodeling linked to high blood pressure, which exacerbates and sustains hypertension.[25] Unlike endothelial cells, smooth muscle cells do not detect luminal shear stress; instead, they undergo cyclic circumferential deformation caused by arterial pulsations. This deformation enhances the synthesis of proteoglycans by smooth muscle cells, which increases LDL retention in the intima.[26] Smooth muscle cells in the intima, activated by proinflammatory cytokines from

macrophages such as interleukin-1, causing more collagen, leading to the arterial fibrosis seen in aging and hypertension. This activation also increases the release of matrix-degrading enzymes like matrix metalloproteinases, which can remodel the arterial extracellular matrix, including the elastin in the external elastic membrane that forms the artery's outer boundary. This permits outward growth, of the developing atheroma, which helps preserve the artery's lumen and maintain blood flow.[27] Eventually, plaque growth can exceed the artery wall's compensatory enlargement, causing the atheroma to encroach on the lumen and result in stenosis.[27] Collagen breakdown caused by enzymes overproduced by macrophages can weaken and thin the fibrous cap, making it vulnerable to disruption. When the fibrous cap fractures, coagulation proteins in the blood come into contact with procoagulant tissue factors produced by macrophages in response to proinflammatory cytokines. This triggers the thrombotic cascade, leading to local clot formation and causing the majority of fatal myocardial infarctions.[28] Acute myocardial infarction is a leading cause of death and disability globally. This largely is due to the remodeling that occurs after the infarction. While cardiac remodeling is typically linked to events happening weeks and months post-infarction, its outcomes are closely tied to the initial size of the infarction.

Myocardial remodeling involves intrinsic changes in both cardiomyocytes and the interstitium. The failing myocardium, regardless of its cause, exhibits common characteristics related to cardiomyocyte viability, neurohumoral regulation, and excitation-contraction coupling, as well as interstitial cells and matrix. Cardiomyocytes make up 20-30% of the heart's cells but account for 70-80% of its mass. According to Bergmann et al cardiomyocytes can regenerate from stem

cells following injury or exercise.[29] [30] Myocytes can undergo hypertrophy and changes in shape, often accompanied by a shift in myosin isoforms, while pressure overload increases thickness, volume overload causes myocyte length increase.[31,32] Autophagy is a natural process, frequently associated with aging, where myocytes break down damaged and altered proteins during conditions like chronic ischemia, hibernation, and post-infarction. Suppressing autophagy worsens adverse remodeling, while enhancing autophagy has been shown to improve experimental post-myocardial infarction remodeling.[33-35] Increased left ventricular wall tension triggers the myocardial renin-angiotensin system, leading to myocardial hypertrophy. Aldosterone and angiotensin II additionally stimulate changes in the heart's interstitial structure. α-Adrenergic stimulation contributes to myocardial hypertrophy. In cases of chronic β-adrenergic stimulation, β-adrenergic receptors are suppressed, Giα proteins are enhanced in heart failure, and myocardial apoptosis is induced. This is the pathway through which heart failure develops from coronary heart disease. [36-41]

Impact on CVD Morbidity and Mortality:

Coronary artery disease (CAD) is prevalent among individuals with chronic kidney disease (CKD), and its occurrence increases steadily as estimated glomerular filtration rate (eGFR) decreases. Managing CAD concurrently poses significant challenges and is linked to unfavorable outcomes in these patients. The primary approach to managing CAD involves lipid-lowering medications. However, the efficacy of statins diminishes as CKD advances, with unclear benefits observed in patients undergoing dialysis.[42] Approximately half of heart failure patients (49%) also suffer

from chronic kidney disease (CKD), which exacerbates mortality and hospitalization rates. The risk of heart failure and mortality increases as renal function declines, regardless of age, duration of heart failure, or presence of diabetes. Diagnosing these conditions presents challenges since symptoms like dyspnea and peripheral edema, indicative of fluid overload, are prevalent in both heart failure and CKD.[43] The presence of comorbidities like hypertension, diabetes, and dyslipidemia can exacerbate the condition, increasing the risk of adverse cardiovascular events and death. According to Takuya et al of the 3,926 CV deaths during a mean follow-up of 6 years CV death were commoner in the older who had higher heart rates and longer QRS duration and QT intervals. [44] EKG abnormalities was an important predictor of cardiovascular death as the normal EKG group experienced an average annual cardiovascular mortality of 0.7%, whereas the abnormal ECG group had a significantly higher rate at 2.9%. Additionally, the abnormal ECG group who exhibited higher mortality rates, older age, elevated heart rate, longer QRS duration, and a higher prevalence of T-wave abnormalities.[44]

Clinical Implications:

Understanding the pathophysiology of CHD and its progression to HF and CVD mortality is crucial for developing targeted interventions to prevent and treat these conditions. Strategies may include lifestyle modifications, pharmacotherapy to manage risk factors, and interventions to restore coronary blood flow and improve cardiac function. The progression of CHD to HF and CVD mortality is a multifactorial process that involves the interplay of atherosclerosis, myocardial damage, cardiac remodeling, and systemic factors such as kidney disease. [45]

Predictors of Mortality in patients with CHD:

According to Dankner et al[46] cardiovascular mortality showed strong associations with past myocardial infarction, peripheral vascular disease, and total cholesterol. High-density lipoprotein cholesterol exhibited its expected protective effect against cardiovascular mortality. Total cholesterol specifically correlated with cardiovascular mortality, while angina pectoris emerged as a predictor for overall mortality.

Smoking was associated with a modest increase in cardiovascular mortality (CM) of 1.29 (95% CI 1.08 to 1.55), but primarily linked to non-cardiovascular mortality (NCM) with a hazard ratio of 1.66 (95% CI 1.33 to 2.08). Among different smoking categories—non-smoking, past smoking, and current smoking—there was an age-adjusted increase in NCM rates from 4.2 (95% CI 3.7 to 4.8) to 4.5 (95% CI 4.0 to 5.0) to 7.9 (95% CI 5.6 to 10.3), respectively. Additionally, higher daily cigarette consumption showed a corresponding increase in age-adjusted NCM rates, rising from 7.9 (95% CI 5.6 to 10.3) for 1 to 20 cigarettes per day to 9.2 (95% CI 6.7 to 11.8) for 21 or more cigarettes per day.[46]

Tpe interval, Tpeak amplitude and QRS duration and their roles in cardiac function.

The Tpe interval represents the time from the peak to the end of the T wave on an electrocardiogram (ECG). The "tangent" method, typically performed manually, identifies the T-peak as the highest absolute deflection of the T-wave from the isoelectric line, and the T-end as the point where the tangent to the T-wave's downslope intersects the isoelectric line. This method has been used in various previously published studies involving leads V2 and V5.[3] It is a measure of the transmural dispersion of repolarization in the ventricles. Mean TpTe was

significantly greater in cases of sudden cardiac death (89.4 ms; 95% CI, 87.7 to 91.2 ms; P=0.0001) than in controls with stable coronary heart disease (76.1 ms; 95% CI, 74.8 to 77.4 ms).[47] According to Panikkath et al[47] the distribution of TpTe in cases versus controls also showed that beyond a TpTe >=85 ms, 72% of subjects were cases of sudden cardiac death, and of >=95 ms, >=80% were cases of sudden cardiac death.[47] A prolonged Tpe interval can indicate an increased risk for ventricular arrhythmias and sudden cardiac death (SCD), as it reflects a period where the ventricular myocardium is vulnerable to reentrant arrhythmias. The Tpe interval is also associated with the arrhythmic condition in various cardiac pathologies and is considered a risk marker for SCD. [3]

The QRS duration measures the time taken for the ventricular depolarization process, which is the spread of electrical impulse through the ventricles that triggers their contraction. A normal QRS duration is essential for the synchronous contraction of the ventricles, ensuring efficient blood ejection. Prolonged QRS duration can be a sign of ventricular dyssynchrony, where different parts of the ventricles contract at different times, leading to inefficient cardiac pumping. It can also indicate the presence of an underlying structural heart disease and is a predictor of CVD mortality.[48]

T-wave amplitude on the initial electrocardiogram of patients receiving thrombolytic therapy for acute myocardial infarction was found to provides valuable prognostic information regarding mortality and morbidity according to Hochrein et al.[49] specifically, patients with high T waves experienced significantly lower 30-day mortality rates and were less likely to develop cardiogenic shock or congestive heart failure.[49]

According to Yamazaki et al[44] there was a progressive increase in risk as the amplitude decreased, flattened, and inverted. From 1.0 to 0.5 to 1.0 mm, the relative risk (RR) confidence interval (CI) was 1.2 to 1.6; from 0.0 to 0.5 mm, the RR CI was 1.9 to 2.5; and with an inverted T wave, the RR CI was 2.9 to 3.8 ($p < 0.0001$).[44]

Both the Tpe interval and QRS duration are critical for maintaining the heart's electrical stability and mechanical efficiency. The Tpe interval's role in cardiac function is mainly related to the risk stratification for arrhythmic events, while the QRS duration is directly involved in the mechanical coordination of the heart's pumping action. Abnormalities in these intervals can lead to arrhythmias, HF, and increased CVD mortality, making them important parameters to monitor in patients with CHD.[50]

De Lazzari et al[51] evaluated the relationship between ECG findings and cardiac magnetic resonance phenotypes in arrhythmogenic cardiomyopathy. They found that both depolarization and repolarization ECG abnormalities were correlated with the severity of dilatation/dysfunction of the ventricles and the presence of late gadolinium enhancement, which are important determinants of the disease outcome. [51]

Chapter 3 Methods:

Study objectives.

Problem Statement:

How do prolonged Tpe interval, T peak amplitude and QRS durations among individuals with coronary heart disease (CHD) in Atlanta associate with future non-fatal HF and fatal CVD outcomes?

The findings from this study may help in improving CHD management by highlighting areas that may require further research and more risk factor management to improve the overall outcome of patients with CHD in Atlanta.

Purpose Statement:

To determine whether increased Tpe interval, decreased T peak amplitude and prolonged QRS duration predicts a higher HF hospitalization and CVD mortality among individuals with stable CHD enrolled in the Mental Stress Ischemia Prognosis Study (MIPS) and the Myocardial Infarction and Mental Stress Study 2 (MIMS2) between June 2011 and March 2016 from hospitals and clinics affiliated with Emory University

Approach:

My null hypothesis is that EKG parameters such as T peak to end interval, T peak amplitude and QRS duration are not useful predictors of nonfatal heart failure and cardiovascular mortality in stable CHD patients enrolled in the Mental Stress Ischemia Prognosis Study (MIPS) and the Myocardial Infarction and Mental Stress Study 2 (MIMS2) between June 2011 and March 2016,

individuals with stable coronary heart disease (CHD) were recruited into two concurrent studies, the Mental Stress Ischemia Prognosis Study (MIPS) and the Myocardial Infarction and Mental Stress Study 2 (MIMS2), which employed similar protocols. Patients were enrolled from Emory University-affiliated hospitals and clinics, with both studies utilizing shared staff, facilities, and equipment.[20,21]

The inclusion and exclusion criteria for this study is outlined below;

Inclusion Criteria:

MIPS, patients were eligible to participate if they were 30 to 79 years of age and had a documented history of CHD. [20]

MIMS2, patients were included if they were hospitalized for a verified myocardial infarction (MI) within the past 8 months and were 18 to 60 years of age at the time of the MI.[21]

Exclusion criteria:

Patients were excluded from both studies if they were pregnant or if they had medical comorbidities expected to shorten life expectancy

Patients enrolled in MIMS2 who also participated in MIPS were excluded

The demographic and clinical parameters of the study population were recorded. Survival times were defined as the date of admission for HF from date of enrolment into the study and date of cardiovascular mortality from date of recruitment into the study whereas date of censorship which was March 2016.

Data description

The data was obtained from 2 prospective studies of patients with stable CHD. In the Mental Stress Ischemia Prognosis Study (MIPS) and the Myocardial Infarction and Mental Stress Study 2 (MIMS2) between June 2011 and March 2016.

The patients were split into two groups based on survival status at the end of the study period heart failure status (yes or no), cardiovascular mortality (dead or alive) and TPeak amplitude (short or tall). The race was split into two groups namely black and nonblack. Age was analyzed per 5 yearly increments. T peak to end duration was derived as the total T wave duration minus time from onset of T waves to peak of T waves in V2.[4] T peak amplitude obtained from limb lead 1 was used in this study.[44] The other relevant data were documented.

Statistics

Continuous variables were expressed as means ± standard deviation, while categorical variables were expressed as frequencies and percentages. The difference between means of two variables was assessed using the student t-test, assuming near normality due to the large sample size. Depending on the similarity of the standard deviations of the two means, either the pooled or non-pooled t-test was used. The Chi-square test was used to assess differences between two categorical variables, with the Fisher's exact test applied as needed.

Candidate predictor variables for mortality were selected using forward selection and backward elimination methods. EKG parameters were included in the Cox proportional hazards regression model as they were the primary exposure variable for this study. Effect modifiers were identified, and stratified estimates were presented if interaction was found.

We evaluated possible interactions between TpTe, Tpeak amplitude and QRSD. The final Cox proportional hazards regression model included age, race, gender, heart rate, diastolic blood pressure, and EKG intervals. Proportional hazard assumptions were assessed using the Schoenfeld and Martingale residuals, and all variables in the final multivariate model met the proportional hazards assumption, including crude survival curves, which were plotted for T peak amplitude. (prolonged TpTe >85 ms, QRSD >=120 ms, and QTc >430 ms for men and >450 ms for women)[47] The level of significance was set at a p-value of less than 0.05 with a 95% confidence interval.

Chapter 4

Results:

Table 1 compares the baseline characteristics of 446 stable CHD patients based on their Tpe interval. The participants are divided into two groups: those with a Tpeak amplitude less than 129.79 (n=226) and those with a Tpeak amplitude greater than or equal to 129.79 (n=220). The mean age of the participants was 55.76 years, with no significant difference between the two groups (p=0.95). The mean BMI was 30.94 kg/m², showing no significant difference between groups (p=0.61). The mean QRS duration was 91.56 ms, with no significant difference between groups (p=0.87). The mean Tpe interval was 104.90 ms, with no significant difference between groups (p=0.57). The mean SBP was 133.23 mmHg, showing no significant difference between groups (p=0.70). The mean DBP was 82.31 mmHg, with no significant difference between groups (p=0.24). The mean heart rate was 66.57 beats/min, with a p-value of 0.09, indicating a trend but no significant difference. Both creatinine and potassium levels showed no significant differences between the two groups (p=0.81 and p=0.18, respectively). The mean hemoglobin level was 13.82 g/dl, with no significant difference between groups (p=0.54). There was a significant difference in EF, with the lower Tpeak amplitude group having a mean EF of 65.78% compared to 72.88% in the higher Tpeak amplitude group (p<0.0001). Gender distribution showed no significant difference (p=0.18). A significant difference was found in racial distribution, with a higher percentage of Black participants in the lower Tpeak amplitude group (p=0.01). Baseline heart failure status also showed a significant difference, with a higher percentage of baseline HF in the lower Tpeak amplitude group (p=0.01).

The baseline characteristics of patients enrolled in the study with stable CHD showed significant differences in ejection fraction, racial distribution, and baseline heart failure status between the two groups. The lower Tpeak amplitude group had a lower ejection fraction and a higher percentage of Black participants and baseline heart failure cases. Other characteristics such as age, BMI, QRS duration, blood pressure, heart rate, creatinine, potassium, and hemoglobin levels showed no significant differences between the two groups.

In table 2 baseline characteristics of study participants were analyzed based on cardiovascular mortality. The TPe interval had a mean value of 104.90 ms, with the CVD Mortality group having a slightly higher mean of 107.0 ms compared to 104.8 ms in the CVD Alive group, with a p-value of 0.72r, which was not significant. The QRS duration averaged 91.56 ms, with the CVD Mortality group at 93.08 ms and the CVD Alive group at 91.52 ms, resulting in a non-significant p-value of 0.66. However, the Tpeak amplitude revealed a significant difference with a mean of 129.79 ms overall, but only 50.17 ms in the CVD Mortality group compared to 134.10 ms in the CVD Alive group, with a statistically significant p-value of 0.01. Of the 446 stable patients 423 were alive at the end of the study period whereas 23 experienced cardiovascular mortality during a median follow up period of 1861.50. Of the 446 patients 401 did not experience heart failure whereas 45 experienced non-fatal HF during a median follow up period of 1835.50 days

From table 3: TPe in lead V2 (per 5ms), the univariate hazard ratio was 0.99 (95% CI: 0.94, 1.056) and the adjusted hazard ratio was 0.96 (95% CI: 0.91, 1.02). For QRSd (per 5ms), the hazard of cardiovascular mortality was higher with a univariate

hazard ratio of 1.01 (95% CI: 0.88, 1.11)

and an adjusted hazard ratio of 1.03 (95% CI: 0.85, 1.18) but this was not significant. TPeak amplitude in limb lead 1 (<6mm vs >=6mm) is a significant predictor of cardiovascular mortality, with a univariate hazard ratio of 2.48 (95% CI: 1.08, 5.66) and an adjusted hazard ratio of 2.94 (95% CI: 1.02, 8.70), suggesting that individuals with lower TPeak amplitude have a higher risk of mortality. Age per 5-year increment, has a univariate hazard ratio of 0.85 (95% CI: 0.68, 1.05), indicating a non-significant trend towards lower mortality risk with increasing age. The heart rate, per 5 beats per minute, shows a univariate hazard ratio of 1.11 (95% CI: 0.89, 1.36) and an adjusted hazard ratio of 0.95 (95% CI: 0.75, 1.20), neither of which are statistically significant. The comparison between nonblack and black individuals reveals a univariate hazard ratio of 3.57 (95% CI: 0.98, 22.86), suggesting a potential but non-significant higher risk for nonblack individuals. Gender comparison (female vs male) shows a univariate hazard ratio of 0.58 (95% CI: 0.21, 1.40), indicating no significant difference in mortality risk between genders. Diastolic blood pressure (DBP), per 5mmHg increase, is a significant predictor with a univariate hazard ratio of 1.26 (95% CI: 1.04, 1.52) and an adjusted hazard ratio of 1.25 (95% CI: 1.01, 1.56), highlighting that higher DBP is associated with increased mortality risk. Statistically significant results are marked with double asterisks. Overall, TPeak amplitude in limb lead 1 and DBP are identified as significant predictors of cardiovascular mortality, while other variables do not show significant associations.

Table 4 showed the Cox Proportional Hazard regression analysis of EKG predictors for heart failure. The TPeak to end in lead V2 (per 5ms) shows

a univariate hazard ratio of 0.98 (95% CI: 0.94, 1.02) and an adjusted hazard ratio of 0.977 (95% CI: 0.94, 1.02), both indicating no

significant association with heart failure. Similarly, QRS (per 5ms) has a univariate hazard ratio of 1.06 (95% CI: 0.98, 1.13) and an adjusted hazard ratio of 1.08 (95% CI: 0.97, 1.17), also showing no significant association.

In contrast, TPeak amplitude in limb lead 1 (<6mm vs >=6mm) is a significant predictor, with a univariate hazard ratio of 2.96 (95% CI: 1.64, 5.33) and an adjusted hazard ratio of 2.95 (95% CI: 1.47, 6.02), both statistically significant. Age (per 5 years) shows a univariate hazard ratio of 0.91 (95% CI: 0.79, 1.06), but no adjusted hazard ratio is provided.

Heart rate (per 5 beats/min) is another significant predictor, with a univariate hazard ratio of 1.29 (95% CI: 1.13, 1.48) and an adjusted hazard ratio of 1.20 (95% CI: 1.03, 1.42), both statistically significant. Comparing nonblack to black participants, the univariate hazard ratio is 1.76 (95% CI: 0.79, 4.44), with no adjusted hazard ratio provided. For gender (female vs male), the univariate hazard ratio is 1.30 (95% CI: 0.71, 2.33), and no adjusted hazard ratio is provided.

Finally, diastolic blood pressure (DBP) (per 5mmHg) is a significant predictor with a univariate hazard ratio of 1.26 (95% CI: 1.10, 1.44) and an adjusted hazard ratio of 1.22 (95% CI: 1.06, 1.40), both statistically significant. Overall, significant predictors of heart failure include TPeak amplitude in limb lead 1, heart rate, and DBP, while other variables did not show significant associations.

Chapter 5

Discussion:

In this study the Tpe interval and QRS duration showed no significant differences between those who died from cardiovascular causes and those who did not. However, Tpeak amplitude was significantly lower in the CVD Mortality group (50.17 mm) compared to the CVD Alive group (134.10 ms), with a p-value of 0.01. Furthermore when we analyzed the hazard ratios for various predictors of cardiovascular mortality. TPe in lead V2 and QRS duration did not significantly predict mortality. However, Tpeak amplitude in limb lead 1 was a significant predictor, with lower Tpeak amplitude associated with higher mortality risk (univariate HR: 2.48, adjusted HR: 2.94). Age and heart rate did not significantly predict mortality

Ventricular depolarization and repolarizations on surface EKGs are associated with cardiovascular mortality, and measures of these can be depicted by abnormalities in the QRS duration, T peak amplitude and TPe interval. In the general population T-wave abnormalities are found in up to 15% of apparently healthy subjects and more frequently in general hospital and clinical settings.[44]

In healthy individuals, T-waves are typically positive in most precordial and limb leads, with the highest amplitude in leads V2–V3.[52] However, deviations from this norm can occur. For instance, abnormally large T-waves (higher than 10 mm in men and 8 mm in women) may indicate hyperkalemia or early myocardial ischemia. Conversely, negative (inverted) T-waves

can be normal in specific leads, but widespread or persistent inversion may signal pathology.[52] Lead II in analyzing T wave abnormalities is important as it is strategically positioned pointing towards the left ventricular apex. [53] We had given preference to lead I in our study as T peak amplitude in lead I was found by Yamazaki et al[44] as the most significant predictor of cardiovascular mortality.[44] Even more lead I is the most frequently used lead for commercial EKG rhythm analysis such as in apple wrist watches, telemetry strips and so on. Given that T wave abnormalities which represent ventricular repolarization and QRS abnormality which represent ventricular depolarization are present in the general population we had hypothesized that repolarization abnormalities such as Prolonged TPe interval, short Twave amplitude, and depolarization abnormalities such as prolonged QRS duration may be more in patients with stable CHD and may be a predictor of non-fatal heart failure and or fatal cardiovascular mortality. In the Framingham study, isolated T-wave flattening or inversion carried a significant increased risk for morbidity and mortality.[54] In our study we found that a lower P peak amplitude predicted a higher risk of both cardiovascular mortality and non-fatal heart failure. Yamazaki et al[44]Found the annual CV mortality for inverted T waves was 3.3% in the normal ECG group and 5.4 in the abnormal ECG group. In our study we found TPeak amplitude in limb lead 1 (<6mm vs >=6mm) is a significant predictor of cardiovascular mortality, with a univariate hazard ratio of 2.48 (95% CI: 1.08, 5.66) and an adjusted hazard ratio of 2.94 (95% CI: 1.02, 8.70), individuals with lower TPeak amplitude have a higher risk of mortality.

According to Dekker et al[55] in Netherlands they reported the predictive value of T-wave amplitude and ST-segment level using lead I in a community population. T-wave amplitude in

lead I had a hazard ratio of 2 for <0.5 mm and 1/3 for 1.5 mm after adjustment for clinical risk factors.[55] Our study confirms the findings.

Even though previous studies have shown increased risk of cardiovascular mortality with prolonged QRS duration as well as in cases of prolonged Tpe interval in our study prolongation of these intervals neither predict cardiovascular mortality nor non-fatal heart failure as our study population contained individual who already had a coronary heart disease.[56-58] We did not compare normal heart in controls vs abnormal heart.

Conclusion:

Of the three EKG parameters analyzed in this study T peak amplitude was found to be a useful predictor of both Cardiovascular mortality and the risk of development of nonfatal heart failure in patients with a stable coronary artery disease in Atlanta.

Limitations and Further Research:

Limitations include population diversity. Further research is needed to address these limitations and expand our understanding of T wave abnormalities as predictors of cardiovascular mortality.

Appendix 1

Table 1a: Baseline characteristics of study participants by Tpe interval

	Total N=446	Tpeak amplitude < 129.79 N = 226	Tpeak amplitude>=129.79 N = 220	p-value
Age(years)	55.76 ± 9.72	55.73±9.57	55.79 ± 9.89	0.95
BMI (Kg/m2)	30.94 ± 6.80	30.78 ± 6.66	31.11 ± 6.95	0.61
QRSd(ms)	91.56± 8.69	91.73 ± 16.65	91.47 ± 17.30	0.87
Tpe(ms)	104.90 ± 28.52	105.70± 32.56	104.10± 23.84	0.57
SBP (mmHg)	133.23 ± 22.00	132.70 ± 23.54	133.70 ± 20.48	0.70
DBP (mmHg)	82.31 ± 13.09	81.35 ± 13.22	83.27 ± 12.95	0.24
Heartrate (beats/min)	66.57 ± 11.45	67.79 ± 10.87	65.39 ± 11.92	0.09
Creatinine (mg/dl)	1.13 ± 0.61	1.14 ± 0.62	1.13 ± 0.62	0.81
Potassium (mmol/L)	3.99 ± 0.37	4.02 ± 0.41	3.96 ± 0.33	0.18
Hemoglobin(g/dl)	13.82±6.48	14.08 ±9.01	13.58±2.21	0.54
EF	69.35±12.17	65.78±14.25	72.88±8.38	<.0001
Gender				
Male, n(%)	274 (61.43)	132 (58.41)	142 (64.55)	0.18
Female, n(%)	172 (38.57)	78 (35.45)	94 (41.59)	
Race, Black, n(%)	233 (52.24)	138 (61.06)	95 (43.18)	0.01**
Race, Nonblack, n(%)	213 (47.76)	88 (38.94)	125 (56.82)	

Baseline HF, n(%)	28(10.73)	20(15.50)	8(6.06)	0.01**
Baseline no HF, n(%)	233(89.27)	109 (84.50)	124(93.94)	

SBP=Systolic blood pressure, DBP= Diastolic blood pressure, **= Statistically significant BMI=Body mass index TPe= T peak to T end EKG interval in milliseconds, TPeak amplitude in lead I >= mean Tpeak amplitude of 129.79, normal TPeak amplitude in lead I <129.79 QRSd is the QRS duration in milliseconds

Table 2: Baseline characteristics of study participants by cardiovascular mortality

	Total N=446	CVD Mortality N = 34	CVD Alive N = 412	p-value
Age(years)	55.76 ± 9.72	54.20 ± 8.58	55.84 ± 9.78	0.43
TPe interval (ms)	104.90 ± 28.52	107.0 ± 29.70	104.8 ± 28.48	0.72
QRSd(ms)	91.56 ± 8.69	93.08 ± 12.59	91.52 ± 17.17	0.67
Tpeak amplitude(mm)	129.79±152.18	50.17±135.40	134.10±152.00	0.01**

**= Statistically significant. TPe= T peak to T end EKG interval in milliseconds, QRSd is the QRS duration in milliseconds

Table 2: Cox Proportional Hazard regression of EKG predictors of cardiovascular mortality.

Parameter	Univariate Hazard ratio	Crude 95% confidence interval	Adjusted Hazard ratio	Adjusted 95% confidence interval
TPe in lead V2 /5ms	0.994	0.944, 1.056	0.959	0.907, 1.025
QRSd /5ms	1.007	0.884, 1.110	1.031	0.849, 1.181
TPeak amplitude in limb lead 1 <6mm vs >=6mm	2.482	1.077, 5.664 **	2.938	1.019, 8.696 **
Age/5years	0.847	0.684, 1.050		
Heart rate/5 beats/minutes	1.110	0.892, 1.362	0.950	0.751, 1.196
Nonblack vs black	3.566	0.981, 22.858		
Female vs Males	0.582	0.210, 1.404		
DBP/5mmHg	1.255	1.035, 1.523**	1.254	1.011, 1.562**

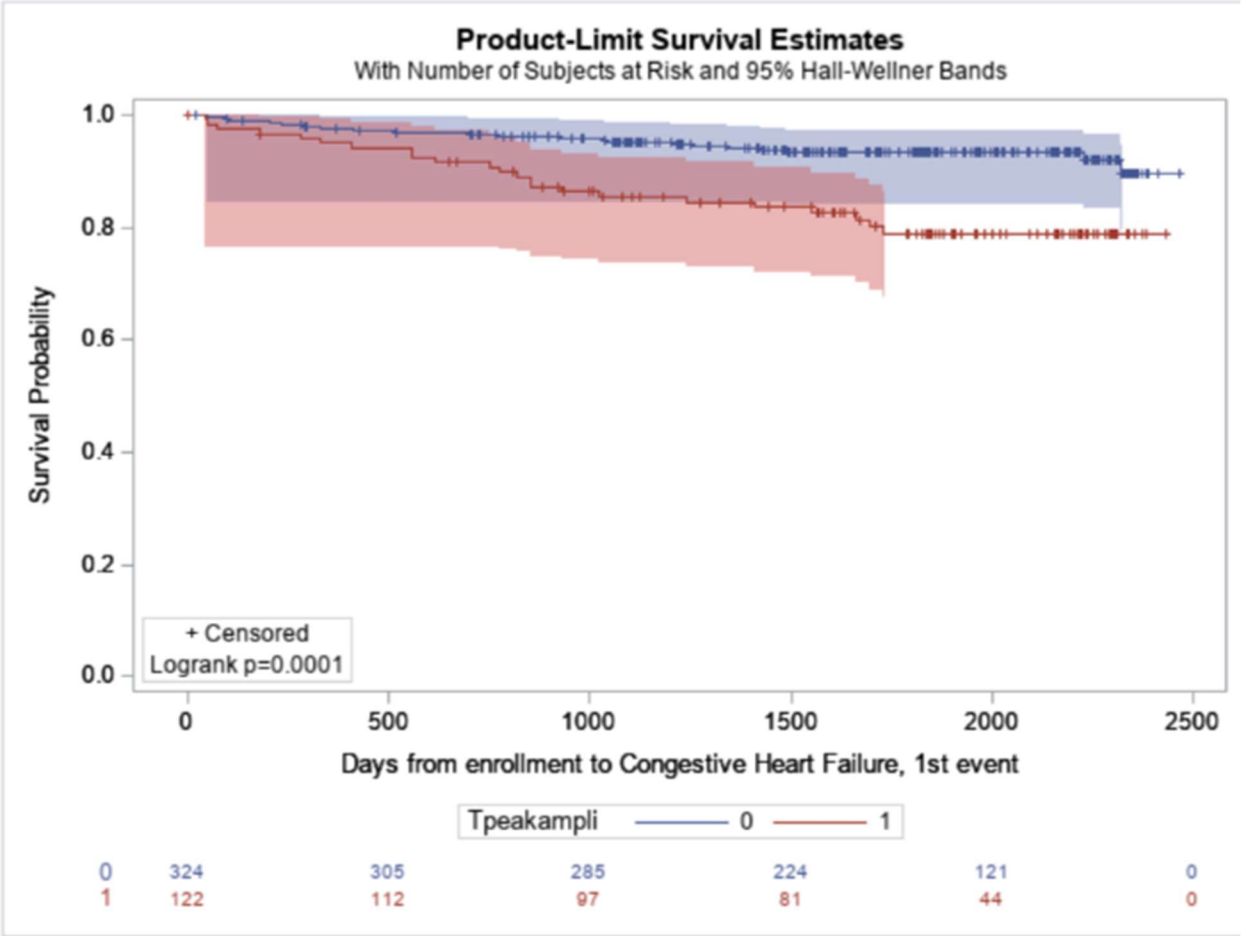
DBP= Diastolic blood pressure, **= Statistically significant. TPe= T peak to T end EKG interval in milliseconds, QRSd is the QRS duration in milliseconds

Table 3: Cox Proportional Hazard regression of EKG predictors of heart failure

Parameter	Univariate Hazard ratio	Crude 95% confidence interval	Adjusted Hazard ratio	Adjusted 95% confidence interval
Tpeak to end in lead V2 /5ms	0.976	0.942, 1.015	0.977	0.937, 1.024
QRS /5ms	1.059	0.978, 1.131	1.081	0.973, 1.171
Tpeak amplitude in limb lead 1 <6mm vs >=6mm	2.955	1.642, 5.332 **	2.951	1.467, 6.020 **
Age/5years	0.914	0.785, 1.064		
Heart rate/5beats/mins	1.294	1.128, 1.477**	1.207	1.029, 1.415 **
Nonblack vs black	1.760	0.794, 4.437		
Female vs Males	1.295	0.711, 2.328		
DBP /5mmHg	1.259	1.104, 1.437**	1.220	1.060, 1.403 **

DBP= diastolic BP ** is statistical significance ms=milliseconds

Kaplan-Meier survival estimates comparing tall versus short T-peak amplitudes



Tpeakampli 0= T peak amplitude >=0.6mm and Tpeakampli 1= T peak amplitude <0.6mm

References

1. National Heart L, Blood I. Morbidity & Mortality: Chart Book on Cardiovascular, Lung and Blood Diseases. *http://www nhlbi nih gov/resources/docs/cht-book/htm*. 1998;

2. Jain R, Singh R, Yamini S, K Das M. Fragmented ECG as a risk marker in cardiovascular diseases. *Current Cardiology Reviews*. 2014;10(3):277-286.

3. Koca H, Koç M. What is the Normal value of Tpe interval and corrected Tpe interval? *Acta Medica*. 2020;51(4):10-15.

4. Rosenthal TM, Masvidal D, Abi Samra FM, et al. Optimal method of measuring the T-peak to T-end interval for risk stratification in primary prevention. *EP Europace*. 2018;20(4):698-705. doi:10.1093/europace/euw430

5. Icli A, Kayrak M, Akilli H, et al. Prognostic value of Tpeak-Tend interval in patients with acute pulmonary embolism. *BMC Cardiovascular Disorders*. 2015/09/03 2015;15(1):99. doi:10.1186/s12872-015-0091-4

6. Okuda K, Watanabe E, Sano K, et al. Prognostic Significance of T-Wave Amplitude in Lead aVR in Heart Failure Patients with Narrow QRS Complexes. *Annals of Noninvasive Electrocardiology*. 2011/07/01 2011;16(3):250-257. doi:https://doi.org/10.1111/j.1542-474X.2011.00439.x

7. Viitasalo M, Oikarinen L, Swan H, et al. Ratio of late to early T-wave peak amplitude in 24-h electrocardiographic recordings as indicator of symptom history in patients with long-QT syndrome types 1 and 2. *Journal of the American College of Cardiology*. 2006;47(1):112-120.

8. Schinkel AFL, Elhendy A, van Domburg RT, et al. Prognostic significance of QRS duration in patients with suspected coronary artery disease referred for noninvasive evaluation of myocardial ischemia. *The American journal of cardiology*. 2009;104(11):1490-1493.

9. Task Force M, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *European heart journal*. 2013;34(38):2949-3003. doi:10.1093/eurheartj/eht296

10. Goblirsch G, Bershow S, Cummings K, et al. Stable coronary artery disease. *annotation*. 2013;21:12.

11. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation*. 2007;116(22):2634-2653.

12. Kitsios GD, Dahabreh IJ, Trikalinos TA, Schmid CH, Huggins GS, Kent DM. Heterogeneity of the phenotypic definition of coronary artery disease and its impact on genetic association studies. *Circulation: Cardiovascular Genetics*. 2011;4(1):58-67.

13. Bauters C, Tricot O, Meurice T, Lamblin N, Investigators C. Long-term risk and predictors of cardiovascular death in stable coronary artery disease: the CORONOR study. *Coronary Artery Disease*. 2017;28(8):636-641.

14. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovascular Research*. 2022;118(17):3272-3287. doi:10.1093/cvr/cvac013

15. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circulation: Heart Failure*. 2013;6(3):606-619.

16. American Heart A. 2023 heart disease and stroke statistics update fact sheet. 2023;

17. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. 2021;

18. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics—2023 update: a report from the American Heart Association. *Circulation*. 2023;147(8):e93-e621.

19. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. *Circulation*. 2020;141(9):e139-e596.

20. Hammadah M, Al Mheid I, Wilmot K, et al. The mental stress ischemia prognosis study: objectives, study design, and prevalence of inducible ischemia. *Psychosomatic medicine*. 2017;79(3):311-317.

21. Vaccarino V, Sullivan S, Hammadah M, et al. Mental stress–induced-myocardial ischemia in young patients with recent myocardial infarction: sex differences and mechanisms. *Circulation*. 2018;137(8):794-805.

22. Vaccarino V, Almuwaqqat Z, Kim JH, et al. Association of Mental Stress–Induced Myocardial Ischemia With Cardiovascular Events in Patients With Coronary Heart Disease. *JAMA*. 2021;326(18):1818-1828. doi:10.1001/jama.2021.17649

23. Heusch G, Libby P, Gersh B, et al. Cardiovascular remodelling in coronary artery disease and heart failure. *The Lancet*. 2014;383(9932):1933-1943.

24. Tanai E, Frantz S. Pathophysiology of heart failure. *Compr Physiol*. 2015;6(1):187-214.

25. Schiffrin EL. Vascular remodeling in hypertension: mechanisms and treatment. *Hypertension*. 2012;59(2):367-374.

26. Lee RT, Yamamoto C, Feng Y, et al. Mechanical strain induces specific changes in the synthesis and organization of proteoglycans by vascular smooth muscle cells. *Journal of Biological Chemistry*. 2001;276(17):13847-13851.

27. Sluijter JPG, de Kleijn DPV, Pasterkamp G. Vascular remodeling and protease inhibition–bench to bedside. *Cardiovascular research*. 2006;69(3):595-603.

28. Libby P. Collagenases and cracks in the plaque. *The Journal of clinical investigation*. 2013;123(8):3201-3203.

29. Boström P, Mann N, Wu J, et al. C/EBPβ controls exercise-induced cardiac growth and protects against pathological cardiac remodeling. *Cell*. 2010;143(7):1072-1083.

30. Bergmann O, Bhardwaj RD, Bernard S, et al. Evidence for cardiomyocyte renewal in humans. *Science*. 2009;324(5923):98-102.

31. Pandya K, Porter K, Rockman HA, Smithies O. Decreased beta-adrenergic responsiveness following hypertrophy occurs only in cardiomyocytes that also re-express beta-myosin heavy chain. *European journal of heart failure*. 2009;11(7):648-652.

32. Heineke J, Molkentin JD. Regulation of cardiac hypertrophy by intracellular signalling pathways. *Nature reviews Molecular cell biology*. 2006;7(8):589-600.

33. Yan L, Vatner DE, Kim S-J, et al. Autophagy in chronically ischemic myocardium. *Proceedings of the National Academy of Sciences*. 2005;102(39):13807-13812.

34. Elsässer A, Vogt AM, Nef H, et al. Human hibernating myocardium is jeopardized by apoptotic and autophagic cell death. *Journal of the American College of Cardiology*. 2004;43(12):2191-2199.

35. Kanamori H, Takemura G, Goto K, et al. The role of autophagy emerging in postinfarction cardiac remodelling. *Cardiovascular research*. 2011;91(2):330-339.

36. Patel BM, Mehta AA. Aldosterone and angiotensin: Role in diabetes and cardiovascular diseases. *European journal of pharmacology*. 2012;697(1-3):1-12.

37. Ahokas RA, Warrington KJ, Gerling IC, et al. Aldosteronism and peripheral blood mononuclear cell activation: a neuroendocrine-immune interface. *Circulation research*. 2003;93(10):e124-e135.

38. Harrison DG, Cai H, Landmesser U, Griendling KK. Interactions of angiotensin II with NAD (P) H oxidase, oxidant stress and cardiovascular disease. *Journal of the renin-angiotensin-aldosterone system: JRAAS*. 2003;4(2):51-61.

39. Jensen BC, O'Connell TD, Simpson PC. Alpha-1-adrenergic receptors: targets for agonist drugs to treat heart failure. *Journal of molecular and cellular cardiology*. 2011;51(4):518-528.

40. Castellano M, Böhm M. The cardiac β-adrenoceptor–mediated signaling pathway and its alterations in hypertensive heart disease. *Hypertension*. 1997;29(3):715-722.

41. Böhm M, Gierschik P, Jakobs K-H, et al. Increase of Gi alpha in human hearts with dilated but not ischemic cardiomyopathy. *Circulation*. 1990;82(4):1249-1265.

42. Sarnak MJ, Amann K, Bangalore S, et al. Chronic Kidney Disease and Coronary Artery Disease: JACC State-of-the-Art Review. *Journal of the American College of Cardiology*. Oct 8 2019;74(14):1823-1838. doi:10.1016/j.jacc.2019.08.1017

43. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *European heart journal*. Feb 2014;35(7):455-69. doi:10.1093/eurheartj/eht386

44. Yamazaki T, Myers J, Froelicher VF. Prognostic importance of isolated T-wave abnormalities. *The American journal of cardiology*. 2005;95(2):300-304.

45. Gardin JM, McClelland R, Kitzman D, et al. M-mode echocardiographic predictors of six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the Cardiovascular Health Study). *The American journal of cardiology*. 2001;87(9):1051-1057.

46. Dankner R, Goldbourt U, Boyko V, Reicher-Reiss H. Predictors of cardiac and noncardiac mortality among 14,697 patients with coronary heart disease. *The American Journal of Cardiology*. 2003/01/15/ 2003;91(2):121-127. doi:https://doi.org/10.1016/S0002-9149(02)03095-3

47. Panikkath R, Reinier K, Uy-Evanado A, et al. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circulation: Arrhythmia and Electrophysiology*. 2011;4(4):441-447.

48. Bleeker GB, Schalij MJ, Molhoek SG, et al. Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. *Journal of cardiovascular electrophysiology*. 2004;15(5):544-549.

49. Hochrein J, Sun F, Pieper KS, et al. Higher T-wave amplitude associated with better prognosis in patients receiving thrombolytic therapy for acute myocardial infarction (a GUSTO-I substudy). *The American journal of cardiology*. 1998;81(9):1078-1084.

50. Quinn TA, Kohl P. Cardiac mechano-electric coupling: acute effects of mechanical stimulation on heart rate and rhythm. *Physiological reviews*. 2021;101(1):37-92.

51. De Lazzari M, Zorzi A, Cipriani A, et al. Relationship between electrocardiographic findings and cardiac magnetic resonance phenotypes in arrhythmogenic cardiomyopathy. *Journal of the American Heart Association*. 2018;7(22):e009855.

52. Gambill CL, Wilkins ML, Haisty Jr WK, et al. T wave amplitudes in normal populations: variation with ECG lead, sex, and age. *Journal of electrocardiology*. 1995;28(3):191-197.

53. Khunti K. Accurate interpretation of the 12-lead ECG electrode placement: A systematic review. *Health Education Journal*. 2014;73(5):610-623.

54. Kannel WB, Anderson K, McGee DL, Degatano LS, Stampfer MJ. Nonspecific electrocardiographic abnormality as a predictor of coronary heart disease: the Framingham Study. *American heart journal*. 1987;113(2):370-376.

55. Dekker JM, Schouten EG, Klootwijk P, Pool J, Kromhout D. ST segment and T wave characteristics as indicators of coronary heart disease risk: the Zutphen Study. *Journal of the American College of Cardiology*. 1995;25(6):1321-1326.

56. Porthan K, Viitasalo M, Toivonen L, et al. Predictive value of electrocardiographic T-wave morphology parameters and T-wave peak to T-wave end interval for sudden cardiac death in the general population. *Circulation: Arrhythmia and Electrophysiology*. 2013;6(4):690-696.

57. Das MK, Zipes DP. Fragmented QRS: a predictor of mortality and sudden cardiac death. *Heart rhythm*. 2009;6(3):S8-S14.

58. Breidthardt T, Christ M, Matti M, et al. QRS and QTc interval prolongation in the prediction of long-term mortality of patients with acute destabilised heart failure. *Heart*. 2007;93(9):1093-1097.