ASSOCIATION BETWEEN THYROID DYSFUNCTION AND CONVENTIONAL RISK FACTORS IN PATIENTS WITH ACUTE CORONARY SYNDROMES

BY

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DECLARATION

I Mustafa Mansur M Ben Hkouma declare that:

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Overview of the Thesis

Background of the Study

Subclinical hypothyroidism and hyperthyroidism have been associated with an increased risk of acute coronary syndrome and mortality. Factors contributing to this association include; a high concentration of total cholesterol and increased risk of atherosclerosis and altered cardiovascular hemodynamics.(1) Several studies have shown that overt hypothyroidism is strongly associated with all components of coronary artery disease (CAD) but studies relating to the relationship between subclinical hypothyroidism and CAD has not been given much consideration.(1) Hypothyroid patients may have a high concentration of creatinine kinase (CK) mostly due to a rise in creatinine kinase MM (CK-MM) which may also lead to high levels of creatinine kinase BB (CK-MB). Therefore, this may cause confusion in the evaluation and diagnosis of myocardial injury in a hypothyroid patient presented with chest pain.

Troponin I is a superior indicator to diagnose myocardial injury, but case reports of hypothyroid patients with increased Troponin I suggest that hypothyroidism might be a risk factor for myocardial injury and increase risk of cardiac death.(2) Hypothyroidism might also lead to hypercoagulability, endothelial dysfunction, hyperhomocysteinemia, impaired fibrinolysis, systemic inflammation and platelet abnormalities and these are considered as risk factors for CAD.(2) Changes in thyroid hormone values in the plasma are linked to higher mortality in patients with acute myocardial infarction suggesting a role for thyroid hormone signalling in post-ischemic cardiac recovery. This hypothesis was done in experimental models of ischemia- reperfusion and myocardial infarction in animals and accumulating evidence reveals that thyroid hormones are critical for the response of the myocardium to ischemic stress and that thyroid hormones may have cytoprotective properties that are not evident in healthy tissue and appear only during stress. This hypothesis was developed in 2011 on 67 patients, 12 of those patients who had altered thyroid hormone values.(2)

Acute myocardial infarctions represent a major public health problem despite improvements in reperfusion therapy. The 2020 World Health Organization (WHO) projections view the high incidence of post-ischemic heart failure as the most important cause of morbidity and

mortality.(2) Therefore, thyroid hormones are increasingly being recognized as significant players in the pathogenesis, recovery and repair period of acute myocardial infarction. Likewise, study findings of subclinical hypothyroidism and hyperthyroidism showed an increase in the point estimates for coronary heart disease and mortality.

Aim of the Study

The study aims to retrospectively look at patients presenting with a myocardial infarction (MI) and: :

- To determine if there was a difference between the demographic status (age, gender and ethnicity) of patients presenting with normal and abnormal thyroid function tests
- To determine if the inpatient's mortality and morbidity as measured by clinical improvement differ according to the patient's thyroid status.
- To calculate if there was an association between the thyroid state and conventional cardiovascular risk factors such as age, blood pressure, lipids (total cholesterol), measured blood glucose and patients' pulse rate.
- To determine if thyroid status was related to the area of infarct stratified by race and gender.

Methodology

A cross-sectional study design was applied utilising a convenience sample of 79 patients presenting with an acute coronary syndrome (ACS) and available thyroid function test results , which are taken routinely, who were admitted during the period of January 2010 to September 2018. The three categories (hyperthyroidism, hypothyroidism and normal euthyroid) were identified in association with an acute coronary syndrome. Demographic status ,Age, gender and ethnicity, of the patients were documented as were the the presence of conventional cardiac risk factors. Sequential patients were sampled once the number of euthyroid patients was identified. Likewise, the selection of specific patients with thyroid dysfunction continued until a sufficient sample size for predetermined statistical analysis was obtained. Participants included in the sample were over 18 years of age**.**

The research location was based at Addington Hospital which serves an urban population in central Durban. The demographic and clinical information about the population sample for

the study was accessed from a hard copy database and was entered into the data collection sheet. Data were processed using IBM SPSS Version 24.0. An abnormal thyroid state was defined as hypothyroidism, a TSH greater than 5.50mIU/L with a FT4 less than 11.5pmol/L or hyperthyroid state as a TSH less than 0.35Miu/l and a FT4 greater than 22.7pmol/L. Conventional cardiovascular risk factors that were used in multivariate analysis included the patients' age, total cholesterol, triglyceride, HDL, pulse rate and blood pressure. The area of infarcted tissue was also compared to the patients' thyroid function.

The following were considered during data analysis:

- Fisher's exact and chi-square were used to test the significant difference between Acute Coronary Syndrome outcomes and thyroid dysfunction
- To determine the risk of having a thyroid abnormality for each race, a multinomial regression was conducted showing the relative risk for each variable by thyroid type using euthyroid patients as the referent group.
- A multinomial logistic regression was done to identify risk factors due to the thyroid state. The model included single variables as independent variables to identify the most statistically significant variable for the multiple regression.

Furthermore, ethical approval was obtained from the University of KwaZulu-Natal (UKZN) Biomedical Research and Ethics Council (BREC) Ethics Committee (BE 454/17). Permission to conduct the research was granted by Addington Hospital. Confidentiality and anonymity of patients were maintained and there was no specific mention of any patient's personal information (such as names, birth dates, identification number and hospital number). The study was completely retrospective and non-interventional.

Result

Black patients were significantly more likely to be hypothyroid when presenting with a myocardial infarction. There was no significant correlation between thyroid function and conventional risk factors in all other groups studied.

Conclusion

There was no significant difference between conventional risk factors with both hypothyroid and hyperthyroid patients presented with myocardial infarction in our study.

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LIST OF ABBREVIATIONS

T3- Triiodothyronine

TSH- Thyroid-Stimulating Hormone

ACS- Acute Coronary Syndromes

STEMI- ST-Elevation Myocardial Infarction

NSTEMI- Non-ST-Elevation Myocardial Infarction

IL- 6- Interleukin 6

TNFα- Tumor Necrosis Factor-α

IFγ- Interferon-γ

sIL-6R- Soluble Interleukin-6 Receptor

CRP C-reactive protein

AMI- Acute Myocardial Infarction

MI- Myocardial Infarction

DM- Diabetes Mellitus

CAD- Coronary Artery Disease

MAPK- Mitogen-Activated Protein Kinase

HSP- Heat shock proteins

CK- Creatine Kinase

HDL- High Density Lipoprotein

CETP- Cholesteryl Ester Transfer Protein

CVD- Cardiovascular Disease

CKD- Chronic Kidney Disease

LDL-C - Low-Density Lipoprotein Cholesterol

FHDM – Family history of diabetes mellitus

RMWA – Regional motion wall abnormalities

FHHypt – Family history of hypertension

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Part 1

Chapter One

Review of Literature

The synthesis of thyroxin (T4) and Triiodothyronine (T3) in the thyroid gland is activated by thyroid-stimulating hormone (TSH). Almost 85% of T4 is primarily secreted by the thyroid gland and then converted in the liver, kidney, and skeletal muscles to T3 by the enzyme 5'-mono-deiodinase.(2) Reverse T3 (rT3) is a biologically inactive alternate product of T4 deiodination. Only a small fraction of the thyroid hormones is unbound and biologically active because most of the circulating thyroid hormones are bound to transport proteins. T4, T3 and TSH changes have been considered as one of the risk events of the cardiovascular system, mainly due to the physiological metabolism of alteration of oxygen consumption and changes in carbohydrate, lipid and protein metabolism.(2) Thyroid hormones have an effect on gene encoding in the regulation of the myocardium and thyroid hormones also play a role in cardiovascular haemostasis. Hypothyroidism causes dynamic changes in cardiovascular function such as a decrease in left ventricular contraction which leads to a decrease in cardiac output.(2)

The role of subclinical hypothyroidism in ischemic heart disease was first suggested by Bastenie et al.(3) It was suggested that hypothyroidism had a role in atherosclerosis and the derangement of risk factors of coronary artery disease. The presence of atherosclerosis in hypothyroidism was most likely secondary to associated hypertension, hypercholesterolemia and hyperhomocysteinemia.(3) Acute coronary syndromes (ACS) are high-risk manifestations of coronary atherosclerosis and acute myocardial ischemia. Disruption of a coronary atherosclerotic plaque with subsequent thrombus formation is the main pathophysiology of such an event, which triggers an immediate inflammatory cascade. Inflammation seems to play a key role in plaque disruption, which stimulates thrombosis, coagulation, activation of the sympathetic system, and release of stress hormones.

Normal thyroid homeostasis seems to change in a subgroup of patients with ACS. Several studies have observed a fall in total T3 and/or fT3 concentration and a rise in rT3

concentration after an acute coronary event.(3,4) The exact prevalence of the low T3 syndrome among patients suffering an ACS seems not to be clearly defined yet. Although studies have reported that a wide range from 5% to 35% and this could be attributed to differences in study populations between the conducted studies. However, the syndrome seems to occur more frequently in ST-elevation myocardial infarction (STEMI) patients compared with non-ST-elevation myocardial infarction (NSTEMI) patients, possibly because of poor early prognosis and the pathophysiologic features of the occlusive thrombus resulting in more myocardium at stake.(4)

The acute effects of cytokines seem to play a key role in the pathogenesis of low T3 syndrome. It has been reported that the administration of interferon-α in healthy volunteers can cause disturbances in TH metabolism, mimicking the syndrome.(5) During critical illness, various pro-inflammatory cytokines such as interleukin 6 (IL- 6), tumor necrosis factor-α (TNFα), and interferon-γ (IFγ) can directly affect the pituitary gland and impair TSH release. Concerning patients with ACS, THs alterations are supposed to develop through the inflammatory response activation. Increases in IL-6, a pleiotropic, proinflammatory cytokine; soluble IL-6 receptor (sIL-6R); and C-reactive protein (CRP) levels may exert an inhibitory effect on thyroid axis function.

The occurrence of decreased thyroid hormones levels during an ACS has been associated with various clinical studies with specific clinical and biochemical parameters.(5) Worsened angina pectoris preceding the acute myocardial infarction (AMI) known as chronic heart failure, or previous myocardial infarction (MI) and diabetes mellitus (DM) have been linked to lower T3 levels during the acute coronary event.(5) In general, although, the available evidence is not strong, factors that seem to be associated with the development of low T3 syndrome among patients with ACS include older age, lower body mass index, DM, and high plasma levels of N-terminal pro-brain natriuretic peptide and CRP.

The first meta-analysis study was published in 2008 which showed a significant association between hypothyroidism and coronary artery disease (CAD) with relative risk RR of 1.533. A second meta-analysis reported the same result with RR of 1.20.(6) T3 which is the most important bioactive thyroid hormone for cardiomyocytes is mostly produced by a process of deiodination of T4. It can affect cardiomyocytes via genome and non-genome action. T3 regulates transcription by binding hormone receptors (TRs) in the nucleus, which then binds thyroid hormone response elements (TREs) present in regulatory regions of target genes.

Non-genome actions of T3 include thyroid hormone signalling, changes in thyroid hormone levels, and changes in thyroid hormone receptor TRα1 can limit myocardial injury and post-ischemic cardiac remodelling through T3 binding.(6) This regulates genes related to contractile protein, pacemaker activity and conduction, cell growth, differentiation and metabolism. Also, thyroid hormones could affect cardiac apoptosis through the suppression of ischemia reperfusion-induced activation of the pro-apoptotic P38 mitogen-activated protein kinase (MAPK) and up-regulation of cardio-protective molecules such as heat shock protein 27 (HSP27) and heat shock protein 70 (HSP70), which are also involved in ischemic preconditioning.(6) More so, T3 may regulate plasma membrane ion currents, activate survival pathways, and decrease oxidative stress in mitochondria.(7) Therefore, heart rate, cardiac contractility, vascular smooth muscle and endothelial function will be modulated. When T3 is low, a negative effect on cardiovascular system will occur.(7) Clinical studies also confirmed that low T3 was associated with larger thrombus burden, higher severity of coronary artery lesions and larger myocardial injury size in ACS patients.(8)

The close link between thyroid hormonal status and cardiovascular diseases is evident by the significant effects of thyroid dysfunction, both subclinical and overt, on the cardiovascular system. On the one hand, hypothyroidism is correlated with diastolic hypertension, dyslipidemia, atherosclerotic plaque progression and instability, and endothelial dysfunction .(9) On the other hand, hyperthyroidism is associated with increased systolic blood pressure, pulmonary hypertension, and atrioventricular valve regurgitation, especially of the tricuspid valve 8. In rare cases, patients with overt hyperthyroidism and thyrotoxicosis can be presented with chest pain and ECG abnormalities due to increases in oxygen demands in response to augmented cardiac contractility and workload or due to coronary vasospasm.(9)

Moreover, patients with hyperthyroidism can be presented with signs and symptoms of heart failure characterized by enhanced cardiac output and contractility. Heart rhythm and rate may be significantly affected by even mildly altered thyroid status.(10) The arrhythmogenic effects of THs include altered electrophysiological characteristics of atrial myocytes, enhanced automaticity, triggered activity in pulmonary vein cardiomyocytes, and shortened action potential duration. Arrhythmias such as sinus tachycardia, atrial flutter, and atrial fibrillation, and to a lesser extent, ventricular arrhythmias are commonly found in patients with overt or mild subclinical hyperthyroidism.(10)

Hypothyroidism is correlated with sinus bradyarrhythmias and various ECG abnormalities. Several clinical and experimental studies have suggested potential anti-proarrhythmic effects of the THs and a direct effect on electrogenesis in myocardial cells.(11,12) Alterations in TH plasma concentrations during a variety of acute and chronic illnesses in patients with unknown intrinsic thyroid disease are described by various terms such as “euthyroid sick syndrome,” “nonthyroidal illness syndrome,” and “low T3 syndrome.” (12) The most frequently observed hormonal profile is characterized by low T3 and/or fT3, elevated rT3 and normal T4 and TSH. The principal pathophysiological mechanism is supposed to be the reduced activity of the enzyme 5’-monodeiodinase, which converts T4 to T3. The euthyroid sick syndrome seems to be a timing-related organ-specific response to inflammation during various critical illnesses and constitute an adaptive, compensatory, beneficial response, and decreasing energy consumption. However, it has been linked to worse prognosis and increased mortality in patients with septic shock or acute stroke. Acute cardiac diseases also have been associated with low serum T3 levels.(13, 14) It has been reported that THs alterations constitute a powerful independent marker of the severity of illness and mortality in patients after resuscitated cardiac arrest. Similarly, lower serum fT3 levels were reported as a strong predictor of mortality in all cardiac patients, with both acute and chronic diseases, as stable coronary artery disease or congestive heart failure.(14)

Subclinical hypothyroidism and hyperthyroidism have been associated with an increased risk of ACS’s and mortality. Factors contributing to this association include; an increase concentration of total cholesterol (15, 16) and increase the risk of atherosclerosis, (17,18) and altered cardiovascular hemodynamics.(19,20,21,22,23,24) Overt hypothyroidism has been proven to be strongly associated with all components of coronary artery disease (CAD) but the relationship between subclinical hypothyroidism and CAD has not been partially proven in different studies.(24-25) Hypothyroid patients may have a high concentration of creatinine kinase mostly due to an increase in CK-MM which may also lead to high levels of CK-MB. This may cause confusion in the evaluation and diagnosis of myocardial injury in a hypothyroid patient presented with chest pain. The Troponin I is a superior indication to diagnose myocardial injury, but case reports of hypothyroid patients with an increased Troponin I suggest that hypothyroidism might be a risk factor for myocardial injury and increase risk of cardiac death.(26,27,28,29,30)

Hypothyroidism might also lead to hypercoagulability, endothelial dysfunction, hyperhomocysteinemia, impaired fibrinolysis, systemic inflammation and platelet abnormalities, all risk factors for CAD.(31) The changes in thyroid hormone values in the plasma are linked to higher mortality in patients with acute myocardial infarction suggesting a role for thyroid hormone signalling in post-ischemic cardiac recovery. This hypothesis was done in experimental models of ischemia-reperfusion and myocardial infarction in animals and accumulating evidence reveals that thyroid hormones are critical for the response of the myocardium to ischemic stress and that thyroid hormones may have cytoprotective properties that are not evident in healthy tissue and appear only during stress. This hypothesis was developed in 2011 on 67 patients, 12 of the patients had altered thyroid hormone values.(32)

Furthermore, during experimental coronary artery ligation in an animal model of acute myocardial infarction, heart failure was found to be associated with the reduction of thyroid hormones receptor expression in the myocardium, leading to tissue hypothyroidism. The administration of Thyroid hormones improved cardiac contractility, augmented myocardial remodeling and improved left ventricular function. Thyroid hormones also regulate angiogenesis, cardio-protection, cardiac metabolism, and myocyte regeneration at a molecular level. In addition, thyroid hormones regulate changes that can reverse left ventricular remodeling by improving myocyte shape and geometry of the left ventricular cavity, then improving recovery from acute myocardial infarction.(33)

Acute myocardial infarctions represent a major public health problem despite improvements in reperfusion therapy. The 2020 World Health Organization (WHO) projections view the high incidence of post-ischemic heart failure as the most important cause of morbidity and mortality. In this regard, thyroid hormones are increasingly being recognized as significant players in the pathogenesis, recovery and repair period of acute myocardial infarction.(34)

Moreover, both subclinical hypothyroidism and hyperthyroidism reviewed showed an increase in the point estimates for coronary heart disease and mortality.(35) A study was done at the hospital of China Medical University, to look at outcomes of patients with ACSs and mild thyroid function abnormalities. The study found a significantly increased risk of all-causes of mortality with patients who had low T3 but not subclinical hypothyroidism or hyperthyroidism compared to euthyroid patients.(36)

Similarly, a study conducted in Nepal in 2017 regarding abnormal thyroid hormone profile related to gender and age group. Findings from this study showed that 27.5% of males had an

abnormal thyroid hormone profile and 21.4% of Females had an abnormal thyroid hormone profile. There was no statistically significant difference in the prevalence of abnormal thyroid profiles (P=0.322). It was accounted that 56% were in the age group of above 60 years, 36% were in the age group of 40-60 years and 8% were in the age group of 20-40 years.(37)

Experimental data suggest a critical role for THs in the response of myocardium to ischemic stress. Few clinical studies involving patients with AMI have addressed the possible correlation of THs with the extent of myocardial injury. Lower fT3 levels have been associated with increased serum levels of cardiac biomarkers (troponin T and N-terminal pro-brain natriuretic peptide) as indicators of myocardial injury, as well as with lower left ventricular ejection fraction.(38,39)

In addition, studies (40) have reported a strong association of low T3 with impaired ventricular function among AMI patients, concluding that T3 levels may represent a predictor of ventricular functional recovery. Interestingly, the findings of another study (41) exhibited that the extent of transmural involvement in patients with STEMI, assessed by cardiac magnetic resonance imaging 40 days after the event, is strongly associated with T3 levels. In this retrospective and small-sized study, the group with high/normal T3 levels had a significantly greater extent of transmural involvement than the low-T3 group, which presented a significantly larger myocardial area at risk. Thus, a greater extent of ischemia and an increased myocardial salvage index.

The findings also revealed that the transient low T3 state during acute myocardial infarction is associated with lower transmurality, suggesting a protective role of the low T3 syndrome. Putting it all together, the existing data indicate that the link of the low T3 syndrome to worse prognosis and mortality among patients suffering an acute myocardial infarction is not necessarily reflected in the possible correlation of the syndrome with the extent of myocardial necrosis. Large initial myocardial ischemia can result in worse short-term prognosis, whereas large transmurality can result in worse long-term prognosis.(41)

Although, thyroid hormone plasma alterations have been studied more extensively in STEMI patients, they can occur in all aspects of ACS. However, it is important to emphasize that the low T3 syndrome is evident in a small group of ACS patients that seem to have a worse outcome. In the absence of robust data derived by large-scale clinical studies, it remains unclear whether the low T3 syndrome is directly linked to worse prognosis or it constitutes a marker of the severity of illness, which is the underlying factor for increased mortality.(42)

However, the syndrome should not be underestimated, as disturbances of T3, fT3, and rT3 levels seem to carry an additive prognostic value in ACS, independently of traditional risk factors. In this setting, although the exact timing of thyroid hormones alterations seems not to be clearly defined yet, routine determination of plasma levels of thyroid hormones among patients suffering an ACS might reveal an otherwise silent prognostic marker.

Nevertheless, further high-quality studies need to confirm this, and additional research is needed to clarify when and how this potentially powerful prognostic marker could be operationalized in the clinical setting. All available data indicate that alterations in thyroid function tests are not uncommon in patients with ACS, especially in STEMI patients.(42) The low T3 syndrome represents a hormonal imbalance that may significantly influence pathophysiological mechanisms and cardiovascular hemodynamics. This altered thyroid state, and more specifically, the fall of T3 and/or fT3 and the rise of rT3 seem to be related to overall worse prognosis, and it could be useful in the prognostic stratification of patients suffering an ACS.(42)

There are central and peripheral effects of thyroid hormones on glucose metabolism and lipid metabolism regulated by insulin secretion and insulin sensitivity on different tissues. In hypothyroidism, there is slow glucose gastrointestinal absorption, retardation of gluconeogenesis, and glucose utilization peripherally with a consequent increase of insulin resistance.(42) Hypothyroidism will alter glycemic and lipid profiles of the patients with prediabetes and will aggravate the course of the disease in those with already known diabetes.(43)

Hyperthyroidism due to a toxic nodular goiter is responsible for increased insulin degradation, increased glucagon secretion, and increased hepatic glucose production, all these factors aggravate the glycemic control in diabetic patients.(44) On the other hand, patients with noncontrolled hyperthyroidism and hypothyroidism showed worsened lipidemic profile.(44,45) In these cases, the coexistence of abnormal glycemic and lipid profiles could be the onset of acute coronary syndrome.(46) Hypothyroid patients might exhibit elevated HDL cholesterol levels mainly due to increased concentration of HDL particles, and also because of the decreased activity of cholesteryl ester transfer protein (CETP).(47)

Dyslipidemia has been established as a well-known risk factor for cardiovascular disease (CVD) in chronic kidney disease (CKD) and large-scale observational studies have shown that total and LDL cholesterol is the most important independent predictors of cardiovascular

morbidity and mortality.(48) Thyroid dysfunction and dyslipidemia in CKD may further increase CVD risk leading to increased morbidity and mortality. Therefore, early diagnosis and treatment of thyroid and lipid disorders in CKD may slow the progression of CKD in addition to the prevention of CVD risk.(49)

Chapter Two

Methodology

Study setting

The study was conducted in Addington hospital that serves an urban population in central Durban in South Africa. Addington hospital is the first functional hospital in Durban and was named after Rt. Hon. Henry Addington who held the post of prime minister of Great Britain in 1801. The hospital was officially opened on 10 November 1967 and its priority is to promote good service, adhere to service standards and recognition of high performing staff.(50)

Study design

Research design can be considered as the structure of research. It is the glue that holds all of the elements in a research project together, in short, it is a plan of the proposed research work.(51) This study adopted a cross-sectional study design utilising a convenience sample of 79 patients presenting with acute coronary syndrome (ACS).

Study population

Robson (52) defines a population as a universe of elements from which the sample elements are drawn. It can be literal population (that could be a number of people) but it is also used more specifically (for example, it could be the population of all hospitals in the region). The study population targets patients admitted to Addington Hospital. The study utilised a convenience sample of 79 patients with acute coronary syndrome and thyroid dysfunction who were admitted from January 2010 to September 2018.

Study sample

The study sample randomly selected 79 patients with ACS and thyroid dysfunction. The three categories (hyperthyroidism, hypothyroidism and normal euthyroid) were investigated in association with ACS. As a result, patients were divided into three groups namely:

- Group 1- included 27 hypothyroid patients
- Group 2 -included 27 euthyroid patients
- Group 3 - included 25 hyperthyroid patients

Demographic status (Age, gender, and ethnicity) of the patients were compared with the presence of conventional cardiac risk factors. Sequential patients were sampled once the number of euthyroid patients was identified. Likewise, the selection of specific patients with thyroid dysfunction continued until a sufficient sample size for predetermined statistical analysis was obtained. Participants were over 18 years of age and had the following documented during admission:

- Thyroid stimulating hormone (TSH)
- Free T4 (FT4)
- Lipid profile
- Random blood glucose level
- Electrocardiogram (ECG)
- Cardiac enzymes

Inclusion criteria

The inclusion criteria were based on the following:

- Males and females
- Patients who were of Black, White and Indian origin
- Patients who were 18 years and above.
- Patients who were diagnosed with acute coronary syndrome
- Patients with thyroid function result between January 2010 and December 2018

Exclusion criteria

The following were excluded from the study:

- Severely ill patients who have clinical evidence of sepsis or with concomitant presence of any predominant severe systemic disease

- In-Hospital death prior to blood draws

Data collection technique

The instrument used for collecting data was a data collection sheet. The demographic and clinical information about the population sample for the study were accessed from a hard copy database and entered into a data collection sheet. The researcher made sure that the confidentiality of patients' data was ensured. This information was filled on an excel spreadsheet which was used to analyze the data using SPSS 25 version 24 with the help of a statistician.

Data analysis

Data were processed using IBM SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). An abnormal thyroid state was defined as hypothyroidism a TSH greater than 5.50mIU/L with an FT4 less than 11.5pmol/L or hyperthyroid state as a TSH less than 0.35Miu/l and an FT4 greater than 22.7pmol/L. Conventional cardiovascular risk factors that were used in multivariate analysis included the patients' age, total cholesterol, triglyceride, HDL, pulse rate, and blood pressure. The area of infarcted tissue was also compared to the patients' thyroid function.

The following were considered during data analysis:

- Fisher's exact and chi-square were used to test the significant difference between acute coronary syndrome outcomes and thyroid dysfunction
- To determine the risk of having a thyroid abnormality for each race, a multinomial regression was conducted showing the relative risk for each variable by thyroid type using euthyroid patients as the referent group.
- Multinomial logistic regression was done to identify risk factors due to the thyroid state. The model included single variables as independent variables to identify the most statistically significant variable for the multiple regression.

Ethical considerations

Creswell (53) posits that the researcher must respect the rights, needs, values, and desires of the participants. Ethical approval was obtained from the University of KwaZulu-Natal (UKZN) Biomedical Research and Ethics Council (BREC) Ethics Committee (BE 454/17). Permission to conduct the research was granted by Addington Hospital. The anonymity of patients included was maintained and there was no specific mention of any patient's personal information (such as names, birth dates identification number and hospital number). The study was completely retrospective and non-interventional. All the records will be safeguarded to ensure no one has access to it and will be deleted by the researcher once submission is done.

REFERENCES

1. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, Michelangeli V. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Archives of internal medicine. 2005 Nov 28;165(21):2467-72. (PMID: 16314542).

2. Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, L'Abbate A, Donato L. Low-T3 syndrome: a strong prognostic predictor of death in patients with heart disease. Circulation. 2003 Feb 11;107(5):708-13.

3. Bastenie PA, Bonnyns M, Vanhaelst L, Neve P, Staquet M. Preclinical hypothyroidism: a risk factor for coronary heart-disease. The Lancet. 1971 Jan 30;297(7692):203-4.

4. Franklyn JA, Gammage MD, Ramsden DB, Sheppard MC. Thyroid status in patients after acute myocardial infarction. Clinical science. 1984 Dec 1;67(6):585-90.

5. Lazzeri C, Sori A, Picariello C, Chiostri M, Gensini GF, Valente S. Nonthyroidal illness syndrome in ST-elevation myocardial infarction treated with mechanical revascularization. International journal of cardiology. 2012 Jun 28;158(1):103-4.

6. Eber B, Schumacher M, Langsteger W, Zweiker R, Fruhwald FM, Pokan R, Gasser R, Eber O, Klein W. Changes in thyroid hormone parameters after acute myocardial infarction. Cardiology. 1995;86(2):152-6.

7. Shan S, Aslam S, Saleem N, Rizvi NB, Elahi S. Thyroid hormone deficiency and coronary artery disease. Anaesth Pain& Intensive Care 2017;(4):489-496.

8. Cao Q, Jiao Y, Yu T, Sun Z. Association between mild thyroid dysfunction and clinical outcome in acute coronary syndrome undergoing percutaneous coronary intervention. Cardiology journal. 2018 Aug 31; 10.5603/CJ.a2018.0097.

9. Qian Cao,Yundi Jiao,Tongtong Yu, Zhaoqing Sun, Association between mild thyroid dysfunction and clinical outcome in acute coronary syndrome undergoing percutaneouscoronaryintervention,DOI: 10.5603/CJ.a2018.0097Pubmed: 30234907.

10. Lamprou V, Varvarousis D, Polytarchou K, Varvarousi G, Xanthos T. The role of thyroid hormones in acute coronary syndromes: prognostic value of alterations in thyroid hormones. Clinical cardiology. 2017 Aug;40(8):528-33.

11. Tribulova N, Knezl V, Shainberg A, Seki S, Soukup T. Thyroid hormones and cardiac arrhythmias. Vascular pharmacology. 2010 Mar 1;52(3-4):102-12.

12. Knezl V, Soukup T, Okruhlicova L, Slezak J, Tribulova N. Thyroid hormones modulate occurrence and termination of ventricular fibrillation by both long-term and acute actions. Physiol Res. 2008 Jan 1;57(Suppl 2):S91-6.

13. Klemperer JD, Klein I, Gomez M, Helm RE, Ojamaa K, Thomas SJ, Isom OW, Krieger K. Thyroid hormone treatment after coronary-artery bypass surgery. New England Journal of Medicine. 1995 Dec 7;333(23):1522-7.

14. Longstreth Jr WT, Manowitz NR, DeGROOT LJ, Siscovick DS, Mayor GH, Copass MK, Weinmann S, Cobb LA. Plasma thyroid hormone profiles immediately following out-of-hospital cardiac arrest. Thyroid. 1996 Dec;6(6):649-53.

15. Ray DC, Macduff A, Drummond GB, Wilkinson E, Adams B, Beckett GJ. Endocrine measurements in survivors and non-survivors from critical illness. Intensive care medicine. 2002 Sep 1;28(9):1301-8.

16. Althaus BU, Staub JJ, LÈCHE AR, Oberhänsli A, Stähelin HB. LDL/HDL-changes in subclinical hypothyroidism: possible risk factors for coronary heart disease. Clinical endocrinology. 1988 Feb;28(2):157-63. (PMID: 3168304).

17. Kanaya AM, Harris F, Volpato S, Pérez-Stable EJ, Harris T, Bauer DC. Association between thyroid dysfunction and total cholesterol level in an older biracial population: the health, aging and body composition study. Archives of internal medicine. 2002 Apr 8;162(7):773-9. (PMID: 11926850).

18. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87:489-99. [PMID: 11836274].

19. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. Jama. 2004 Jan 14;291(2):228-38.. [PMID: 14722150].

20. Klein I. Thyroid hormone and the cardiovascular system. The American journal of medicine. 1990 Jun 1;88(6):631-7.

21. Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. Circulation. 1993 May;87(5):1435-41.

22. Klein I, Levey GS. The cardiovascular system in thyrotoxicosis. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's the thyroid: a fundamental and clinical text. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2000:596-604.

23. Graettinger JS, Muenster JJ, Selverstone LA, Campbell JA. A correlation of clinical and hemodynamic studies in patients with hyperthyroidism with and without congestive heart failure. The Journal of clinical investigation. 1959 Aug 1;38(8):1316-27.

24. Klein I, Ojamaa K. The cardiovascular system in hypothyroidism. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's the thyroid: a fundamental and clinical text. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2000:777-82. 35.

25. Klein I, Ojamaa K. Thyrotoxicosis and the heart. Endocrinal Metab Clin North Am 1998; 27:51-62.

26. Shan S, Aslam s, Saleem N, Rizvi NB, Elahi S, Thyroid hormone deficiency and coronary artery disease. Anaesth Pain & intensive Care 2017;21(4):489-496.

27. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Annals of Internal Medicine. 2000; Feb 15; 132(4):270-8 (PMID: 10681281).

28. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. New England Journal of Medicine. 2001 Feb 15;344(7):501-9.

29. Grewal J, Gin K. Troponin Marks the spot!. Perspectives in Cardiology. 2004 Nov; 50(11): 20:35–40.

30. Khan IA, Tun A, Wattanasauwan N, Win MT, Hla TA, Hussain A, Vasavada BC, Sacchi TJ. Elevation of serum cardiac troponin I in noncardiac and cardiac diseases other than acute coronary syndromes. The American journal of emergency medicine. 1999 May 1;17(3):225-9.

31. Cohen LF, Mohabeer AJ, Keffer JH, Jialal I. Troponin I in hypothyroidism. Clinical chemistry. 1996 Sep 1;42(9):1494-5.

32. Pingitore A, Galli E, Barison A, Iervasi A, Scarlattini M, Nucci D, L'Abbate A, Mariotti R, Iervasi G. Acute effects of triiodothyronine (T3) replacement therapy in patients with chronic heart failure and low-T3 syndrome: a randomized, placebo-controlled study. The Journal of Clinical Endocrinology & Metabolism. 2008 Apr 1;93(4):1351-8.

33. Lymvaios I, Mourouzis I, Cokkinos DV, Dimopoulos MA, Toumanidis ST, Pantos C. Thyroid hormone and recovery of cardiac function in patients with acute myocardial infarction: a strong association?. European Journal of Endocrinology. 2011 Jul 1;165(1):107-14.

34. Pingitore A, Chen Y, Gerdes AM, Iervasi G. Acute myocardial infarction and thyroid function: new pathophysiological and therapeutic perspectives. Annals of medicine. 2012 Dec 1;44(8):745-57.

35. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, Tracy RP, Ladenson PW. Thyroid status, cardiovascular risk, and mortality in older adults. Jama. 2006 Mar 1;295(9):1033-41.

36. Iervasi G, Molinaro S, Landi P, Taddei MC, Galli E, Mariani F, L'Abbate A, Pingitore A. Association between increased mortality and mild thyroid dysfunction in

cardiac patients. Archives of internal medicine. 2007 Jul 23;167(14):1526-32. [PMID: 1764660.

37. Vijay Kumar Sah1, Satyam Prakash, Suresh Chandra Kohli. Thyroid Hormone Profile in Patients with Acute Coronary Syndrome, Endocrinol Thyroid Res 2(4): JETR.MS.ID.555592 2017. 001.

38. Wang WY, Tang YD, Min YA, Cheng CU, Mu MU, Jie QI, Yang YJ. Free triiodothyronine level indicates the degree of myocardial injury in patients with acute ST-elevation myocardial infarction. Chinese medical journal. 2013 Oct 20;126(20):3926-30.

39. Zhang B, Peng W, Wang C, Li W, Xu Y. A low fT3 level as a prognostic marker in patients with acute myocardial infarctions. Internal Medicine. 2012;51(21):3009-15.

40. Kim DH, Choi DH, Kim HW, Choi SW, Kim BB, Chung JW, Koh YY, Chang KS, Hong SP. Prediction of infarct severity from triiodothyronine levels in patients with ST-elevation myocardial infarction. The Korean journal of internal medicine. 2014 Jul;29(4):454.

41. Lymvaios I, Mourouzis I, Cokkinos DV, Dimopoulos MA, Toumanidis ST, Pantos C. Thyroid hormone and recovery of cardiac function in patients with acute myocardial infarction: a strong association?. European Journal of Endocrinology. 2011 Jul 1;165(1):107-14.

42. Maratou E, Hadjidakis DJ, Kollias A, Tsegka K, Peppa M, Alevizaki M, Mitrou P, Lambadiari V, Boutati E, Nikzas D, Tountas N. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. European journal of endocrinology. 2009 May 1;160(5):785-90.

43. L. Chaker, S. Ligthart, T. I. Korevaar et al. Thyroid function and risk of type 2 diabetes: a population-based prospective cohort study, BMC Medicine, vol. 14, no 1, p 150,2016.

44. Dimitriadis GD, Raptis SA. Thyroid hormone excess and glucose intolerance. Experimental and Clinical Endocrinology & Diabetes. 2001;109(Suppl 2):S225-39.

45. Pearce EN, Wilson PW, Yang Q, Vasan RS, Braverman LE. Thyroid function and lipid subparticle sizes in patients with short-term hypothyroidism and a population-based cohort. The Journal of Clinical Endocrinology & Metabolism. 2008 Mar 1;93(3):888-94.

46. Notara V, B Panagiotakos D, Michalopoulou M, Kouvari M, Tsompanaki E, Verdi M, Vassileiou N, Kalli E, Mantas Y, Kogias Y, Stravopodis P. Diabetes mellitus, hypertension and hypercholesterolemia in relation to the 10-year ACS prognosis; the GREECS study. Current vascular pharmacology. 2016 May 1;14(3):295-301.

47. Dullaart RP, Hoogenberg K, Groener JE, DIKKESCHEO L, Erkelens DW, Doorenbos H. The activity of cholesteryl ester transfer protein is decreased in

hypothyroidism: a possible contribution to alterations in high-density lipoproteins. European journal of clinical investigation. 1990 Dec;20(6):581-7.

48. Collaboration PS, Lewinngton S, Whitlock G, Clarke R, Sherlinker P, Emberson J, et al. Blood cholesterol and vascular mortality by age, sex and blood pressure a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 2007;370(9602):1829-39.

49. Lo JC, Chertow GM, Go AS, Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney international. 2005 Mar 1;67(3):1047-52.

50. KwaZulu-Natal Department of Health. Addington Hospital. Retreived from: http://www.kznhealth.gov.za/Addington/vision.htm. 2001. Accessed May 15, 2019.

51. Yilmaz K. Comparison of quantitative and qualitative research traditions: Epistemological, theoretical, and methodological differences. European Journal of Education. 2013 Jun;48(2):311-25.

52. Adolph KE, Robinson SR. Sampling development. Journal of Cognition and Development. 2011 Oct 1;12(4):411-23.

53. Creswell JW. Writing strategies and ethical considerations. Research design: Qualitative, quantitative, and mixed.

Part 2: A submission ready manuscript

Association between thyroid dysfunction and conventional risk factors in patients with acute coronary syndrome

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Abstract

Background: Thyroid dysfunction is a major risk factor for increasing acute coronary syndrome and mortality It is possible that this association is through the modification of conventional risk factors for ischaemic heart disease. The aim of our study was to examine the association and outcome among patients with hyperthyroidism, hypothyroidism and thyroid function who were presented with an acute coronary syndrome (ACS).

Methods: A cross-sectional study was utilised which included 79 patients admitted between January 2010-September 2018 with acute Myocardial infarction. The patients were divided into three groups:

Group 1: included 27 hypothyroid patients, Group 2: included 27 euthyroid patients and Group 3: 25 hyperthyroid patients. The patients were compared with age, gender and ethnicity and the presence of conventional cardiac risk factors.

Result: Black patients were significantly more likely be hypothyroid when presenting with myocardial infarction, there was no significant correlation between thyroid function and conventional risk factors in all other groups studied.

Conclusion: There was no significant difference between conventional risk factors with both hypothyroid and hyperthyroid patients presenting with myocardial infarction in our study.

Introduction

Subclinical hypothyroidism and hyperthyroidism have been associated with an increased risk of acute coronary syndrome and mortality. Factors contributing to this association include; a high concentration of total cholesterol (1,2,3,4) and increase risk of atherosclerosis, **(5,6)** and altered cardiovascular hemodynamics. (7,8,9,10,11,12). Studies have shown that overt hypothyroidism is strongly associated with all components of coronary artery disease (CAD) but the relationship between subclinical hypothyroidism and CAD has not been ascertained.(13) Hypothyroid patients may have an increased concentration of creatinine kinase (CK) mostly due to an increase in CK-MM which may also lead to high level of CK-MB. This may cause confusion in the evaluation and diagnosis of myocardial injury in a hypothyroid patient presenting with chest pain.

The Troponin I is a superior indicator to diagnose myocardial injury, but case reports of hypothyroid patients with increased Troponin I suggest that hypothyroidism might be a risk factor for myocardial injury and increase risk of cardiac death.(14,15,16,17,18) Hypothyroidism might also lead to hypercoagulability, endothelial dysfunction, hyperhomocysteinemia, impaired fibrinolysis, systemic inflammation and platelet abnormalities, all risk factors for CAD.(19) Changes in thyroid hormone values in the plasma are linked to a higher mortality in patients with acute myocardial infarction suggesting a role for thyroid hormone signalling in the post-ischemic cardiac recovery. This hypothesis was done in experimental models of ischemia-reperfusion and myocardial infarction in animals and accumulating evidence reveals that thyroid hormones are critical for the response of the myocardium to ischemic stress and that thyroid hormones may have cytoprotective properties that are not evident in healthy tissue and appear only during stress. This hypothesis was developed in 2011 on 67 patients, 12 of those patients had altered thyroid hormone values. (20,21)

During experimental coronary artery ligation in an animal model of acute myocardial infarction, heart failure was found to be associated with the reduction of thyroid hormone receptor expression in the myocardium, leading to tissue hypothyroidism.(22) Thyroid hormone administration improved cardiac contractility, augmented myocardial remodelling and improved left ventricular function. Thyroid hormones also regulate angiogenesis, cardio-protection, cardiac metabolism, and myocyte regeneration at molecular level; changes that

can reverse left ventricular remodelling by improving myocyte shape and geometry of left ventricular cavity, then improving recovery from acute myocardial infarction.(22)

Acute myocardial infarctions represent a major public health problem despite improvements in reperfusion therapy. The 2020 World Health Organization (WHO) projections view the high incidence of post-ischemic heart failure as the most important cause of morbidity and mortality. Therefore, thyroid hormones are increasingly being recognized as significant players in the pathogenesis, the recovery and repair period of acute myocardial infarction.(23) Studies showed that subclinical hypothyroidism and hyperthyroidism presented an increase in the point estimates for coronary heart disease and mortality.(24)

The aim of this study was to retrospectively look at patients presenting with a myocardial infarction (MI) and the following were the objectives of the study:

- To determine if there was a difference between the demographic status (age, gender and ethnicity) of patients presenting with normal and abnormal thyroid function tests
- To determine if the inpatient's mortality and morbidity as measured by clinical improvement and not of the patient's' condition on discharge differ according to the patient's thyroid status.
- To calculate if there was an association between the thyroid state and conventional cardiovascular risk factors such as: age, blood pressure, lipids (total cholesterol), measured blood glucose and patients' pulse rate.
- To determine if thyroid status was related to the area of infarct stratified by race and gender.

Mortality was to be noted for in-patient stay and a file review at one-month post discharge when the patient attended for routine follow up. Patients who died prior to blood tests were excluded from the study.

Methodology

A cross-sectional study design was applied utilising a convenience sample of 79 patients with acute coronary syndrome (ACS) and thyroid dysfunction who were admitted during the period of January 2010 to September 2018. The three categories (hyperthyroidism, hypothyroidism and normal euthyroid) were investigated in association with acute coronary

syndrome. Demographic status (Age, gender and ethnicity) of the patients were compared with the presence of conventional cardiac risk factors. Sequential patients were sampled once the number of euthyroid patients was identified. Likewise, the selection of specific patients with thyroid dysfunction continued until a sufficient sample size for predetermined statistical analysis was obtained. Participants included in the sample were over 18 years of age**.**

The research location was based at Addington Hospital which serves an urban population in central Durban. The demographic and clinical information about the population sample for the study was accessed from a hard copy database and was entered into the data collection sheet. Data were processed using IBM SPSS Version 24.0. An abnormal thyroid state was defined as hypothyroidism, a TSH greater than 5.50mIU/L with a FT4 less than 11.5pmol/L or hyperthyroid state as a TSH less than 0.35Miu/l and a FT4 greater than 22.7pmol/L. Conventional cardiovascular risk factors that were used in multivariate analysis included the patients' age, total cholesterol, triglyceride, HDL, pulse rate and blood pressure. The area of infarcted tissue was also compared to the patients' thyroid function.

The following were considered during data analysis:

- Fisher's exact and chi-square were used to test the significant difference between Acute Coronary Syndrome outcomes and thyroid dysfunction
- To determine the risk of having a thyroid abnormality for each race, a multinomial regression was conducted showing the relative risk for each variable by thyroid type using euthyroid patients as the referent group.
- A multinomial logistic regression was done to identify risk factors due to the thyroid state. The model included single variables as independent variables to identify the most statistically significant variable for the multiple regression.

Furthermore, ethical approval was obtained from the University of KwaZulu-Natal (UKZN) Biomedical Research and Ethics Council (BREC) Ethics Committee (BE 454/17). Permission to conduct the research was granted by Addington Hospital. Confidentiality and anonymity of patients were maintained and there was no specific mention of any patient's personal information (such as names, birth dates, identification number and hospital number). The study was completely retrospective and non-interventional.

Results

Data was collected from one regional hospital, 79 patients were included, 27(34.18%) patients were euthyroid, 27(34.18%) patients were hypothyroid and 25 (31.65%) patients were hyperthyroid, the demographics of the study participants showed 58 (73.42%) were Indian, 9 (11.39%) were black and 12 (15.19%) were white. Gender distribution was 30 (37.97%) were female and 49 (62.03%) were male.

Table 1: Gender and thyroid function of study participants

	Gender		**P-value**	**Race**			**P-value**
Thyroid type	**Female**	**Male**		**Indian**	**Black**	**White**	
Hyperthyroid	12 48.00%	13 52.00%	0.099	20 34%	2 22%	3 25%	0.474
Hypothyroid	11 40.74%	16 59.26%	0.248	16 28%	7 78%	4 33.33 %	0.019
Thyroid abnormality	23 76.67%	29 59.18%	0.088	36 62.07 %	9 100%	7 58.33 %	0.051
Euthyroid	7 25.93%	20 74.07%		22 38%	0 0%	5 41.67 %	

Our study cohort comprised 29 men with abnormal thyroid function, 23 women with abnormal thyroid function, 20 men who were euthyroid and 7 women were euthyroid. The table indicates that 59 % of men had abnormal thyroid function versus 77% of women (p=0.08). Men were more likely to have hypothyroidism and women hyperthyroidism but these differences were not statistically significant (p= 0.1868).

Black patients were most likely to have thyroid dysfunction if they were presented with MI (100%) compared to white patients who were least likely to have concomitant thyroid disease (58%). Black patients were significantly more likely to be hypothyroid than either white or Indian patients (p=0.019).

We found nine Black patients with abnormal thyroid function, seven white patients with abnormal thyroid function. Zero Black patients with normal thyroid function and five white patients with normal thyroid function. There was a significant difference between the two ethnic groups, p-value = 0.039. Risk ratio = 1.71 with p-value = 0.0265.

Table 2: Hyperthyroid status of patients

	Gender		**Race**		
ACS	**Female**	**Male**	**Indian**	**Black**	**White**
1. Anterior	3 42.86%	4 57.14%	5 71.43%	1 9.09%	1 18.18%
2. Inferior	6 46.15%	7 53.85%	10 76.92%	1 7.69%	2 15.38%
3. Anterolateral	1 50.00%	1 50.00%	2 100.00%	0 0%	0 0%
4. Antero-septal	2 66.67%	1 33.33%	3 100.00%	0 0%)	0 0%
5. Antero-inferior	0 0%	0 00.00%	0 0%	0 0%	0 0%

Table 3: Hypothyroid status of patients

	Gender		Race		
ACS	**Female**	**Male**	**Indian**	**Black**	**White**
1. Anterior	4 50.00%	4 50.00%	5 62.50%	1 12.50%	2 25.00%
2. Inferior	5 41.67%	7 58.33%	9 75.00%	2 16.67%	1 8.33%
3. Anterolateral	2 66.67%	1 33.33%	2 66.67%	1 33.33%	0 0%
4. Antero-septal	0 0%	4 100%	0 0%	3 75.00%	1 25.00%
5. Antero-inferior	0 0%	0 0%	0 0%	0 0%	0 0%

Table 4: Euthyroid status of patients

	Gender		Race		
ACS	**Female**	**Male**	**Indian**	**Black**	**White**
Anterior	4 57.14%	3 42.86%	6 85.71%	0 0%	1 14.29%
Inferior	2 14.29%	12 85.71%	10 71.43%	0 0%	4 28.57%
Anterolateral	0 0%	2 100%	2 100.00%	0 0%	0 0%
Antero-septal	1 33.33%	2 66.67%	3 100.00%	0 0%	0 0%
Antero-inferior	0 0%	1 100%	1 100.00%	0 0%	0 0%

Table 5: ACS by Thyroids

	Thyroid (n = 79)			p-value
ACS	Hyperthyroid	Hypothyroid	Euthyroid	
1 Anterior	7 (28.00%)	8 (29.63%)	7 (25.93%)	1.000
2 Inferior	13 (52.00%)	12 (44.44%)	14 (51.85%)	0.957
3 Anterolateral	2 (8.00%)	3 (11.11%)	2 (7.41%)	1.000
4 Antero-septal	3 (12.00%)	4 (14.81%)	3 (11.11%)	1.000
5 Antero-inferior			1 (3.70%)	1.000
Total	25	27	27	

Table 2, 3, 4 and 5 show a stratification of patients by gender, race and thyroid function to determine if the thyroid status was related to the area of infarct. Results show that there were no significant differences between race, gender and thyroid status and the area of infarcted tissue.

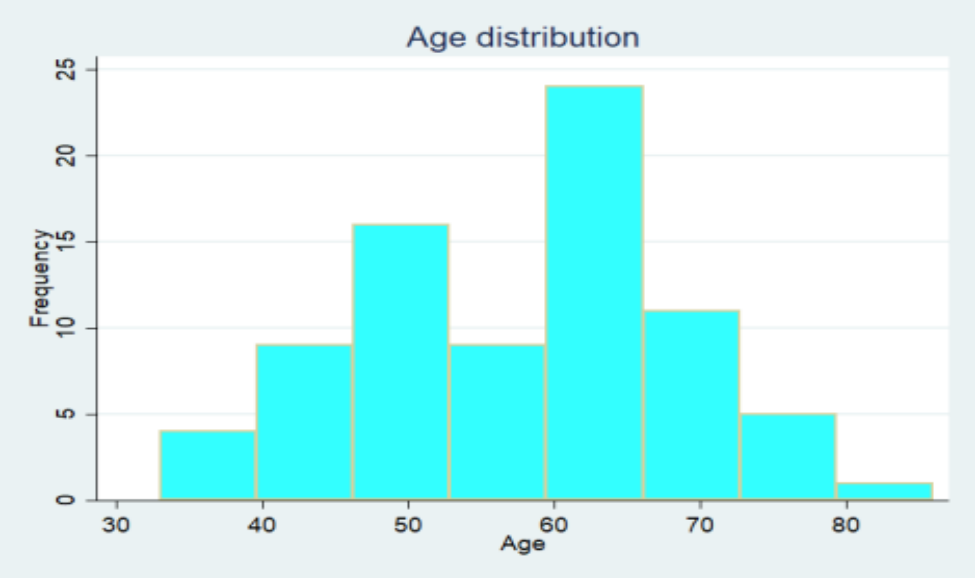

Figure 1: Age distribution of patients presenting with Myocardial infarction

The average age of the patients was 58.23 years with a standard deviation of 11.08, the minimum age was 33 years while the maximum was 86 years. The median age was 60 years with an inter quartile range of 50 – 66 years.

Table 6: Correlation between Age groups and thyroid status

	Age groups					
Thyroid	33-40	41-50	51-60	61-70	>70	**Total**
Hyperthyroid	2	4	5	10	4	**25**
Hypothyroid	1	8	7	8	3	**27**
Euthyroid	1	6	8	9	3	**27**
Total	**4**	**18**	**20**	**27**	**10**	**79**

Exact p-value = 0.957

Table 6 indicates that when interquartile ranges in patients presenting with Myocardial infarction were studied there was no difference in the age at presentation and patients' thyroid status.

Table 7: Correlation between total Cholesterol and thyroid status

Cholesterol	**Hyperthyroid**	**Hypothyroid**	**Euthyroid**	**Total**
Abnormal	14	20	22	56
%	25	35.71	39.29	100
Normal	11	7	5	23
%	47.83	30.43	21.74	100
Total	25	27	27	79
	31.65	34.18	34.18	100
Fisher's exact =	0.423	0.148		

There were 23 (29.11%) participants with recommended total cholesterol level of< 4 mmol/l and 56 (70.89%) with above a recommended value of > 4 mmol/l. There was no correlation

between total Cholesterol and thyroid status. HDL was above the recommended value of > 1.2 mmol/l in 13 women and above the recommended value of > 1 mmol/l in 27 men.

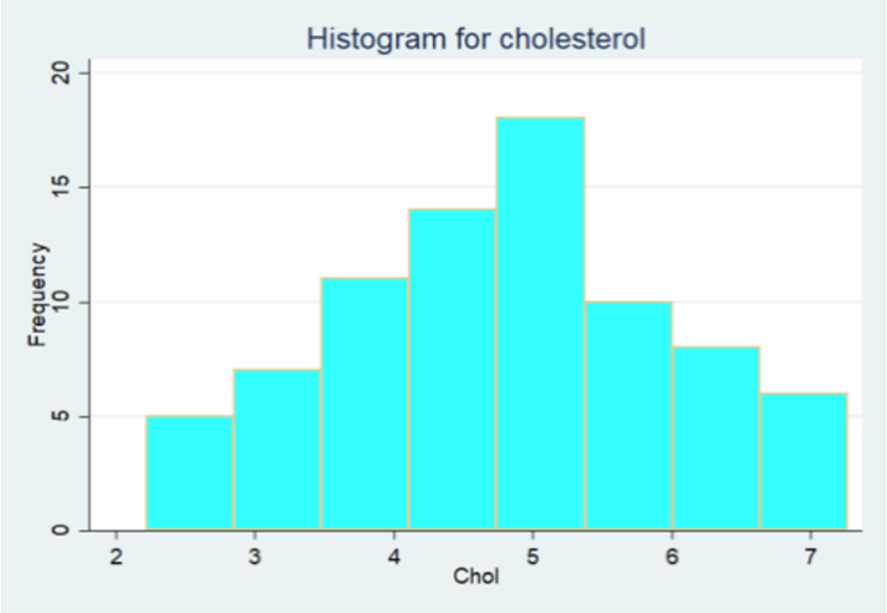

Figure 2: Cholesterol distribution of patients

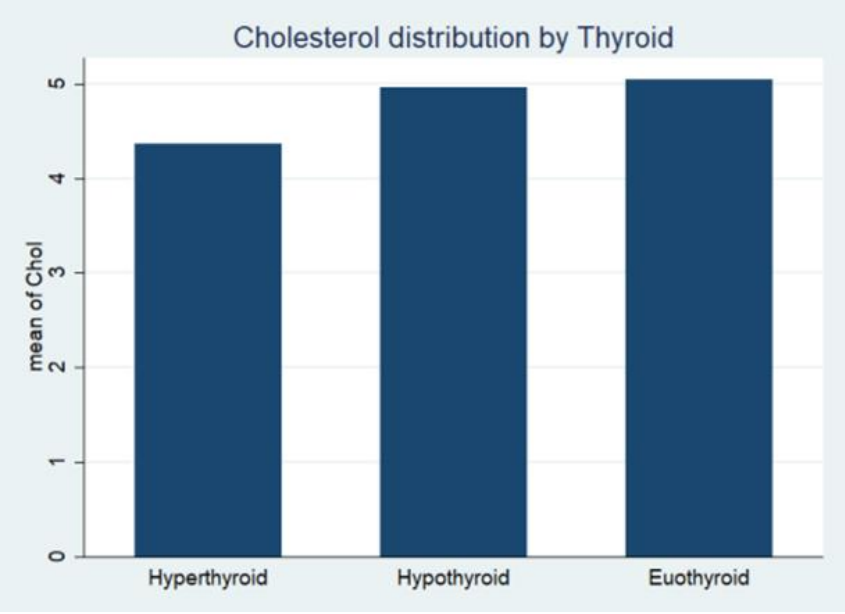

Figure 3: Cholesterol distribution by thyroid

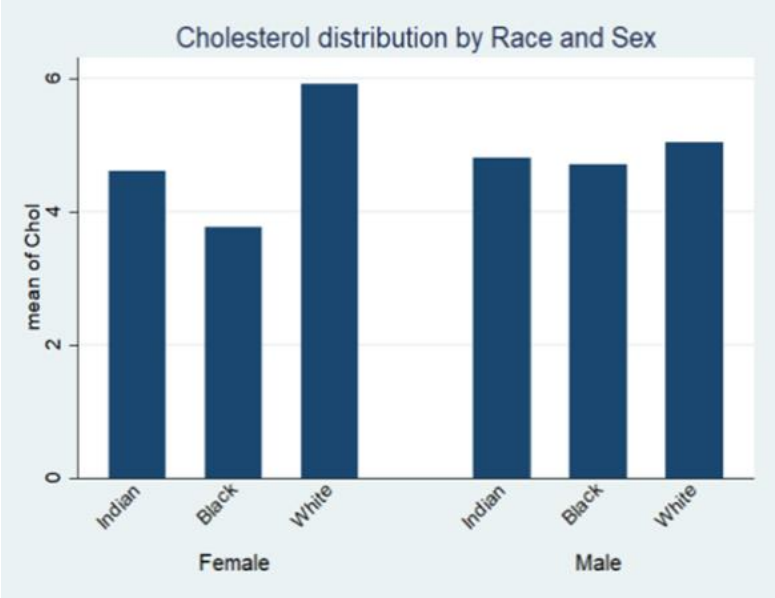

Figure 4: Cholesterol distribution by race and sex

Table 8: Correlation of LDL Cholesterol with thyroid status

	LDL		
Thyroid	Coef	p-value	95% CI
Hyperthyroid	-0.034	0.70	-0.21 – 1.40
Hypothyroid	-0.036	0.68	-0.21 – 0.13

Thyroid state did not correlate with LDL Cholesterol

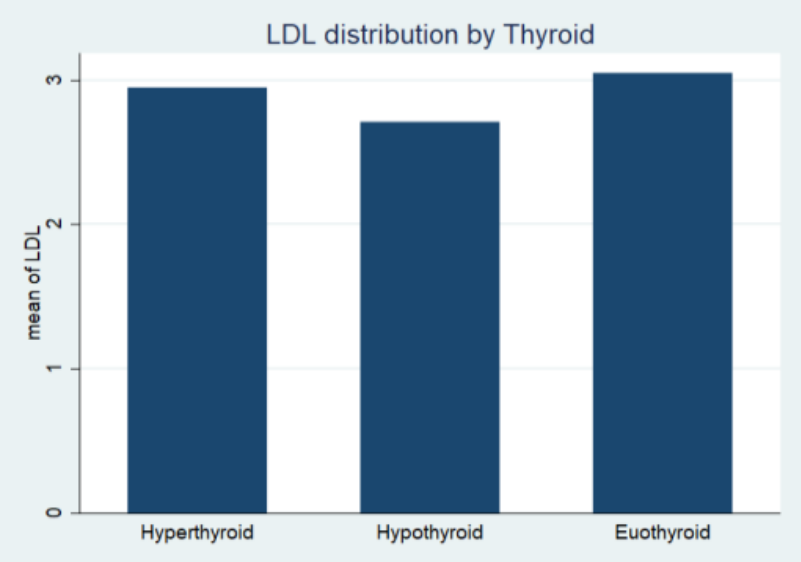

Figure 5: LDL distribution by thyroid

Table 9: LDL in diabetic and non-diabetic

LDL	**DM abnormal**	**DM normal**	**Total**
Normal	9	10	19
Abnormal	34	26	60
Total	43	36	79

Normal LDL in non-diabetic (less than 2.5mm/l) and in diabetic (less than 1.8mmol/l)

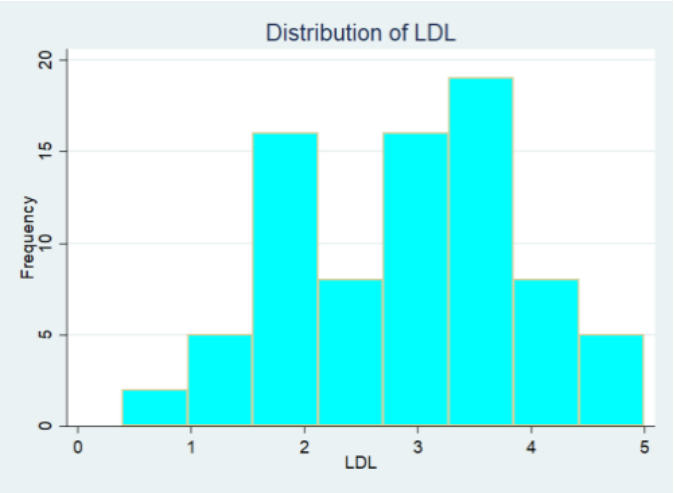

Figure 6: Distribution of LDL

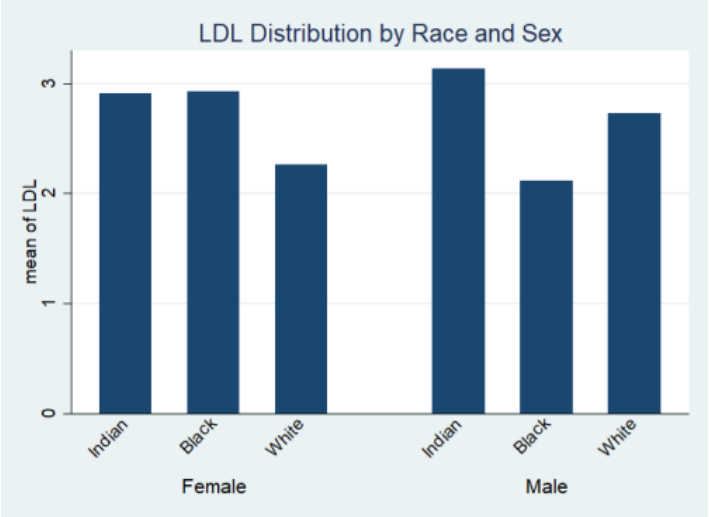

Figure 7: LDL distribution by Race and Sex

Table 10: Correlation of HDL Cholesterol with thyroid status

	HDL		
Thyroid	Coef	p-value	95% CI
Hyperthyroid	-0.06	0.79	-0.489- 0.371
Hypothyroid	-0.01	0.97	-0.429- 0.413

Table 11: Correlation between Triglyceride and thyroid status

Trig	**Hyperthyroid**	**Hypothyroid**	**Euthyroid**	**Total**
Abnormal	7	14	10	31
%	22.58	45.16	32.26	100
Normal	18	13	17	48
%	37.5	27.08	35.42	100
Total	25	27	27	79
	31.65	34.18	34.18	100
Fisher's exact = 0.231				

Table 11 shows Triglyceride level of < 1.7mmol/l was found in 48 (61%) participants of which 17 were women (35.42) and 31 were men (64.58%). There was no correlation between Triglyceride and thyroid status.

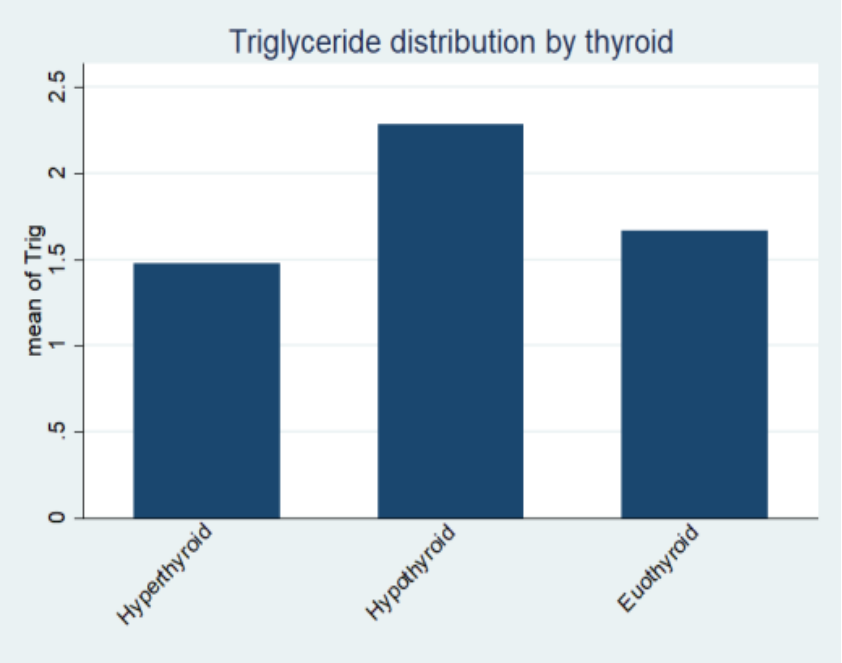

Figure 8: Triglyceride distribution by thyroid status

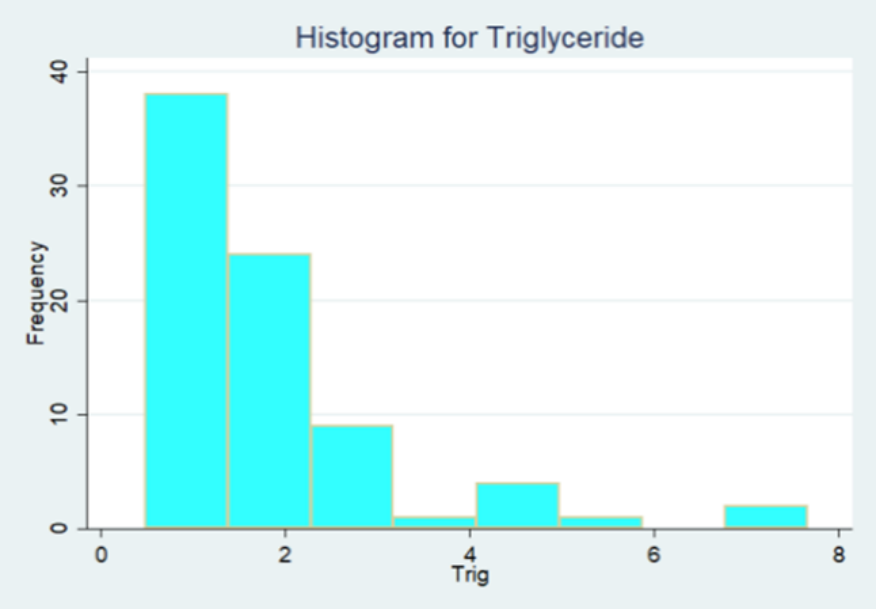

Figure 9: Triglyceride histogram

Table 12: Correlation between pulse and thyroid status

Pulse	Hyperthyroid	Hypothyroid	Euthyroid	Total
Abnormal	15	14	13	42
%	35.71	33.33	30.95	100
Normal	10	13	14	37
%	27.03	35.14	37.84	100
Total	25	27	27	79
	31.65	34.18	34.18	100
Fisher's exact =		0.664		

Table 12 shows that pulse which is the measure of heart beats per minute was in the normal range **(60 – 99 beats/minute)** among 71 (89.87%) participants, 27 (38.03%) women and 44 (61.97%) men. There was no correlation between pulse rate and thyroid status.

Table 13: Correlation between systolic blood pressure and thyroid status

SBP	Hyperthyroid	Hypothyroid	Euthyroid	Total
Abnormal	12	12	13	37
%	32.43	32.43	35.14	100
Normal	13	15	14	42
%	30.95	35.71	33.33	100
Total	25	27	27	79
	31.65	34.18	34.18	100
Fisher's exact =		1.000		

There were 51 participants with normal SBP (100 -139 mmHg), 18 (35.29%) women and 33 men (64.71%) while normal diastolic pressure (70-89mmHg) was found in 54 participants, 21 women (38.89%) and 33 men (61.11%). There was no correlation between systolic blood pressure and thyroid status.

Table 14: Correlation between Diastolic blood pressure and thyroid status

DBP	**Hyperthyroid**	**Hypothyroid**	**Euthyroid**	**Total**
Abnormal	13	11	10	34
%	38.24	32.35	29.41	100
Normal	12	16	17	45
%	26.67	35.56	37.78	100
Total	25	27	27	79
	31.65	34.18	34.18	100
Fisher's exact =		0.603		

Table 14 indicates that there was no correlation between Diastolic blood pressure and thyroid status.

Table 15: Correlation between Serum random glucose and thyroid status

Glucose	Hyperthyroid	Hypothyroid	Euthyroid	Total
Abnormal	12	8	11	31
%	38.71	25.81	35.48	100
Normal	13	19	16	48
%	27.08	39.58	33.33	100
Total	25	27	27	79
	31.65	34.18	34.18	100
Fisher's exact =	0.423			

Table 15 indicates that Serum random Glucose was less 7mmol/l among 53 participants of which 17 (32.08%) were men and 36 (67.92%) were women. There was no correlation between Serum random Glucose and thyroid status.

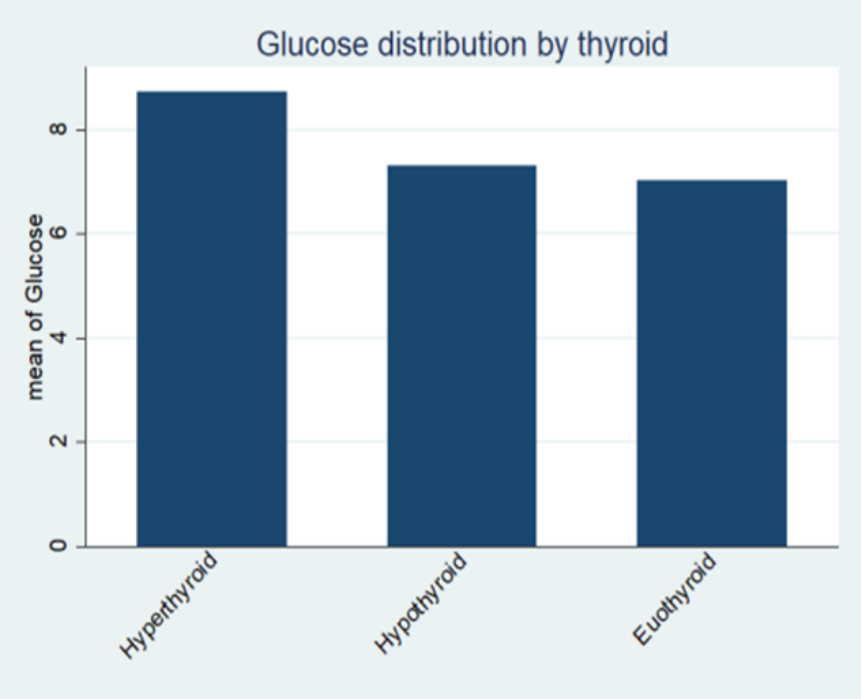

Figure 10: Random glucose distribution by thyroid status

Table 16: Correlation between CPK and thyroid status

CPK	Hyperthyroid	Hypothyroid	Euthyroid	Total
Abnormal	11	21	10	42
%	26.19	50	23.81	100
Normal	14	6	17	37
%	37.84	16.22	45.95	100
Total	25	27	27	79
	31.65	34.18	34.18	100
Fisher's exact =		0.006		

Creatine phosphokinase (CPK) with range (20 – 180) was normal among 37 (46.84%) participants, 14 (37.84%) women and 23 (62.16%) men. There was a significant difference between CPK and thyroid status. Hypothyroid patients were significantly more likely to have high CPK than Euthyroid or Hyperthyroid patients.

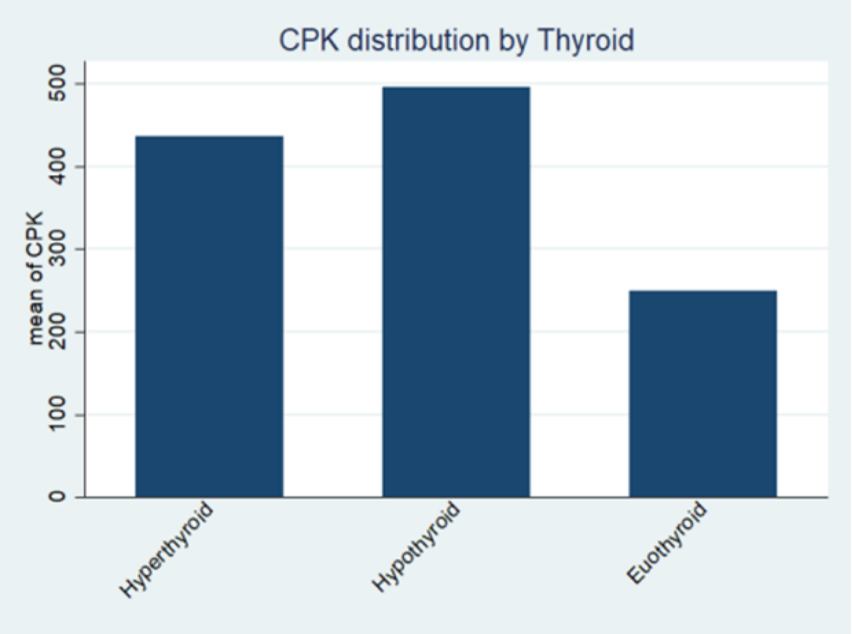

Figure 11: CPK distribution by thyroid status

Table 17: Baseline continuous variables of the study cohort

Variables	Mean (SD)	Median (IQR)	Min	Max
Cholesterol (mmol/l)	4.80 (1.24)	4.87 (3.89 – 5.73)	2.22	7.27
HDL (mmol/l)	1.19 (0.44)	1.13 (0.94 – 1.31)	0.50	3.99
Triglyceride (mmol/l)	1.82 (1.38)	1.41 (0.96 – 2.23)	0.49	7.67
Glucose	7.66 (3.73)	6.7 (5.7 – 8.1)	3.8	32.6
Systolic blood pressure (mmhg)	129.06 (23.75)	129 (113 – 148)	56	183
Diastolic blood pressure (mmhg)	78.51 (14.90)	79 (69 – 90)	30	110
Pulse (beat/min)	84.09 (14.98)	85 (72 – 95)	58	130
CPK (U/L)	392.77 (614.08)	185 (101 – 351)	44	3938
TSH (mlU/L)	5.63 (19.13)	1.43 (0.32 – 3.04)	0.01	149.36
FT4 (pmol/l)	13.84 (4.24)	13.1 (11.3 – 15.3)	2.20	26.30
LDL (mmol/l)	2.90 (1.03)	2.9 (2.1 – 3.7)	0.4	5

Table 18: Categorical variables

Variables	Male - n (%)	Female - n (%)
Hypertension (n = 79)		
0	6 (20%)	23 (46.94%)
1	24(80%)	26(53.06%)
Diabetes (n = 79)		
0	11 (36.67%)	32 (65.31%)
1	19 (63.33%)	17 (34.69%)
Smoking (n = 79)		
0	20 (66.67%)	15 (30.61%)
1	10 (33.33%)	34 (69.39%)
Family history of hypertension (n = 79)		
0	10 (33.33%)	32 (65.31%)
1	20 (66.67%)	17(34.69%)
Family history of diabetes (n = 79)		
0	6 (20.00%)	24 (48.98%)
1	24 (80.00%)	25 (51.02%)
ECG (n = 79)		
Anterior = 1	11 (50%)	11(50%)
Inferior = 2	13 (33.33%)	26 (66.67%)
Anterolateral = 3	3 (42.86%)	4 (57.14%)
Antero-septal = 4	3 (30.00%)	7 (70.00%)
Antero-inferior = 5	0 (0%)	1 (100.00%)
ECHO (n = 79)		
No RMWA = 0	5 (50.00%)	5(50.00%)
RMWA = 1	25 (36.23%)	44 (63.77%)

0 = Abnormal or No, 1 = Normal or Yes

30 participants (38%) had a normal range Ejection Fraction (54% - 66%) for their ECHO, of these 21 (70%) had RMWA and 9 (30%) had No RMWA. Of these 21, there were 10 women but only five with the cut-off age of 65 years and above, while 11 men fitted the criteria, however only five men had the cut-off age of 55 years and above.

To determine the risk of having a thyroid abnormality for each race, a multinomial regression was conducted showing the relative risk for each variable by thyroid type using euthyroid as the reference group. The result below shows the relative risk ratio (RRR) for Indians for each risk factor. This model was developed in a stepwise fashion, that is, by adding one variable at a time and adjusting the model. In some cases, a poor estimate was produced whereby standard errors and RRR were too large because a convergence could not be achieved. This means the categories had too small numbers for each thyroid state. This was more pronounced in the white and black ethnic groups with 12 and 9 observations respectively. For instance, in the black ethnic groups, euthyroid could not be used as a base outcome, as there were no observations for most of the risk factors, thus hyperthyroidism was used. It is important to note, none of the variables were statistically significant.

Table 19: Relative risk for Indians

Thyroid	**RRR**	**Std. Err**	**Z**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
Hyperthyroid						
Chol	0.7427	0.2649	-0.83	0.404	0.3691	1.4943
Sex	0.3772	0.3455	-1.06	0.287	0.0627	2.2709
DM	1.9299	1.9908	0.64	0.524	0.2555	14.5748
SBP	0.9663	0.0246	-1.35	0.177	0.9192	1.0157
DBP	1.0524	0.0402	1.34	0.181	0.9766	1.1342
Hypt	0.4661	0.4173	-0.85	0.394	0.0806	2.6948
Smoking	0.4707	0.412	-0.86	0.389	0.0847	2.6168
FHDM	3.5719	4.1905	1.09	0.278	0.3583	35.6044

FHHypt	0.5522	0.5679	-0.58	0.564	0.0736	4.145
ECG	0.9085	0.3464	-0.25	0.801	0.4303	1.9183
Age	1.0034	0.0467	0.07	0.942	0.916	1.0991
_cons	9.9348	40.6041	0.56	0.574	0.0033	29928.33
Hypothyroid						
Chol	1.1782	0.4408	0.44	0.661	0.5659	2.4529
Sex	0.8111	0.767	-0.22	0.825	0.1271	5.1765
DM	2.6994	2.8418	0.94	0.346	0.3429	21.2517
SBP	0.9764	0.0271	-0.86	0.389	0.9248	1.0309
DBP	1.0513	0.0422	1.25	0.212	0.9718	1.1373
Hypt	2.9189	2.8545	1.1	0.273	0.4294	19.8439
Smoking	0.4584	0.4178	-0.86	0.392	0.0768	2.7354
FHDM	0.5548	0.6957	-0.47	0.638	0.0475	6.4792
FHHypt	0.6256	0.7393	-0.4	0.691	0.0617	6.3418
ECG	0.5698	0.244	-1.31	0.189	0.2461	1.3189
Age	0.9995	0.0551	-0.01	0.992	0.8972	1.1134
_cons	0.4507	2.2939	-0.16	0.876	0	9681.374
Euthyroid	Base outcome					

The result from table 16 shows that if you are Indian and Hyperthyroid, you were more likely to have lower cholesterol than if you were Euthyroid. RRR = 0.74. Similarly, if you are Indian and Hyperthyroid, you were more likely to have a higher blood pressure than if you were Euthyroid. RRR=0.4661. Hypothyroid Indians are more likely to have lower cholesterol than if they were Euthyroid. RRR =1.1782. If you were Indian and Hypothyroidism, you were more likely to have a higher blood pressure than if you were Euthyroid. RRR= 2.9189.

Table 20: Relative risk for White patients

Hyperthyroid	**RRR**	**Std err**	**Z**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
Age	1.1983	0.1350	1.61	0.108	0.9610	1.4944
Chol	0.0903	0.1350	-1.61	0.108	0.0005	1.6891
Hypothyroid						
Age	1.0130	0.0551	0.24	0.812	0.9105	1.1270
Chol	0.8609	0.4958	-0.26	0.795	0.2780	2.6616
Euthyroid	Base outcome					

The result indicates that if you are white, conventional risk factors of age and total cholesterol are not changed by thyroid status.

Table 21: Relative risk for Blacks

Thyroid	**RRR**	**Std err**	**Z**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
Hypothyroid						
Sex	0.2566	0.5082	-0.69	0.492	0.0053	12.449
Chol	1.3058	0.9131	0.38	0.703	0.3317	5.1411
FT4	1.0726	0.2908	0.26	0.796	0.6304	1.8248
Hyperthyroid	**(base outcome)**					

Black males were more likely to have hypothyroidism than to be Euthyroid if they presented with Myocardial Infarction. Black females were also more likely to have hypothyroidism than to be Euthyroidism if they presented with Myocardial Infarction.

Table 22: Correlation of SBP with thyroid status

	SBP		
Thyroid	Coef	p-value	95% CI
Hyperthyroid	-<0.001	0.63	-0.005 – 0.003
Hypothyroid	-<0.001	0.99	-0.00 – 0.004

Table 23: Correlation of DBP with thyroid status

	DBP		
Thyroid	Coef	p-value	95% CI
Hyperthyroid	-0.001	0.75	-0.008 – 0.006
Hypothyroid	-<0.001	0.89	-0.006 – 0.007

Table 24: Correlation of Race with thyroid status

	Race		
Thyroid	Coef	p-value	95% CI
Hyperthyroid	-0.19	0.47	-0.32 – 0.70
Hypothyroid	-0.31	0.21	-0.18 – 0.80

Table 25: Correlation of Sex with thyroid status

	Sex		
Thyroid	Coef	p-value	95% CI
Hyperthyroid	-0.69	0.17	-1.69 – 0.30
Hypothyroid	-0.66	0.18	-1.61 – 0.29

Table 26: Correlation of Hypertension with thyroid status

	Hypertension		
Thyroid	Coef	p-value	95% CI
Hyperthyroid	-0.19	0.59	-0.90 – 0.51
Hypothyroid	-0.11	0.74	-0.54 – 0.77

Table 27: Correlation of FHDM with thyroid status

	FHDM		
Thyroid	Coef	p-value	95% CI
Hyperthyroid	-0.44	0.42	-0.62 – 1.49
Hypothyroid	-0.41	0.52	-1.65 – 0.83

Table 28: Correlation of DM with thyroid status

	DM		
Thyroid	Coef	p-value	95% CI
Hyperthyroid	-0.33	0.61	-1.59 – 0.93
Hypothyroid	0.28	0.69	-1.10 – 1.67

Table 29: Correlation of Age with thyroid status

	Age		
Thyroid	Coef	p-value	95% CI
Hyperthyroid	0.01	0.43	-0.01 – 0.18
Hypothyroid	0.00	0.98	-0.01 – 0.01

Table 30: Correlation of smoking with thyroid status

	Smoking		
Thyroid	Coef	p-value	95% CI
Hyperthyroid	-0.73	0.17	-1.77 – 0.32
Hypothyroid	-0.07	0.89	-1.10 – 0.95

Table 31: Correlation of FHHypt with thyroid status

	FHHypt		
Thyroid	Coef	p-value	95% CI
Hyperthyroid	0.30	0.51	-0.60 – 1.18
Hypothyroid	-0.51	0.88	-1.04 – 0.89

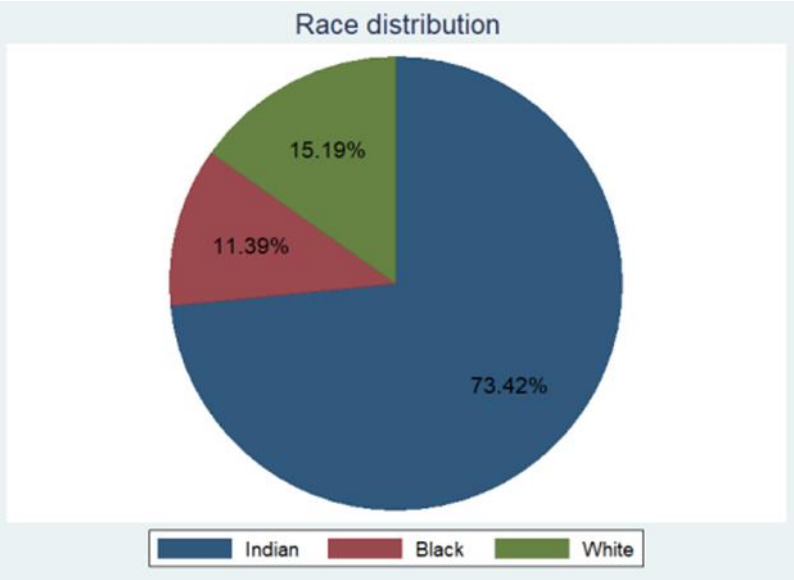

Figure 12: Race distribution of patients presenting with Myocardial infarction

Patient outcome:

There was no in-hospital mortality during the admission for the index of an acute coronary syndrome. Thirty-day mortality 1/79 (1.3%), inpatient with hypothyroidism.

Discussion

The principal finding of our study is that there was no significant correlation between thyroid function and Myocardial infarction in all groups studied except for those with black ethnicity. Black patients in our study were more likely to be hypothyroid when presented with myocardial infarction. There was no significant difference between gender and thyroid status or the area of infarcted tissue. More so, there was no significant difference between conventional risk factors: total cholesterol, calculated LDL cholesterol, HDL cholesterol, triglyceride, random plasma glucose, pulse, systolic blood pressure and diastolic blood pressure with both hypothyroid and hyperthyroid patients with myocardial infarction in our study. Therefore, our findings differ from previous studies that showed elevation of cholesterol and heart rate which was more in females than in males.

Furthermore, there was a significant correlation between thyroid status and creatinine phosphokinase, hypothyroid patients were significantly more likely to high CPK than euthyroid or Hyperthyroid patients. Because our patients had wall motion abnormalities and ECG changes consistent with acute coronary syndrome, it is unlikely that our patients were incorrectly diagnosed with myocardial infarction. Due to resource limitations, unfortunately, FT3 was not measured although many previous studies showed a highly inverse correlation exists between coronary heart disease and thyroid hormone which was extended across a wide spectrum of value of fT3.

In addition, no previous studies comparing ethnicity in myocardial infarction and thyroid dysfunction are described in the literature. Our study showed that Black patients were most likely to have thyroid dysfunction if they are presented with a MI (100%) compared to white patients who were least likely to have concomitant thyroid disease (58%). Black patients were significantly more likely to be hypothyroid than either white or Indian patients (p=0.019).

Mortality in our cohort was low and due to small numbers, no comparison with thyroid status could be made. This finding is different from other studies where it was found that there was an association between Hypothyroidism and decreased survival in Myocardial infarcted patients with statistical significance (RRs of 1.18 to 1.55) (24).

Study limitations and advantages

The limitation of this study was that it was a single-centre study. Small numbers of patients in each ethnic group other than Indian made statistical analysis challenging, furthermore this was a retrospective review, so all clinical data relied on record keeping.

Study advantages: this is the first published data of thyroid dysfunction cross different ethnic groups in South Africa.

Disclosure statement

No potential conflict of interest was reported by the authors.

REFERENCES

1. Althaus BU, Staub JJ, LÈCHE AR, Oberhänsli A, Stähelin HB. LDL/HDL-changes in subclinical hypothyroidism: possible risk factors for coronary heart disease. Clinical endocrinology. 1988 Feb;28(2):157-63. (PMID: 3168304).

2. Kanaya AM, Harris F, Volpato S, Pérez-Stable EJ, Harris T, Bauer DC. Association between thyroid dysfunction and total cholesterol level in an older biracial population: the health, aging and body composition study. Archives of internal medicine. 2002 Apr 8;162(7):773-9. (PMID: 11926850).

3. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87:489-99. [PMID: 11836274].

4. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. Jama. 2004 Jan 14;291(2):228-38.. [PMID: 14722150].

5. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Annals of Internal Medicine. 2000; Feb 15; 132(4):270-8 (PMID: 10681281).

6. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, Michelangeli V. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Archives of internal medicine. 2005 Nov 28;165(21):2467-72. (PMID: 16314542).

7. Klein I. Thyroid hormone and the cardiovascular system. The American journal of medicine. 1990 Jun 1;88(6):631-7.

8. Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. Circulation. 1993 May;87(5):1435-41.

9. Klein I, Levey GS. The cardiovascular system in thyrotoxicosis. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's the thyroid: a fundamental and clinical text. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2000:596-604.

10. Graettinger JS, Muenster JJ, Selverstone LA, Campbell JA. A correlation of clinical and hemodynamic studies in patients with hyperthyroidism with and without congestive heart failure. The Journal of clinical investigation. 1959 Aug 1;38(8):1316-27.

11. Klein I, Ojamaa K. The cardiovascular system in hypothyroidism. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's the thyroid: a fundamental and clinical text. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2000:777-82. 35.

12. Klein I, Ojamaa K. Thyrotoxicosis and the heart. Endocrinal Metab Clin North Am 1998; 27:51-62.

13. Shan S, Aslam s, Saleem N, Rizvi NB, Elahi S, Thyroid hormone deficiency and coronary artery disease. Anaesth Pain & intensive Care 2017;21(4):489-496.

14. Chan KM, Ladenson JH. Increased creatine kinase MB in the absence of acute myocardial infarction. Clinical Chemistry. 1986; 32:2044–51.

15. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. New England Journal of Medicine. 2001 Feb 15;344(7):501-9.

16. Grewal J, Gin K. Troponin Marks the spot!. Perspectives in Cardiology. 2004 Nov; 50(11): 20:35–40.

17. Khan IA, Tun A, Wattanasauwan N, Win MT, Hla TA, Hussain A, Vasavada BC, Sacchi TJ. Elevation of serum cardiac troponin I in noncardiac and cardiac diseases other than acute coronary syndromes. The American journal of emergency medicine. 1999 May 1;17(3):225-9.

18. Cohen LF, Mohabeer AJ, Keffer JH, Jialal I. Troponin I in hypothyroidism. Clinical chemistry. 1996 Sep 1;42(9):1494-5.

19. Pingitore A, Galli E, Barison A, Iervasi A, Scarlattini M, Nucci D, L'Abbate A, Mariotti R, Iervasi G. Acute effects of triiodothyronine (T3) replacement therapy in patients with chronic heart failure and low-T3 syndrome: a randomized, placebo-controlled study. The Journal of Clinical Endocrinology & Metabolism. 2008 Apr 1;93(4):1351-8.

20. Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, L'Abbate A, Donato L. Low-T3 syndrome: a strong prognostic predictor of death in patients with heart disease. Circulation. 2003 Feb 11;107(5):708-13.

21. Lymvaios I, Mourouzis I, Cokkinos DV, Dimopoulos MA, Toumanidis ST, Pantos C. Thyroid hormone and recovery of cardiac function in patients with acute myocardial infarction: a strong association?. European Journal of Endocrinology. 2011 Jul 1;165(1):107-14.

22. Pingitore A, Chen Y, Gerdes AM, Iervasi G. Acute myocardial infarction and thyroid function: new pathophysiological and therapeutic perspectives. Annals of medicine. 2012 Dec 1;44(8):745-57.

23. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, Tracy RP, Ladenson PW. Thyroid status, cardiovascular risk, and mortality in older adults. Jama. 2006 Mar 1;295(9):1033-41.

24. Iervasi G, Molinaro S, Landi P, Taddei MC, Galli E, Mariani F, L'Abbate A, Pingitore A. Association between increased mortality and mild thyroid dysfunction in cardiac patients. Archives of internal medicine. 2007 Jul 23;167(14):1526-32. [PMID: 1764660.

Appendices

Appendix 1: The final Study Protocol (Include the final protocol which was given full approval by Brec and/or the postgrad office)

Re-amended Research protocol: MMED (Internal Medicine)

Student: Dr. Mustafa Ben Hkouma

Student number: 214585722

Supervisor: Dr. Susan L Brown

Title of study:

Association Between Thyroid Dysfunction and conventional risk factors In Patients With An Acute Coronary Syndromes

Aim of study:

To examine the association and outcome between patients with hyperthyroidism , hypothyroidism and patients with normal thyroid function presenting with an Acute Coronary Syndrome.

Specific objective:

. To describe the demographic profile of patients presenting with thyroid dysfunction and Acute Coronary Syndrome and compare them with euthyroid patients.

. To compare the prevalence of hyper – and hypothyroidism in patients with Acute Coronary Syndrome.

. To compare the clinical outcomes of thyroid dysfunction and acute coronary syndrome.

. To determine the risk factors associated with thyroid dysfunction and acute coronary syndrome.

Outcome measures:

. To calculate if there is a difference in the age , gender and ethnicity between patients presenting with normal and abnormal thyroid function tests.

. To determine the prevalence of thyroid dysfunction in patients presenting with thyroid dysfunction

. To determine if the inpatient mortality and morbidity as measured by clinical improvement or not of the patient's condition on discharge.

. To calculate if there is an association between the thyroid state and conventional cardiovascular risk factors; age , Blood pressure , lipids, glucose status and the patient's eventual outcome.

Background and literature:

Subclinical hypothyroidism and subclinical hyperthyroidism have been associated with an increased risk of acute coronary syndromes and mortality. Factors contributing to this association include; an increase concentration of cholesterol (1, 2,17,18) and increase risk of atherosclerosis, (3, 4) and altered cardiovascular hemodynamics. (5, 6, 7, 8, 9 and 10).

Hypothyroid patients may have an increased concentration of creatinine kinase mostly due to increase CK-MM which also lead to increase level of CK-MB. This may confuse doctors during their evaluation and diagnosis of myocardial injury in a hypothyroid patient presenting with chest pain.

The Troponin I is a superior marker to diagnose myocardial injury, but cases reports of hypothyroid patients with an increased Troponin I , suggest that hypothyroidism might be a risk factor for myocardial injury and increase risk of cardiac death (11, 12, 13, 14and 15).

Clinical and experimental data have suggested a potential negative effect of low T3 on the prognosis of cardiac disease and increase mortality rate (16).

Low T3 concentrations are a strong independent predictive marker for poor prognosis in cardiac patient based on study was done in 2002 on 573 patients (173 patients with low T3 and 400 patients with normal T3 (12).

The reduction of ft3 level in patients with CAD is a marker of disease rather than an element contributing directly to disease prognosis. However, because ft3 represents the biologically active form of thyroid hormone, then as isolated reduction in ft3 levels could constitute a model of abnormal thyroid hormone metabolism acting as a risk factor for CAD in a similar fashion to overt or subclinical hypothyroidism. For example the prevalence of dyslipidemia and arterial hypertension, is greater in patients affected by hypothyroidism (19).

Hypothyroidism might also lead to hypercoagulability, endothelial dysfunction, hyperhomocysteinemia, impaired fibrinolysis, systemic inflammation and platelet abnormalities (19).

The changes in thyroid hormone in the plasma are linked to high mortality in patients with acute myocardial infarction, indicating strong implication of thyroid hormone signaling in the post-ischemic cardiac recovery , this hypothesis was done in experimental models of ischemia- reperfusion and myocardial infarction in animals and accumulating evidence reveals that thyroid hormone is critical for the response of the myocardium to ischemic stress and thyroid hormone may have cytoprotective properties that are ((silent)) in healthy tissue appear only during stress. This hypothesis was done in 2011 on 67 patients with 12 patients have thyroid hormone changes (20).

During experimental coronary artery ligation in an animal model of acute myocardial infarction, heart failure found to be associated with reduction of thyroid hormone receptor expression in the myocardium, leading to tissue hypothyroidism.The thyroid hormone administration improves cardiac contractility, augments myocardial remodeling and improve left ventricular function. Also regulate angiogenesis, cardio-protection, cardiac metabolism, and myocyte regeneration at molecular level, changes that can reverse left ventricular

remodeling by improving myocyte shape and geometry of left ventricular cavity, then improving recovery from acute myocardial infarction (21).

Acute myocardial infarction represent a major public health problem. Despite improvements in reperfusion therapy, the 2020 World Health Organization projections view the high incidence of post-ischemic heart failure as the most important cause of morbidity and mortality. In this regard, thyroid hormones are increasingly being recognized as significant players in the pathogenesis and the recovery and repair period of acute myocardial infarction (22).

Study location:

Addington Hospital, KwaZulu-Natal, Republic of South Africa.

Study population:

The study population is selected patients admitted to Addington Hospital with Acute Coronary Syndrome.

Study sample:

The study sample is randomly selected patients with Acute Coronary Syndrome and thyroid dysfunction admitted during the period January 2010 to September 2018.

Sample size: 79

Sampling technique:

The parameter will be used to calculate sample size:

1. Statistical test: Chi square test
2. Effect size: 0.40
3. Type one error (α): 0.05 (5%) (recommended in literature of medical study)
4. Type tow error (β) : 0.2 (20%) (recommended in literature of medical study)
5. Statistical power (1-β)= 0.8 (80%) .

Output parameter:

1. non centrality parameter (λ) : 12.96.
2. critical chi square= 11.07
3. Total sample size =79
4. Actual statistical power= 0.8 (80%).

The three categories (hyperthyroidism, hypothyroidism and normal thyroid function) will be investigated in association with Acute Coronary Syndrome.

Therefore means that the total number of 79 participants will be divided by three to give a minimum number of individuals from each thyroid function category to be included in the study ie. 79/3= 27/27/25.

Therefore means that a minimum of 25 patients of Hyperthyroidism, 27 patients of Hypothyroidism and 27 patients of normal thyroid function will be included in the study. In the situation where they are more than 27 individual in the category, a simple random sampling procedures will included.

Inclusion criteria:

All participant in study must have:

- Age of 18 and more
- Diagnosis of acute coronary syndrome with ECG changes and positive cardiac enzymes
- Patients with thyroid function results

Exclusion criteria:.

- severly ill patients, that is, with clinical evidence of sepsis or with concomitant presence of any predominant sever systemic disease.

- In-Hospital death prior to blood draws

Method:

Study design: retrospective cross-section analytic study.

All participants in the study will have the following documented during admission:

. Admission diagnosis

The following investigations will be done in all the participant who meet the inclusion criteria as part of their standard care:

. Thyroid function test (TSH, FT4).

. Lipid profile

. Blood glucose level

. ECG

. Cardiac enzymes.

Study period:

January 2010 to September 2018.

Data collection Technique:

Data will be accessed from a hard copy database and will be entered onto a data collection sheet. The patient records although are retrospectively analyzed, Confidentiality of patient data will be ensured.

Limitation of the study:

Due to retrospective nature of the study, incomplete data and poor follow up may decrease the sample size. The study is limited to one center that may not be truly representative of the general population

Funding:

Self-funded.

Ethical consideration:

The anonymity of patients included in the study will be maintained. There will be no specific mention of any personal patient information in the study. The study is completely retrospective and non-interventional.

Data analysis techniques:

Data will be processed using the following statistical tools, SAS (SAS Institute Inc. 2016. Base SAS® 9.4 Procedures Guide. Cary, NC: SAS Institute Inc), IBM SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Continues variables will be summarized using mean and standard deviation. Skewed (non-normal) data will be summarized using median and tertiles. Differences in means between continues variable will be analyze using Student's t-test. However, if data is not normal Wilcoxon test will be used. Association between Acute Coronary Syndrome outcomes and thyroid dysfunction will be analyze using Pearson's Chi squared test, or fisher's exact where data is <5 per contingency table cell.

References:

1- Althaus BU, Staub JJ, Ryff- De Leche A, Oberhansli HB. LDL/ HDL- changes in subclinical hypothyroidism: possible risk factors for coronary heart disease Clin Endocrinal (Oxf). 1988; 28:157-63. (PMID: 3168304).

2- Kanaya AM, Harris F, Volpato S, Perez-stable EJ, Harris T, Bauer DC. Association between thyroid dysfunction and total cholesterol level in an older biracial population: the health, aging and body composition study. Arch Intern Med. 2002; 162:773-9. (PMID: 11926850).

3- Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med. 200; 132:270-8 (PMID: 10681281).

4- Walsh IP, Bremner AP, Bulsara MK, O"Leary P, Leedman PI, Feddema P, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Intern Med. 2005; 165:2467-72. (PMID: 16314542).

5- Klein I. Thyroid hormone and the cardiovascular system. Am J Med 1990; 88:631-637.

6- Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. Circulation1993;87:1435-1441

7- Klein I, Levey GS. The cardiovascular system in thyrotoxicosis. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's the thyroid: a fundamental and clinical text. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2000:596-604.

8- Graettinger JS, Muenster JJ, Selverstone LA, Campbell JA. A correlation of clinical and hemodynamic studies in patients with hyperthyroidism with and without congestive heart failure. J Clin Invest 1959; 38:1316-1327.

9- Klein I, Ojamaa K. The cardiovascular system in hypothyroidism. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's the thyroid: a fundamental and clinical text. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2000:777-82.

10- Klein I, Ojamaa K. Thyrotoxicosis and the heart. Endocrinal Metab Clin North Am1998;27:51-62.

11- Chan KM, Ladenson JH (1986) Increased creatine kinase MB in the absence of acute myocardial infarction. Clin Chem 32:2044–51

12- Klein I, Ojamaa K (2001) Thyroid hormone and the cardiovascular system. New Engl J Med 344:501–509

13- Grewal J, Gin K (2004) Troponin Marks the spot!. Perspectives in Cardiology 20:35–40

14- Khan IA, Tun A, Wattanasauwan N, Win MT, Hla TA, Hussain A, Vasavada BC, Sacchi TJ (1999) Elevation of serum cardiac troponin I in noncardiac and cardiac diseases other than acute coronary syndromes. Am J Emerg Med 17:225–9

15- Cohen LF, Mohabeer AJ, Keffer JH, Jialal I (1996) Troponin I in hypothyroidism. Clin Chem 42:1494–5.

16- Giorgio Iervasi, MD; Alessandro Pingitore, MD, PhD; Patrizia Landi, BSc;Mauro Raciti, BSc; Andrea Ripoli, PhD; Maria Scarlattini, BSc; Antonio L'Abbate, MD; Luigi Donato, MD.

17- Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87:489-99. [PMID: 11836274].

18- Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;291:228-38. [PMID: 14722150].

19- Pingitore A, Galli E, Barison A, et al. Acute effects of triiodothyronine replacement therapy in patients with chronic heart failure and low-t3 syndrome: a randomized, placebo-controlled study. *J Clin Endocrinol Metab*. 2008;93:1351–1358.

20- Ioannis Lymvaios, Iordanis Mourouzis, Dennis V Cokkinos, Meletios A Dimopoulos, Savvas T Toumanidis, and Constantinos Pantos Thyroid hormone and recovery of cardiac function in patients with acute myocardial infarction: a strong association?Eur J Endocrinol 165 107-114, doi: 10.1530/EJE-11-0062 First published online 13 April 2011.

21- Pingitore A, Chen Y, Gerdes AM, Iervasi G. Acute myocardial infarction and thyroid function: new pathophysiological and therapeutic perspectives. Ann Med. 2012;44:745–57. doi: 10.3109/07853890.2011.573501.

22- Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, et al. Thyroid status, cardiovascular risk, and mortality in older adults. JAMA. 2006;295:1033-41.

Appendix 2: The Guidelines for Authorship for the Journal selected for submission of the manuscript

Author Guidelines

Instructions for authors

SA Heart publishes peer reviewed articles dealing with cardiovascular disease, including original research, topical reviews, state-of-the-art papers and viewpoints. Regular features include an ECG quiz, image in cardiology and local guidelines. Case reports are considered for publication only if the case or cases are truly unique, incorporates a relevant review of the literature and makes a contribution to improved future patient management.

Publication policy

Articles must be the original, unpublished work of the stated authors. Written permission from the author or copyright holder must be submitted with previously published material including text, figures or tables. Articles under consideration elsewhere or previously published (except as abstracts not exceeding 400 words) may not be submitted for publication in SA Heart. On acceptance transfer of copyright to the South African Heart Association will be required. No material published in SA Heart may be reproduced without written permission. Permission may be sought from the Chief Editor (Email: **afd@sun.ac.za**).

Disclosures

Authors must declare all financial disclosures and conflicts of interest in the cover letter and on the title page of the manuscript.

Ethics

All studies must be in compliance with institutional and international regulations for human and animal studies such as the Helsinki declaration (2008) (http://www.wma.net/en/30publications/10policies/b3/17c.pdf) and the South African MRC ethics guidelines (http://www.sahealthinfo.org/ethics/index.htm). Human studies require ethics committee approval and informed consent which must be documented in your manuscript. Animal studies require ethics committee approval and must conform to international guidelines for animal research, as well as the South African National Standard for the care and use of animals for scientific purposes. Compliance with these requirements must be documented in your manuscript.

Content

1. Title page: It should contain the title of the manuscript, the names of all authors in the correct sequence, their academic status and affiliations. If there are more than 4 authors, the contribution of each must be substantiated in the cover sheet. The main author should include his/her name, address, phone, fax and email address.

2. Authors are solely responsible for the factual accuracy of their work.

3. Articles should be between 3 000 and 5 000 words in length.

4. A 200-word abstract should state the main conclusions and clinical relevance of the article.

5. All articles are to be in English.

6. Abbreviations and acronyms should be defined on first use and kept to a minimum.

7. Tables should carry Roman numeral, I, II etc., and figures Arabic numbers 1, 2 etc.

8. References should be numbered consecutively in the order that they are first mentioned in the text and listed at the end in numerical order of appearance. Identify references in the text by Arabic numerals in superscript after punctuation, e.g. …trial.

9. Articles are to be submitted directly via the journal. The text should be in MS Word. Pages should be numbered consecutively in the following order wherever possible: Title page, abstract, introduction, materials and methods, results, discussion, acknowledgements, tables and illustrations, references.

10. Where possible all figures, tables and photographs must also be submitted electronically. The illustrations, tables and graphs should not be imbedded in the text file, but should be provided as separate individual graphic files, and clearly identified. The figures should be saved as a 300 dpi jpeg file. Tables should be saved in a MS Word or PowerPoint document. If photographs are submitted, two sets of unmounted high quality black and white glossy prints should accompany the paper. Figures and photographs should be of high quality with all symbols, letters or numbers clear enough and large enough to remain legible after reduction to fit in a text column. Each figure and table must have a separate self-explanatory legend.

11. Remove all markings such as patient identification from images and radiographs before photographing.

Appendix 3: Ethical approvals

Included hospital and provincial approvals as well as the BREC approval (or waiver if appropriate).

Attached

Appendix 4: Data collection tools (for example)

Attached

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

ADDINGTON HOSPITAL

P.O. BOX 977
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4000
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www.kznhealth.gov.za

OFFICE OF THE CHIEF EXECUTIVE OFFICER

Reference: *9/2/3/R*

Date: 16th November 2018

Principal Investigator:
- **Dr MMMB Hkouma**

PERMISSION TO CONDUCT RESEARCH AT ADDINGTON HOSPITAL: "ASSOCIATION BETWEEN THYROID DYSFUNCTION AND ADVERSE OUTCOMES IN PATIENTS PRESENTING WITH AN ACUTE CORONARY SYNDROME"

I have pleasure in informing you that permission has been granted to you by Addington Hospital Management to conduct the above research.

Please note the following:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Please ensure this office is informed before you commence your research.
4. Addington Hospital will not provide any resources for this research.
5. You will be expected to provide feedback on your findings to Addington Hospital.

DR M NDLANGISA
HOSPITAL MANAGER
ADDINGTON HOSPITAL

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI
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Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

14 October 2019

Dr MMMB Hkouma (214585722)
School of Clinical Medicine
College of Health Sciences
m.hokoma@yahoo.com

Dear Dr Hkouma

PROTOCOL: Association between thyroid dysfunction and conventional risk factors in patients with an acute Coronary Syndromes.
Degree: MMed
BREC Ref No: BE454/17

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	07 December 2019
Expiration of Ethical Approval:	06 December 2020

I wish to advise you that your application for Recertification received on 05 October 2019 for the above protocol has been **noted and approved** by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be advised of the above at a meeting to be held on 12 November 2019.

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc: S.I.brown.mail@gmail.com SCMpgrad@ukzn.ac.za

health
Department:
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www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

HRKM Ref: 466/17
NHRD Ref: KZ_201711_022

Date: 20 December 2018
Dear Dr MB Hkouma
UKZN

Approval of research

1. The research proposal titled **'Association between thyroid dysfunction and adverse outcomes in patients presenting with an acute Coronary Syndrome'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Addington Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge

Chairperson, Health Research Committee

Date: 20/12/18

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

18 July 2017

Dr Susan L Brown
Department of Internal Medicine
School of Clinical Medicine

Dear Dr Brown

PROTOCOL: "Association between thyroid dysfunction and adverse outcomes in patients presenting with an acute Coronary Sundrome " Student: Dr Mustafa ben Hkouma, student number: 214585722 (Department of Internal Medicine)

I am pleased to inform you that the abovementioned study has been approved.

Please note:

- The Academic Leader: Research must review any changes made to this study.
- The study may not begin without the approval of the Biomedical Research Ethics Committee.

May I take this opportunity to wish the student every success with the study.

Yours sincerely

Dr C Aldous
Academic Leader School Research
School of Clinical Medicine

C Biomedical Research Ethics Committee
Westville Campus
C Mustafa ben Hkouma

ID	CODE	Race	Sex	Age	Chol	Trig	HDL	MI
1	1	Indian	M	51	6.49	7.67	0.8	X
2	1	Indian	F	63	3.45	1.15	1.22	X
3	1	Indian	M	70	4.6	1.02	0.94	X
4	1	Indian	M	38	2.97	1.31	1.03	X
5	1	White	F	86	5.31	0.93	1.79	X
6	1	Indian	F	66	2.26	1.93	1.2	X
7	1	Indian	F	64	2.22	0.73	1.2	X
8	1	Black	M	43	5.19	1.71	0.99	X
9	1	Indian	M	60	4.9	0.74	0.66	X
10	1	Indian	M	49	6.37	0.67	1.56	X
11	1	Indian	F	63	3.88	0.62	1.6	X
12	1	Indian	F	66	5.06	0.78	1.98	X
13	1	Black	M	47	5.2	1.15	1.31	X
14	1	Indian	F	75	3.4	1.31	0.77	/
15	1	White	M	33	2.3	1	0.67	X
16	1	Indian	M	66	5.2	2.09	0.87	X
17	1	Indian	M	64	3.5	0.95	0.89	X
18	1	Indian	F	69	3.6	0.59	1.2	X
19	1	Indian	M	58	3.4	0.64	1.93	X
20	1	Indian	F	43	5.31	1.46	1.09	X
21	1	Indian	M	71	3.9	1.02	0.93	X
22	1	Indian	F	61	4.51	1.85	0.98	X
23	1	White	F	73	5.45	2.23	1.9	/
24	1	Indian	F	58	4.9	1.94	0.95	/
25	1	Indian	M	54	5.74	1.43	1.26	X
26	2	Black	M	60	6.65	2.26	0.9	X
27	2	Indian	M	44	6.59	4.33	1.33	X
28	2	Indian	M	65	4.7	0.96	1.07	X
29	2	White	M	66	5.8	2.11	1.19	X
30	2	White	M	62	5.29	0.84	1.21	X
31	2	Indian	M	50	5.86	2.93	0.89	X
32	2	Indian	M	52	6.21	4.63	0.72	X
33	2	Black	M	42	3.04	0.89	0.95	X
34	2	Black	F	35	5.2	1.09	1.13	X
35	2	White	F	69	7.27	4.96	1.11	/
36	2	Indian	F	71	3.69	1.06	1.11	/
37	2	Indian	M	61	4.21	1.62	1.42	X
38	2	Black	M	44	3.33	0.5	1.51	X
39	2	Indian	M	51	5.1	5.25	0.6	/
40	2	White	F	69	6.36	2.65	1.01	X
41	2	Indian	F	52	6.76	4.28	1.18	X
42	2	Indian	F	56	3.12	1.05	0.94	X
43	2	Indian	F	78	5.14	1.46	1.6	X
44	2	Indian	M	50	4.26	2.38	0.9	X
45	2	Indian	F	56	4.61	0.97	1.5	/
46	2	Indian	M	69	4.25	1.7	0.8	X

47	2	Indian	F	71	5.73	7.4	0.5	X
48	2	Indian	M	43	7.06	0.65	3.99	X
49	2	Black	F	45	2.24	0.49	1.16	X
50	2	Black	M	46	4.87	2.22	0.91	X
51	2	Black	F	60	3.83	2.35	1.06	/
52	2	Indian	M	64	2.67	0.57	1.15	/
53	3	Indian	M	76	4.37	1.21	1.27	X
54	3	Indian	M	77	4.14	1.33	0.73	/
55	3	Indian	F	64	4.24	1.85	1.6	X
56	3	Indian	M	68	6.14	1.63	1.07	X
57	3	Indian	M	52	5.69	1.04	0.97	/
58	3	Indian	M	36	5.95	2.49	1.28	X
59	3	Indian	M	62	5.05	2.61	0.82	X
60	3	Indian	F	66	6.79	1.33	1.11	X
61	3	Indian	F	56	6.81	2.14	1.28	X
62	3	Indian	M	59	4.82	0.86	0.9	/
63	3	Indian	F	61	6.29	2.49	1.18	X
64	3	Indian	F	50	4.44	1.4	1.32	X
65	3	Indian	M	59	3.89	0.77	1.19	/
66	3	Indian	M	50	3.7	0.93	1.41	X
67	3	Indian	M	51	4.59	1.3	1.4	/
68	3	White	M	50	5.99	3.25	1.53	X
69	3	Indian	M	69	3.92	0.78	1.45	X
70	3	White	F	64	5.23	1.46	1.06	X
71	3	Indian	M	60	4.22	1.41	1.58	X
72	3	White	M	53	4.87	2.75	0.9	X
73	3	White	M	44	6.45	2.78	1.24	X
74	3	Indian	F	66	5.28	2.28	1.05	X
75	3	Indian	M	52	3.97	1.18	1.31	/
76	3	Indian	M	64	3.55	0.99	1.2	X
77	3	Indian	M	48	5.56	1.7	1.11	X
78	3	Indian	M	50	5.69	1.64	1.25	X
79	3	White	M	71	4.58	1.44	0.98	X

Hypt	DM	Smoking	CAD	FH Hypt	FH DM	Pulse	SBP	DBP
/	/	/	/	/	/	100	124	81
/	/	X	/	/	/	80	113	69
/	X	X	/	X	/	80	150	90
X	X	X	/	X	/	110	91	57
/	/	X	/	/	/	90	145	91
X	/	X	/	/	/	80	115	76
/	/	X	/	/	/	120	142	97
/	X	/	X	X	/	65	145	90
X	X	/	/	X	/	68	109	80
X	X	/	/	X	X	90	108	67
/	X	X	X	X	X	60	76	50
/	/	X	/	X	/	115	170	90
X	X	X	X	X	X	92	102	69
/	/	X	/	/	/	95	157	57
X	X	X	X	X	X	90	109	69
X	X	/	X	X	X	82	142	96
X	/	/	X	X	/	70	143	83
/	/	X	X	/	/	96	128	71
/	/	/	/	/	/	75	155	95
/	X	/	/	/	/	85	130	90
X	/	/	/	/	/	90	56	30
X	/	/	/	/	/	70	115	72
/	X	/	/	/	/	72	111	72
/	/	X	/	/	/	85	129	90
X	X	X	/	/	/	88	130	88
/	X	/	X	X	X	60	165	103
X	X	/	X	X	X	110	111	84
/	/	X	/	/	/	96	138	96
/	/	/	X	/	/	110	150	90
X	X	/	X	X	X	90	130	92
/	/	/	/	X	/	89	157	94
X	X	/	X	X	X	72	120	69
/	X	/	X	X	X	106	116	79
X	X	/	/	X	X	72	135	85
/	/	/	/	X	/	80	122	70
/	/	X	X	/	/	96	137	79
/	X	/	X	X	X	96	130	91
X	X	X	X	X	X	90	118	74
/	X	X	X	X	X	58	123	75
X	X	X	X	/	/	74	143	59
/	X	/	/	/	/	65	96	59
/	/	/	/	X	/	98	142	79
/	/	X	/	/	/	70	168	82
X	X	/	/	X	X	73	137	84
/	/	X	/	/	/	95	151	92
/	/	/	/	/	/	71	152	82

/	/	X	/	/	/	87	107	71
/	X	X	X	X	X	91	143	98
/	/	/	X	/	/	65	133	95
X	X	/	X	X	X	87	97	64
/	X	X	/	X	X	77	129	76
/	X	X	X	X	X	94	96	61
/	/	X	X	X	X	71	131	70
X	X	/	/	X	X	98	120	62
/	/	X	/	/	/	97	159	86
/	/	/	/	/	/	84	125	57
/	/	/	/	/	/	70	157	72
X	X	/	/	/	/	63	102	62
/	/	/	/	/	/	88	120	84
/	/	/	/	X	/	75	150	47
X	X	/	X	X	X	59	125	80
/	X	/	/	/	/	94	95	61
X	X	X	X	X	X	130	138	75
/	X	X	/	/	/	80	152	91
/	X	/	X	X	X	71	99	59
X	X	/	/	/	/	93	89	60
/	/	/	/	X	X	71	151	91
/	/	X	X	/	/	74	127	79
X	X	/	X	X	/	86	127	75
/	X	X	X	X	X	61	183	93
/	X	/	X	X	X	99	156	106
/	X	/	X	X	X	96	153	103
X	/	X	X	X	X	65	115	72
/	/	X	/	/	/	82	124	84
X	X	/	X	X	X	73	101	73
X	/	X	X	X	/	84	110	72
X	X	/	/	/	/	77	118	76
/	X	/	/	/	/	87	148	99
/	/	X	/	/	/	95	180	110

PCK	T on adm	Glucose	TSH	FT4	ECG	ECHO	LDL
99	13937	7.9	0.7	23.5	Ant STEMI	No RMWA EF60%	4.9
73	6041	7.5	0.25	22.4	Ant STEMI	RMWA EF63%	1.7
66	> 50.000	5.7	0.31	12.8	Inf STEMI	RMWA EF42%	3.2
92	46940	6.4	0.08	22.8	Antrolatera	RMWA EF45%	1.3
1837	>50.000	5.6	0.21	16.2	Ant STEMI	RMWA EF42%	3.1
79	6031	11	0.13	16.5	Inf STEMI	No RMWA EF62%	0.4
629	11764	9.6	0.62	24.2	Antrosepta	RMWA EF30%	0.9
172	14344	6	0.31	15.4	Inf STEMI	RMWA EF52%	3.4
112	1089	5.8	0.27	13.9	Ant STEMI	No RMWA EF62%	3.9
3938	>50.000	7.3	0.32	13.6	Ant STEMI	RMWA EF38%	4.5
93	1665	6.1	0.19	12.5	Inf STEMI	RMWA EF35%	2
52	10499	16.9	4.01	22.8	Antrolatera	RMWA EF35%	2.7
69	24747	7.9	0.06	12.3	Ant STEMI	RMWA EF35%	3.4
285	345	7.2	0.29	18.2	Antrosepta	RMWA EF38%	2
258	7124	7.1	0.01	21	Inf STEMI	RMWA EF50%	1.2
264	27957	6.7	0.28	14.2	Antrosepta	RMWA EF43%	3.4
1216	40488	8.1	0.22	15.3	Inf STEMI	No RMWA EF57%	2.2
161	42824	11.1	0.28	13.8	Inf STEMI	RMWA EF57%	2.1
129	9509	7.8	0.21	13.6	Inf STEMI	RMWA EF53%	1.2
63	20988	5.6	0.32	13	Inf STEMI	RMWA EF52%	3.6
353	3066	6.4	0.18	23.4	Inf STEMI	RMWA EF42%	2.5
351	33138	32.6	1.49	23.4	Inf STEMI	RMWA EF61%	2.7
207	802	3.8	0.2	13.1	Inf STEMI	RMWA EF57%	2.5
96	>50.000	13.3	2.29	26.3	Ant STEMI	RMWA EF71%	3.1
222	47	4.6	0.15	12.5	Inf STEMI	RMWA EF42%	3.8
370	189	5.3	2.08	11.4	Antrosepta	RMWA EF57%	4.7
184	18	6.2	0.71	10.2	Ant STEMI	RMWA EF42%	3.3
181	7126	7.9	24.82	11.2	Inf STEMI	RMWA EF43%	3.2
619	2207	7.3	1.56	11.3	Antrosepta	RMWA EF50%	3.6
2365	>50.000	8.3	0.61	10.3	Ant STEMI	RMWA EF47%	3.7
158	8466	6.1	17.08	12.3	Inf STEMI	RMWA EF50%	3.6
580	28245	6.1	1.72	9.5	Ant STEMI	No RMWA EF57%	3.8
274	11500	6.7	0.64	10.2	Antrosepta	RMWA EF36%	1.6
188	27427	6.3	1.53	10.5	Ant STEMI	No RMWA EF61%	3.6
214	3165	10.2	7.02	11	Ant STEMI	RMWA EF44%	4.4
212	11743	10.4	3.77	11.4	Inf STEMI	RMWA EF62%	2.1
364	39368	5.2	4.13	11.3	Ant STEMI	RMWA EF32%	2
606	>50.000	5	0.48	10.8	Antrosepta	No RMWA EF30%	1.6
159	9378	12.2	0.36	10.4	Inf STEMI	RMWA EF48%	3.8
75	2856	5.7	2.26	10.5	Inf STEMI	No RMWA EF63%	4.1
1310	>50.000	5.9	9.08	7.9	Inf STEMI	RMWA EF50%	3.6
667	25963	14.7	2.47	9.6	Inf STEMI	RMWA EF59%	1.7
185	5619	7.1	8.34	12.2	Antrolatera	RMWA EF56%	2.9
2007	>50.000	6.7	2.15	10.9	Antrolatera	RMWA EF45%	2.3
213	4236	6.4	75.48	7.8	Ant STEMI	RMWA EF62%	2.7
323	17475	6.3	38.67	6.9	Inf STEMI	RMWA EF54%	2.7

111	6721	6.6	149.36	2.2	Ant STEMI	RMWA EF52%	4.2
94	5601	7	0.43	10.3	Inf STEMI	RMWA EF47%	3.7
281	12911	10.7	3.59	10	Antrolatera	No RMWA EF64%	1
303	3527	6.7	3.32	10.2	Inf STEMI	RMWA EF62%	2.9
1168	37633	5.5	11.93	11.5	Inf STEMI	RMWA EF57%	1.7
162	>50.000	4.6	6.99	14.5	Inf STEMI	RMWA EF43%	1.3
215	12444	8.7	1.74	16.6	Antrosepta	RMWA EF35%	2.5
1812	>50.000	4.3	3.48	12	Inf STEMI	RMWA EF34%	2.8
87	>50.000	7.3	2.68	14.1	Ant STEMI	RMWA EF45%	1.8
55	436	7.1	1.25	12	Antrosepta	RMWA EF60%	4.3
101	3375	9.6	0.49	13.2	Inf STEMI	RMWA EF40%	4.2
116	11206	5.2	1.43	12.8	Inf STEMI	RMWA EF56%	3.5
168	2859	5	2.43	14.2	Anteroinfe	RMWA EF45%	3
156	74	11.3	3.03	12.8	Ant STEMI	RMWA EF54%	5
766	>50.000	8.1	3.53	12.9	Inf STEMI	RMWA EF50%	4.5
143	36	6	2.72	13	Inf STEMI	RMWA EF35%	3.5
205	9905	6.2	2.38	14.3	Ant STEMI	RMWA EF44%	4.4
123	31	5.8	0.47	16.5	Ant STEMI	RMWA EF43%	2.5
119	10914	5.3	0.73	13.4	Ant STEMI	RMWA EF55%	2.3
195	8	5.6	2	12.8	Inf STEMI	RMWA EF52%	1.9
625	27	8.2	1.67	13.8	Inf STEMI	RMWA EF58%	2.6
258	15322	10.7	0.37	15.5	Inf STEMI	RMWA EF57%	3
175	22761	4.8	1.32	14	Ant STEMI	RMWA EF40%	2.1
132	17154	6.5	3.94	14.1	Inf STEMI	No RMWA EF65%	3.5
217	41444	6.7	0.4	13.6	Inf STEMI	RMWA EF38%	2
97	2238	6.2	3.04	12	Inf STEMI	RMWA EF42%	2.7
91	2556	9.6	1.29	16.1	Ant STEMI	RMWA EF57%	3.9
44	>50.000	11.2	1.89	16.6	Antrosepta	RMWA EF43%	3.2
220	<6	7	0.69	15.1	Antrolatera	RMWA EF35%	2.1
137	7099	7.6	0.8	16.4	Inf STEMI	RMWA EF62%	1.9
360	421	5.7	0.07	13.3	Inf STEMI	RMWA EF60%	3.7
77	1250	4.9	4.91	14.3	Antrolatera	RMWA EF53%	3.7
46	11519	5.2	2.13	14.9	Inf STEMI	RMWA EF50%	2.9