ASSOCIATION BETWEEN SERUM C-REACTIVE PROTEIN AND ECG DETERMINED LEFT VENTRICULAR HYPERTROPHY IN ADULT HYPERTENSIVE PATIENTS IN FEDERAL MEDICAL CENTRE IDO EKITI

A DISSERTATION SUBMITTED TO THE NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF FELLOWSHIP OF THE FACULTY OF INTERNAL MEDICINE.

(CARDIOLOGY SUB-SPECIALTY)

BY

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NOVEMBER, 2017
DECLARATION

It is hereby declared that this work is original unless otherwise acknowledged. The work has neither been presented to any other college for an award nor, has it been submitted elsewhere for publication.

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GLOSSARY

ATP III – ADULT TREATMENT PANEL III
BMI – BODY MASS INDEX
BP – BLOOD PRESSURE
CAD – CORONARY ARTERY DISEASE
CVD – CARDIOVASCULAR DISEASE
DBP – DIASTOLIC BLOOD PRESSURE
DM – DIABETES MELLITUS
ECG – ELECTROCARDIOGRAPHY/ELECTROCARDIOGRAM
ELISA – ENZYME LINKED IMMUNOSORBENT ASSAY
FBG – FASTING BLOOD GLUCOSE
GFR – GLOMERULAR FILTRATION RATE
HDL-c – HIGH DENSITY LIPOPROTEIN CHOLESTEROL
(Hs)CRP – (HIGH SENSITIVITY) C-REACTION PROTEIN
HT – SYSTEMIC HYPERTENSION
IFG – IMPAIRED FASTING GLUCOSE
IHD – ISCHAEMIC HEART DISEASE
LDL-c – LOW DENSITY LIPOPROTEIN CHOLESTEROL
LGA – LOCAL GOVERNMENT AREA
LVH – LEFT VENTRICULAR HYPERTROPHY
MAP – MEAN ARTERIAL PRESSURE
MOPC – MEDICAL OUT-PATIENT CLINIC
NCD – NON-COMMUNICABLE DISEASES
NO – NITRIC OXIDE
PP – PULSE PRESSURE
SBP – SYSTOLIC BLOOD PRESSURE
TC – TOTAL CHOLESTEROL
TG - TRIGLYCERIDE
TOD – TARGET ORGAN DAMAGE
WC – WAIST CIRCUMFERENCE
WHO – WORLD HEALTH ORGANISATION
WHR – WAIST HIP RATIO
ABSTRACT

Background: Morbidity and mortality associated with systemic hypertension (HT) has been linked to its complications, left ventricular hypertrophy (LVH) inclusive. Inflammation is one of the potential mechanisms or emerging epiphenomena being pushed forward to explain risks associated with LVH, as various studies have documented association between C-reactive protein (CRP), a marker of inflammation, and echocardiographic-LVH.

Aim: To determine association between serum CRP and ECG-LVH among adult patients with hypertension. There is paucity of data on CRP and no study in hypertensive Nigerians relating serum CRP to ECG-LVH.

Objectives: To determine prevalence of elevated CRP and ECG LVH. Also to determine association between elevated CRP and traditional cardiovascular risk factors among adults with HT.

Methods: It is a cross sectional descriptive hospital based study that consecutively recruited age- and sex- matched consenting adults ≥18years. Two hundred and fifty hypertensive adults and 250 normotensive apparently healthy controls participated in the study. Ethical clearance was obtained. Anthropometric, demographic data and relevant clinical details were obtained using proforma designed for this study. Blood pressure was measured and urinalysis was done. Blood was
obtained from participants after an overnight fast for lipid profile, fasting blood glucose and serum CRP (ELISA). A resting 12 lead ECG was done for all participants. Serum CRP ≥2.0mg/l was regarded to as elevated and LVH was determined by using Araoye code system and /or Sokolow-Lyon criteria.

Results: Prevalence of elevated CRP and ECG-LVH were 51.2% and 54.3% respectively, among patients with hypertension. Among controls elevated CRP and ECG-LVH were present in 38.8% and 43.1% respectively. Hypertensive adults had significantly higher CRP than controls, 3.02±1.26mg/l vs 1.95±0.22mg/l (p<0.001). There was significant association between elevated CRP and age, female gender, cigarette smoking, SBP, PP, MAP, TG, TC, LDL-c, low HDL-c, BMI, WC, WHR, QTc and ECG-LVH in univariate analysis. In binary logistic regression age, MAP, WC, WHR, QTc, TG, low HDL-c and ECG-LVH were determinants of elevated CRP among hypertensive adults.

Conclusion: ECG-LVH, among other CV risk factors, contributed to elevated CRP among hypertensive adults suggesting link between inflammation and LVH.
CHAPTER ONE
INTRODUCTION

Systemic hypertension (HT) is an important risk factor for cardiovascular diseases (CVD).\textsuperscript{1} CVD is the main cause of death in the industrialised countries. The limited information from large population studies on HT and CVD in developing countries suggests that a similar epidemic is inevitable if current trends go unchecked.\textsuperscript{2} Globally, the overall prevalence of HT in adults aged 25 years and over was about 40\% in 2008.\textsuperscript{3} According to World Health Organisation (WHO), the prevalence of HT is highest in Africa, where it is 46\% for both sexes combined.\textsuperscript{4} The lowest prevalence of HT is in the Americas at 35\% for both sexes. Men in this region had higher prevalence than women (39\% for men and 32\% for women). In all WHO regions, men have slightly higher prevalence of HT than women.\textsuperscript{4} HT is an important risk factor for CVD.\textsuperscript{1} The prevalence of HT in Nigeria varies across the country (8\%-46.4\%) depending on study target population and cut-off value used in defining HT.\textsuperscript{5} It is the most prevalent non-communicable chronic disease (NCD) in Nigeria, with few available population studies putting the prevalence at about 25\% in the adult population.\textsuperscript{6, 7} HT is a major public health problem. Due to paucity of recent national population data, the actual burden of HT in Nigeria might be underestimated.\textsuperscript{8}
Primary HT is characterized by increased peripheral vascular resistance to blood flow and this occurs largely in resistance arteries. Resistance arteries play important role in the development of HT and may also contribute to its complications.\textsuperscript{9,10} Vascular radius of resistance arteries is one of the important determinants of arterial pressure. Resistance to flow varies inversely with the fourth power of the radius, and consequently small decreases in the lumen of the small arteries significantly increase resistance. In HT, resistance arteries undergo vascular remodelling (reduced lumen with increased media width) that may be structural, mechanical or functional\textsuperscript{11}, thus increasing the resistance of small arteries and arterioles. It has been shown that inflammation, apoptosis and vascular fibrosis contribute to vascular remodelling.\textsuperscript{11}

HT in itself may induce a pro-inflammatory response and other associated risk factors also have inflammatory component. Atherosclerosis has a well recognised inflammatory component that plays major role in development of cardiovascular events.\textsuperscript{12} Vascular inflammation in atherosclerosis is diffuse and systemic. The increasing recognition of inflammation as an important component of atherogenesis provides the plausibility for the potential use of inflammation markers such as c-reactive protein (CRP), interleukin-6 (IL-6) and serum amyloid A (SAA)
as indicators for atherogenesis or as a predictor of atherosclerosis/ or coronary artery disease (CAD) complications.\textsuperscript{13, 14}

These inflammation markers are not specific as their levels may rise from other causes of systemic inflammation (such as with connective tissue disease, local infection like gingivitis or prostatitis), studies have shown a relationship between high levels of these markers and high incidence of CAD and sudden death. Chronic inflammation has also been associated with cardiovascular risk factors such as obesity and insulin resistance.\textsuperscript{15, 16}

Patients with hypertensive target organ damage (TOD) are at particularly high risk for the development of cardiovascular and cerebrovascular events.\textsuperscript{17} Left ventricular hypertrophy (LVH), an hypertensive TOD, is strongly predictive of future cardiovascular morbidity and mortality.\textsuperscript{18} Morbidity and mortality associated with HT has been linked to its complications which include LVH (electrocardiographic or echocardiographic).\textsuperscript{18} Myocytic hypertrophy alone could not fully explain risks associated with LVH. Inflammation is one of the potential mechanisms or epiphenomena being pushed forward to fully understand risks associated with LVH.\textsuperscript{19} CRP is a marker of inflammation and has been studied extensively. It is a predictor of untoward cardiovascular prognosis beyond traditional risk factors in different populations.\textsuperscript{20} CRP
level is generally elevated in patients with HT. High CRP may even precede and predict the development of arterial HT.\textsuperscript{21, 22} Despite availability and use of antihypertensive drugs that reduce left ventricular mass in patients with HT, cardiovascular morbidity and mortality associated with LVH is still disproportionately high.\textsuperscript{19} Understanding the mechanism(s) that underlies the process of poor cardiovascular morbidity and mortality pertaining to LVH will assist in its evaluation and or treatment. Therefore, understanding the relationships between LVH and inflammation such as CRP is clinically and prognostically important, and may provide additional basis for assessing severity of HT.

There is paucity of data on CRP in hypertensive Nigerians and, to my knowledge, there is no study in hypertensive Nigerians relating CRP and TOD (LVH), hence, the need of this research. This research study provided valuable scientific information that will have clinical relevance in the management of HT in Nigeria and sub-Saharan Africa.

\textbf{AIM}

To determine the association between ECG determined LVH and elevated CRP in adult Nigerians with systemic HT attending medical outpatient
OBJECTIVES

1. To determine the prevalence and pattern of elevated CRP (≥2.0mg/l) and ECG-LVH in adult Nigerians with systemic HT.

2. To determine the association between elevated CRP and demographic and clinical variables [such as age, gender, cigarette smoking, family history of HT, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), mean arterial pressure (MAP)].

3. To determine the association between elevated CRP and other cardiovascular risk factors [such as obesity, total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), triglycerides (TG), low density lipoprotein cholesterol (LDL-c) and diabetes mellitus (DM)].

4. To determine the association between elevated CRP, LVH and other ECG abnormalities such as QTc interval.

RATIONALE FOR THE STUDY
It has been postulated that developing countries are experiencing an epidemiological transition from communicable to NCD due to adoption of Western lifestyle and other stress of urbanization. There is significant dearth of information about the prevalence of elevated CRP (emerging cardiovascular risk factor for CVD) in adult hypertensive Nigerians living in rural community. Similarly, the relationship between CRP and LVH in the adult hypertensive Nigerian population has not been studied. Available studies on CRP in adult Nigerians were done in urban settings and/or in subjects with type 2 DM, stroke and CKD. Using landmark trials (JUPITER and EURIKA) as guide, CRP ≥2mg/l was defined as being elevated. ECG was considered because it is cheaper and readily available in most secondary/tertiary hospitals. Echocardiogram machine availability is limited to tertiary hospitals and may not be functional always.

This study was designed to answer the question about prevalence of elevated CRP in adult hypertensive Nigerians, to determine relationship between elevated CRP and LVH in adult hypertensive specifically in a rural setting of the south-western part of the country.

CHAPTER TWO
LITERATURE REVIEW

EPIDEMIOLOGY OF SYSTEMIC HYPERTENSION

Globally there is increase in the burden of HT, more in the low and middle income countries, and this has been attributed to adoption of western lifestyle, with its attending increase in incidence of obesity, and population aging. Worldwide there is variation in the prevalence of HT. For instance, according to WHO, the prevalence of HT in Africa is 46% and 35% in America for both gender combined. Similarly, the prevalence HT varies across the continent. In South Africa prevalence of HT is 26.2% and 32.7% in Algeria.

In a study published recently, the prevalence of HT in Nigeria also varies across the country (8%-46.4%) depending on study target population and cut-off value used in defining HT. This review study considered hospital and community-based studies. The entire cross sectional studies were done in 12 out of 36 states of Nigeria and majority of the studies were done in the south-western part of the country. In all the studies it seems to be higher in urban than rural areas. Adedoyin et al showed that 36.6% and 13.35% had HT in a semi urban community sample of 2,097 adults using blood pressure (BP) cut-off value of 140/90mmHg and 160/95mmHg respectively.
In a recently conducted rural community-based study in south-western part of Nigeria by Asekun-Olarinmoye et al, prevalence of HT was 13.6%. Also a study conducted in Niger Delta region found the prevalence of HT to be 16% and 12% for males and females respectively. Akinkungbe put the prevalence in Nigeria between 15-20%. A community based study conducted by Oladapo et al to assess cardio metabolic risk factors among a rural Yoruba south-western Nigerian population obtained prevalence of 20.8% and a recent community-based study of rural and semi urban population in Enugu, Nigeria put the prevalence of HT in Nigeria at 32.8%

Projections from WHO data showed that by 2030, prevalence of HT will increase by 7.2% from 2013 estimates. Recent meta-analysis of estimate of prevalence of HT in Nigeria put the overall prevalence between 24.6% - 31.9%, gender prevalence of 29.5% and 25% for male and female respectively. It should be noted that few hospital based studies were reviewed in this analysis.

**SYSTEMIC HYPERTENSION AND CARDIOVASCULAR DISEASE**

Systemic HT is characterized by increased peripheral vascular resistance to blood flow. This resistance results mostly from energy dissipation in
small arteries and arterioles. Resistance arteries may play an important role in the development and complications of HT.\textsuperscript{36} Systemic HT is a major risk factor for developing ischemic heart disease, stroke, heart failure, aortic dissection and peripheral artery disease. Cardiovascular risk increases with the presence of TOD caused by HT.\textsuperscript{37} The TOD may be subclinical or clinical. The subclinical TOD includes LVH, ultrasound evidence of arterial wall thickening or atherosclerotic plaque, estimated glomerular filtration rate (eGFR) less than or equal to 60ml/min/1.73m\textsuperscript{2} and microalbuminuria (MA). Clinical TOD includes stroke, chronic kidney disease (CKD), hypertensive retinopathy and peripheral vascular disease (PVD).\textsuperscript{35} The additive effect of TOD and presence of other cardiovascular risk factors thus make laboratory testing for the determination of blood electrolytes, fasting plasma glucose, and serum creatinine levels (with eGFR), fasting lipid panel, spot urinalysis and a resting 12-lead electrocardiogram (ECG) minimal requirements for evaluating patients with HT.\textsuperscript{35}
The ability of resistance vessels to undergo changes in their structure without changing their volume is called remodelling. The essence of vascular remodelling is adaptive initially to reduce vascular wall stress from HT. This eventually becomes maladaptive, compromise organ function, contribute to complications and maintain HT. In HT, vascular remodelling contributes to increased peripheral resistance, which affects both development and complications of HT.

Smooth muscle cell growth is the mechanism classically associated with vascular remodelling, it has increasingly been appreciated that apoptosis, inflammation, and vascular fibrosis are dynamic processes that also influence the degree of remodelling. Inflammation may be stimulated by Angiotensin II, endothelin I or by increased oxidative stress in the vascular wall thereby eliciting growth-factor-mediated extracellular matrix remodelling. Induction of changes in the anchorage of cells to extracellular fibrillar components may change cellular attachment, modifying vessel wall architecture and may promote abnormal intercellular transduction of extracellular input to the cytoskeleton of smooth muscle cells, contributing to smooth muscle cell restructuring.

Chronic vasoconstriction may result in an inwardly remodelled blood vessel. The contracted vessel structure becomes embedded in a remodelled extracellular matrix; further promoting rearrangement of
smooth muscle cells around a smaller lumen.\textsuperscript{38} Growth factors, apoptosis, inflammation, fibrosis and chronic vasoconstriction of blood vessels thus may all contribute to vascular remodelling.

\textbf{LEFT VENTRICULAR HYPERTROPHY AND SYSTEMIC HYPERTENSION}

LVH is perhaps the most important indicator of prognosis in hypertensive patients. It is often considered the “hemoglobin A1c of blood pressure” because it objectively measures both the severity and the duration of elevated blood pressure.\textsuperscript{18} Structural alteration in hypertensive heart is more than myocytic hypertrophy. It comprises intramyocardial coronary arteries medial hypertrophy and cardiac fibrosis from collagen deposition. These result from pressure overload and neurohormonal activation that contribute to HT. The hormones (Angiotensin II, aldosterone, norepinephrine and prorenin) promote pressure overload, cardiac fibrosis and also have inflammatory effects.\textsuperscript{39}

The prevalence of LVH among hypertensive varies depending on the population and the diagnostic tool applied. Among the Caucasians,
prevalence of echocardiographic (ECHO) LVH ranges between 20%-50% from various clinical studies. Katibi et al in a study in Ilorin, a north-central city in Nigeria, among hypertensive Nigerians reported a prevalence rate of 35% for Echo LVH. Adebiyi et al in Ibadan reported prevalence of ECHO LVH ranging between 30.9–56.0%. ECHO LVH is diagnosed based on cut-off values developed from population-based studies in which left ventricular mass (LVM) is indexed to body surface area (BSA), height or height raised to the power of 2.7, the allometric growth rate of the heart.

On the contrary, prevalence rates for ECG LVH among hypertensive range between 3.5% and 32% in various published literature among Caucasians. The prevalence rate for ECG LVH would depend on the ECG diagnostic criteria used. The popular ECG criteria use among the Whites is Sokolow- Lyon's criteria. Araoye et al in a study of 288 hypertensive Nigerians reported a prevalence rate of 70.5% using Sokolow-Lyons criteria. Katibi et al reported prevalence rate of 71.7%, 56.7% and 20% applying Sokolow-Lyon's, Araoye's and Estes' criteria among hypertensive Nigerians for ECG LVH respectively.

Ogunlade et al in a study of 90 subjects in Ife found lower prevalence of LVH by voltage criteria; 45.6%, 42.2%, 34.4%, 13.3% by Sokolow–Lyon, Araoye code system, Cornell, and Gubner–Ungerleider criteria,
respectively. Ogunlade et al in their study which compared four ECG criteria, reported that Araoye code system, Cornell and Sokolow–Lyon criteria compared favourably well with echocardiography and may be used in the initial assessment of LVH in adult hypertensive subjects. However, they concluded that combination of any of the three criteria with Gubner–Ungerleider criterion will be more clinically useful. Several explanations have been put forward for the remarkably higher prevalence rate of ECG LVH among hypertensive Blacks than their White counterparts. The most prominent of them all arise from the observation that the Blacks generate higher voltages than the whites.

**Pathophysiology of Left Ventricular Hypertrophy**

When the heart encounters a hemodynamic stress, compensation occurs through the following mechanisms: (1) the Frank-Starling mechanism to increase formation of cross-bridge; (2) increased muscle mass to carry the extra load; and (3) activation neuro-hormonal mechanisms to increase contractility. The capability of first mechanism is very limited while the third mechanism has a deleterious consequence on long term. Thus, augmenting muscle mass takes a pivotal position in the compensation for hemodynamic overload. Hypertrophy of existing myocytes rather than
hyperplasia result into increase in mass, because myocytes become terminally differentiated three months after birth. Pressure overload in conditions such as HT, causes parallel addition of sarcomeres which causes an increase in myocyte width, which in turn increases wall thickness. This remodelling results in concentric hypertrophy (increase in ratio of wall thickness/chamber dimension).  

In La Place’s Law, the force or load on any area of the myocardium is as follows: (pressure × radius) / (2×wall thickness). Thus, an increase in pressure can be offset by an increase in wall thickness. Because systolic stress (afterload) is a major determinant of ejection performance, the normalization of systolic stress helps maintain a normal ejection fraction even when needing to generate high levels of systolic pressure. Volume overload in conditions such as chronic aortic regurgitation or mitral regurgitation, causes lengthening of myocyte through sarcomere replication in series and an increase in ventricular volume. This pattern of eccentric hypertrophy (cavity dilatation with a decrease in ratio of wall thickness/chamber dimension) is also initially compensatory, such that the heart can meet the demand to sustain a high stroke volume. However, chronic hypertrophy may be deleterious because it increases the risk for the development of heart failure and premature death.
Prognostic Implication of Left Ventricular Hypertrophy and Electrocardiogram

LVH is associated both epidemiologically and pathophysiologically with intimal hyperplasia of the epicardial coronary arteries, increased coronary vascular resistance, increased severity and frequency of ventricular dysrhythmias, decreased flow reserve, and reduced diastolic relaxation.\textsuperscript{18} Framingham Heart Study showed that ECG evidence of LVH has been associated with an approximately three-fold increase in the incidence of cardiovascular events when compared with those without it.\textsuperscript{18} In a variety of reports, LVH has been the most influential of all traditional cardiovascular risk factors in predicting not only death or myocardial infarction, but also stroke, heart failure, and other cardiovascular endpoints.\textsuperscript{50} LVH is a prominent feature of evolving or manifest congestive heart failure. Approximately 20\% of congestive heart failure cases had antecedent signs of LVH in the ECG and 60–70\% according to the more sensitive echocardiography.\textsuperscript{18} The most contentious aspect of LVH lies in its treatment and possible reversal. Short-term clinical studies that evaluated changes in LVH show different conclusions about which class of antihypertensive drug best regresses LVH. The LIFE (Losartan Intervention for Endpoint Reduction in HT) study is currently the only
outcome study to show a correlation between reduction in LVH and prevention of cardiovascular events.\textsuperscript{18}

All antihypertensive drugs will reduce ventricular mass to more or lesser degree but without proportional reduction of risk. Because LVH is unlikely to regress without reducing blood pressure, most authorities recommend allocating resources to blood pressure control, rather than on serial echocardiograms, to see whether the LV mass index is returning to normal during treatment.\textsuperscript{19} The risk associated with LVH cannot be fully explained by myocytic hypertrophy, some of the identified epiphenomenal risk associated with LVH development are fibrosis, inflammatory factors, apoptosis and ischemia.\textsuperscript{19}

Abnormalities found on a resting 12-lead ECG have been validated by several epidemiological studies to predict occurrence of cardiovascular mortality.\textsuperscript{51,52} Specific ECG findings that have been linked to cardiovascular risk in patients with systemic HT include LVH (especially when accompanied by repolarisation changes), QRS prolongation, ST-segment depression, T-wave inversion, and pathological Q waves.\textsuperscript{51} The resting 12-lead ECG may also reveal existence of other CVD, particularly cardiac arrhythmias, by documenting extra systoles, atria fibrillation and ventricular pre-excitation or prolonged QT interval.\textsuperscript{51}
To reduce the effect of the grave complications from HT, primary preventive measures targeting population at risk should be implemented. For instance a reduction of blood pressure by a little amount leads to significant decline in mortality and morbidity. That is, a 5 mmHg reduction of SBP would result in a 14% overall reduction in mortality due to stroke, a 9% reduction in mortality due to CAD, and a 7% decrease in all-cause mortality.

C-REACTIVE PROTEIN AND SYSTEMIC HYPERTENSION
CRP, a 115-kDa pentamer, produced almost exclusively by hepatic cells as part of the non-specific acute-phase response to tissue damage, infection, inflammation and malignant neoplasia. CRP has a long plasma half-life. It is a mediator and a marker of atherothrombotic disease. CRP (marker of chronic low-grade systemic inflammation) is an emerging cardiovascular risk factor and can predicts negative cardiovascular prognosis beyond traditional risk factors in different populations. Its levels are generally elevated in patients with HT, and high CRP may even precede and predict the development of arterial HT. Several epidemiological studies have shown that the plasma CRP level is a powerful predictor of ischemic cardiovascular events (stroke, PVD,
sudden cardiac death and myocardial infarction) in patients with stable or unstable angina, and even among apparently healthy subjects.\textsuperscript{55, 56}

The pathophysiological importance of CRP is far from being fully understood and whether CRP is a risk factor for or mediator of vascular disease remains a subject of ongoing debate. It is likely that CRP is more than an inflammatory marker of increased CVD risk. Deposits of CRP have been demonstrated by immunohistochemical staining in atherosclerotic plaques where it co-localizes with the terminal complement complex and appears to be involved in foam cell formation.\textsuperscript{57}

CRP promotes monocyte chemotaxis and facilitates LDL-c uptake by macrophages in vitro.\textsuperscript{57, 58} In vascular smooth muscle cells (VSMCs), CRP has been shown to increase angiotensin type 1 receptor number, angiotensin type 1 receptor-mediated reactive oxygen species (ROS) formation and activation of the stress-activated protein kinases p38 and c-jun N-terminal kinase (JNK).\textsuperscript{59, 60}

In endothelial cells, CRP facilitates the release of plasminogen activator inhibitor-1 (PAI-1)\textsuperscript{61} and endothelin-1.\textsuperscript{62} CRP increases the expression of cell adhesion molecules\textsuperscript{63, 64} and reduces nitric oxide (NO) bioavailability.\textsuperscript{64, 65} In particular, CRP inhibited endothelium dependent NO-mediated dilatation in coronary arterioles by producing superoxide from NAD(P)H oxidase via p38 kinase activation.\textsuperscript{66}
CRP may possess anti-inflammatory actions as it inhibits neutrophil activation and adhesion. Accordingly, it has been proposed that distinct isoforms of CRP are formed during inflammation. CRP could dissociate into individual subunits that undergo conformational changes. The resulting CRP isoforms referred to as modified or monomeric CRP, express several neo-epitopes and display properties distinct from those of native CRP. Monomeric CRP antigens were detected in inflamed tissues and in the wall of human normal blood vessels. Monomeric CRP displays potent prothrombotic activities under low levels of shear, whereas native CRP inhibits platelet activation, prevents neutrophil–endothelial-cell adhesion and neutrophil–platelet adhesion. Thus monomeric CRP rather than native CRP may precipitate acute coronary syndromes.

Thus whether CRP is marker or mediator of cardiovascular risk and disease is still a matter of controversy, as is its power as a marker of ischemic events. This does not imply that human CRP may not be a pro-inflammatory molecule under certain circumstances, as well as a marker to consider in medium-risk cardiovascular patients. Abundant laboratory and experimental evidence demonstrate that atherothrombosis, is a disease of lipid accumulation and also represents a chronic inflammatory process.
In terms of clinical application, elevated CRP level seems to be a stronger predictor of cardiovascular events than LDL-c. It adds prognostic information at all levels of calculated Framingham Risk and at all levels of the metabolic syndrome.\(^{72}\) Using widely available high-sensitivity assays, CRP levels of <1, 1 to 3, and >3 mg/l correspond to low-, moderate-, and high-risk groups for future cardiovascular events.\(^{73}\) Individuals with LDL-c below 130 mg/dl who have CRP levels >3 mg/l represent a high-risk group often missed in clinical practice.\(^{74}\) A large prospective JUPITER trial (Justification for the use of statins in primary prevention trial evaluating rosuvastatin) defined high sensitivity CRP ≥2mg/L as being elevated.\(^{75}\) The trial demonstrated significantly less cardiovascular risk for patients with hsCRP < 2.0mg/l and that aggressive treatment strategies may be warranted in patients with hsCRP ≥ 2.0mg/l.\(^{75}\) The addition of CRP to standard cholesterol evaluation may thus provide a simple and inexpensive method to improve global risk prediction and compliance with preventive approaches.\(^{74}\)

To date, over a dozen prospective epidemiological studies carried out among individuals with no prior history of CVD demonstrate that a single, non-fasting measure of CRP is a strong predictor of future vascular events.\(^{72}\) The relationship between a patient’s baseline level of CRP and future vascular risk has been consistent in studies from the United States
and Europe. In most cases it has proven independent of age, smoking, cholesterol levels, blood pressure, and DM (the major “traditional” risk factors evaluated in daily practice). These effects are present among women as well as men, among the elderly as well as those in middle age, among smokers and non-smokers, and among those with and without DM. CRP levels have long-term predictive value. In one recent study, CRP was a strong predictor of risk even 20 years after initial blood samples were obtained.\textsuperscript{76} Iwashima \textit{et al} in Japan concluded in a study of 629 asymptomatic adults with primary HT that the CRP level is independently associated with LV mass index.\textsuperscript{77} After correcting for the effects of antilipemic and antihypertensive medications, increasing levels of CRP were still predictors of LV mass index. In multivariate analysis including age, BMI, diabetes, duration of HT, systolic blood pressure, diastolic blood pressure, heart rate, total cholesterol, triglycerides, HDL-c and smoking status, CRP category independently associated with LV mass index both in male and female. In follow up study patients with higher CRP level and LV mass index had more CVD.\textsuperscript{77} It is important to note that apparently healthy individuals were not recruited into the study and their CRP level is not known. CRP categories of <1mg/L, 1-2mg/L and ≥2mg/L were used in determining association between CRP and ECHO LVH. The study
concluded that measurement of CRP may provide clinically important prognostic information to supplement. LVH.\textsuperscript{77}

In a recent cross-sectional study conducted by Baba \textit{et al} in Ile Ife, Nigeria among apparently healthy adults, CRP was found to be higher in female compared to male but not statistically significant.\textsuperscript{25} Idemudia \textit{et al} found that adult hypertensive Nigerians have significantly higher CRP than their normotensive counterparts, which correlates with CAD risk.\textsuperscript{26} However, very few normotensive adults participated in the study. This is similar to what Joseph C.M found among adult hypertensive and hypertensive-diabetic patients in Eku Delta State, Nigeria.\textsuperscript{27}
CHAPTER THREE

METHODOLOGY

Study Area: The study was conducted in the Medical Outpatient Clinic (MOPC) of the FMC, Ido- Ekiti. It is an agrarian rural community situated in Ido-Osi Local Government Area (LGA). The MOPC runs daily under the supervision of consultant physicians with the assistance of resident doctors.

Study Design: The study was a descriptive cross sectional hospital-based study of serum CRP and LVH in adult patients with systemic HT who attended the MOPC during the study period (April 2015 and June 2016).

Study Population: All consenting patients with systemic HT that met the inclusion and exclusion criteria for the study attending MOPC of the FMC, Ido- Ekiti during study period were recruited. Records of patients
recruited were assigned numbers to avoid double recruitment during subsequent clinic visits.

**Inclusion criteria:**

1. Patients aged 18 years and above.
2. Patients with systemic HT or on antihypertensive medications attending MOPC.
3. Patients who gave informed consent.

**Exclusion criteria:**

1. Lack of informed consent.
4. Patients with clinical and/or laboratory evidence of infection and malignancy.
5. Patients with symptoms of heart failure, chronic kidney disease or on hemodialysis for CKD.

**Control Group:**

Age- and sex-matched normotensive Nigerians, who were apparently healthy with blood pressure less than 140/90mmHg documented on each of three successive determinations, attending the hospital for various reasons/complaints or health check-up. This included staff of the hospital.

**Inclusion Criteria**
1. Aged 18 years and above.
2. Individuals who gave informed consent.

**Exclusion Criteria:**
1. Lack of informed consent.
2. Pregnancy.
3. Individuals with clinical and/or laboratory evidence of infection.
4. Individuals with symptoms of heart failure and history suggestive of chronic kidney disease.
5. Individuals with blood pressure ≥ 140/90mmHg or on antihypertensive medications.
6. Individuals with fasting blood glucose ≥ 6.1mmol/L or on antidiabetic medications.

**Sample Size:** The sample size was determined using the following formula\(^7\)

\[
n = \left[\frac{z^2p(1 - p)}{d^2}\right]
\]

Where \(n\) = the desired sample size.
\(z\) = 1.96 at 95% confidence interval obtained from standard statistical table of normal distribution.
\(p\) = estimated prevalence of HT.
\(d\) = degree of accuracy desired usually set at ± 0.05
From the various studies\textsuperscript{29,30,32,33} on prevalence of HT in southwest Nigeria as previously mentioned an estimated prevalence of 20\% was used for sample size calculation.

Based on the above information the sample size for the study is:

\[ n = 1.96^2 \times 0.2(1-0.2) \div 0.05^2 \]

\[ n = 245.8 \]

The sample size was approximated to 250. Therefore 250 patients and 250 normotensive healthy adults matched for age and sex were recruited for the study.

\textbf{Data Collection}: Pre-tested semi-structured questionnaire (Appendix I) drafted in English language was administered by the researcher during the clinic visits on consenting patients (Appendix II) to obtain relevant information. The questionnaire featured the following;

Protocol 1: Clinical Evaluation

Detailed biodata and socio-economic parameters were obtained from each participant. Also, in-depth history was obtained particularly on symptoms of infection and cardiovascular risk factors such as cigarette smoking, DM and family history of CVD.

Anthropometric Measurement

Anthropometric measurements including height, weight, waist circumference (WC) and hip circumference (HC) were obtained from
each participant. The height was measured without shoes to the nearest centimeter using a graduated height scale (SECA 217 stadiometer) with the participant in erect position and the feet together. Weight was measured to the nearest 0.1 kg on a standard scale (HARSON H89) with the participant wearing light outdoor clothing and no shoes.

Body mass index (BMI) was calculated from weight (in kg) divided by a square of the height (in metres).

\[ \text{BMI (kg/m}^2) = \frac{\text{Weight (Kg)}}{(\text{Height})^2 (m)} \]

BMI was classified into the following classes:

- Underweight: \( \text{BMI} < 18.5 \)
- Normal: \( \text{BMI} 18.5 - 24.9 \)
- Overweight: \( \text{BMI} 25 - 29.9 \)
- Obese: \( \text{BMI} \geq 30 \)

Waist circumference was measured midway between the iliac crest and the lower-most margins of the ribs with bare belly (at the level of the umbilicus), at the end of normal expiration. Hip girth was measured at the intertrochanteric level according to the WHO guidelines.\(^8\) An inelastic tape was used. Abdominal obesity was defined as WC of \( \geq 94 \) cm in men and \( \geq 80 \) cm in women.\(^8\) Waist hip ratio (WHR) > 0.85 for females and > 0.90 for males were considered abnormal.\(^8\)
Blood Pressure Measurement

Blood pressure (BP) were measured, after 5 minutes rest, on the arm of the seated participants with a mercury-column sphygmomanometer (ACCOSON, Dekamet MK. 3) and an appropriately sized cuff; the average of two obtained measures constituted the examination BP. Participants were allowed 5-10 minutes rest between the measurements. SBP and DBP were determined using phase I and V Korotkoff sounds respectively. Systemic HT was defined as SBP equal to or greater than 140mmHg and/or DBP equal to or greater than 90mmHg or being on pharmacological treatment for HT. The different grades of HT were defined as follows: mild (140/90mmHg to 159/99mmHg), moderate (160/100 to 179/109mmHg), and severe hypertension (≥180/110mmHg).

Pulse pressure (PP) ≥ 50mmHg was regarded as abnormal or elevated while mean arterial pressure (MAP) ≥ 110mmHg was regarded as elevated.

Protocol 2: Laboratory Evaluation

10mls of fasting blood was collected from each consenting participant using aseptic procedure for venipuncture. Samples were dispensed into
well labelled sample bottles (name, test and date), 3mls into sodium fluoride bottle for FPG; 3mls into plain bottle for hsCRP and 4mls into lithium heparin bottle for fasting lipid profile.

Samples were centrifuged to separate plasma/serum from cells same day (not later than 7hrs after collection) at 3000 revs/min for 15 minutes. Serum/plasma samples were pipetted into separate well-labelled plain bottles and stored in deep freezer at -20°C at department of Chemical Pathology, FMC Ido –Ekiti. Samples were analysed in batches of 50-96 every 30days to ensure integrity of samples and limit variations from repeated opening of sensitive kits.

Blood Glucose

Obtained samples were analysed using Randox Laboratories Ltd glucose (GLUC-PAP) kits. The diagnosis of DM was made if participants have FBG ≥7.0 mmol/l in the presence of symptoms or reported a history of DM or use of glucose lowering drugs. Impaired fasting glycaemia (IFG) was defined as FBG 6.1 to 6.9mmol/L.

Serum Lipids

Lipid measurements were performed on SpectroScan 60DV automatic analyzer. LDL-c values(mmol/l) were calculated by Friedwald formula [TC] – [HDL-c] – TG/2.2. TC and TG concentrations were determined
enzymatically using cholesterol oxidase (CHOD) – phenol+aminoantipyrine (PAP) and lipase/glycerol-3-phosphate oxidase (GPO)/ phenol+ 4-aminophenazone (PAP) methods respectively. The HDL-c concentration was measured by phosphotungistic acid and magnesium chloride (MgCl₂) precipitation approach. The reagents were obtained from Randox Laboratories Ltd. Participants were classified as follows:

TC: mg/dl (mmol/l)
Desirable: < 200 (5.17)
High: ≥ 200 (5.17)

HDL-c, mg/dl (mmol/l)
Low: Male <40 (1.03), female < 50 (1.3)
High: ≥60 (1.55)

LDL-c, mg/dl (mmol/l)
Optimal: <100 (2.57)
Near optimal/ above optimal: 100-129 (2.57- 3.33)
High: ≥ 130 (3.36)

TG mg/dl (mmol/l)
Normal: <150 (1.69)
Borderline High: ≥ 150 (1.69)
Protocol 3: Resting 12-Lead Electrocardiography

A resting 12-lead ECG was recorded on all the participants in this study. American Heart Association guideline on ECG\textsuperscript{87,88} was followed and a standard machine (Welch Allyn Schiller AT-Z CH-6341) was used. Recordings were taken after allowing some minutes of rest with tracing running on paper speed of 25mm/sec. ECG interpretation was done by the researcher. The following variables were evaluated on the ECG.

a. Heart rate (using Lead II as rhythm strip)

b. R wave amplitude (Leads I, V\textsubscript{5}, V\textsubscript{6}).

c. S wave amplitude (Leads V\textsubscript{1}, V\textsubscript{2})

d. QRS duration (Lead II).

e. Electrical axis of the QRS complex.

f. ST-segment and T-wave morphology.

g. Q waves amplitude/duration.

h. QT\textsubscript{c} interval (Lead II).

i. Presence and type of arrhythmia

The following were regarded as abnormal:

I. Heart rate greater than 100 beats per minute or less than 60 beats per minute.

II. QRS axis greater than -30\textdegree or greater than +90\textdegree
III. LVH (Appendix III): (A) Araoye’s criteria: R(I) > 1.2mV, flat or inverted T wave (strain pattern) in V5 or V6, SV2+RV6 > 4.0mV in males, >3.5 mV in females.89,90 (B) Sokolow-Lyon criteria: SV1 + RV5 OR V6 > 3.5mV.91 However, these criteria were not applied in patients with bundle branch block and subsequently not included during data analysis. Bundle branch block was present in 5 hypertensive adults and 2 controls.

IV. QTc greater than 0.43 in males and greater than 0.44 in females.92,93

V. Q wave duration greater than 0.04sec.

VI. QRS duration greater than 120msec.

VII. Flat or inverted T wave in V5 or V6.

VIII. Heart block of any type.

Appendix III contain examples of ECG tracing among the participants.

Protocol 4: CRP Measurement

High sensitivity CRP (hs-CRP) was measured using Monobind Inc, (Lake Forest, USA) high sensitivity enzyme-linked immunosorbent assay kit. This assay is based on double-antibody sandwich technique. The kit
contained a precoated plate with 96 wells. Monoclonal antibody specific for human CRP (mouse anti-human CRP) in each well bind to any human CRP introduced into the well. CRP calibrators (supplied with kit) and samples were incubated on the precoated wells. Horseradish peroxide-labelled monoclonal was added to detect any captured CRP. The two antibodies (horseradish and mouse) bind to separate locations on the CRP molecule, thereby forming a sandwich.

Enzymatic activity of horseradish peroxidase was determined by adding chromogenic substrate, tetramethylbenzidine. The reaction was stopped with addition of hydrochloric acid after formation of product with distinct yellow colour and absorbance was measured at 450nm using microplate reader. Absorbances of the supplied CRP calibrators with their known CRP concentration were used to draw a best-fit curve (figure 1). CRP concentration of the samples were determined on the horizontal axis by finding intersect point on the curve from absorbance value on vertical axis of the graph. For example, absorbance value of 2.00 intersected the curve at 6mg/l on CRP concentration axis (horizontal).
Figure 1: Best-fit curve of absorbance versus CRP concentration (mg/l).
Data Analysis

Statistical analysis was done using the Personal Computer (PC). Statistical Package for Social Sciences (SPSS Inc, Chicago, IL) version 17. Results were expressed as either mean values (standard deviation) or percentages. Analyses for statistical significance and association between variables were determined using student’s $t$-test for continuous variables or chi-square analysis for categorical variables.

Binary logistic regression analysis was performed between elevated serum CRP and variables that demonstrated significant association at univariate analysis. The effects of the variables on elevated CRP were measured by adjusted odd ratio. Age, BMI, SBP, PP, TC, TG, LDL-c, HDL-c and QTc were analysed as continuous variables. Gender, cigarette smoking, MAP, WC, WHR and LVH were analysed as categorical variable. Female, non-smoker, normal MAP, normal WC, normal WHR and absence of LVH were used as reference. The level of significance was set at 5%.

COST: The cost of the study was borne by the researcher and no financial aid from the institution.
CHAPTER FOUR
RESULTS
A total of 500 participants were included in this study, consisting of 250 hypertensive patients and 250 apparently healthy controls. The participants were matched for age (p=0.109) and sex (0.640). As shown in table Ia, modal age group among the participants was 55-64 years. The difference in age of the subjects and controls was found not to be statistically significant (56.36±9.83 versus 54.76 ± 13.19, p=0.123). Median ages of hypertensive and non-hypertensive groups were 60 and 62 years respectively. There were more females than males. The majority of the participants were non-smokers (490 out of 500). Family history of HT was commoner among non-hypertensive than hypertensive group, but was found not be statistically significant (p=0.280).
Table Ia: Socio-demographic characteristics of the participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HT (N = 250)</th>
<th>Control (N = 250)</th>
<th>χ²</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (in years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 35</td>
<td>13 (5.2)</td>
<td>22 (8.8)</td>
<td>7.556</td>
<td>0.109</td>
</tr>
<tr>
<td>35 – 44</td>
<td>23 (9.2)</td>
<td>20 (8.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 – 54</td>
<td>39 (15.6)</td>
<td>56 (22.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55 – 64</td>
<td>126 (50.4)</td>
<td>114 (45.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65</td>
<td>49 (19.6)</td>
<td>38 (15.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean±SD</strong></td>
<td>56.36±9.83</td>
<td>54.76±13.19</td>
<td>1.545*</td>
<td>0.123</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>86 (34.4)</td>
<td>91 (36.4)</td>
<td>0.219</td>
<td>0.640</td>
</tr>
<tr>
<td>Female</td>
<td>164 (65.6)</td>
<td>159 (63.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9 (3.6)</td>
<td>1 (0.4)</td>
<td>5.000</td>
<td>0.025</td>
</tr>
<tr>
<td>No</td>
<td>241 (96.4)</td>
<td>249 (99.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FH of HT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50 (20)</td>
<td>60 (24)</td>
<td>1.166</td>
<td>0.280</td>
</tr>
<tr>
<td>No</td>
<td>200 (80)</td>
<td>190 (76)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend: HT- Hypertensives; X² – Chi square; Yates – Continuity correction ; *- independent t test. Bold figures indicate statistical significance. FH of HT- family history of hypertension.
CLINICAL CHARACTERISTICS OF THE PARTICIPANTS

As listed in Table Ib, 61(24.4%) hypertensive patients had blood pressure control below or at 139/89 mmHg and all individuals in control group were normotensive. One hundred and fifty five (62%) hypertensive patients had mild and moderate HT while 34 (13.6%) had severe HT. In table Ic, mean SBP and DBP were 148±93mmHg and 85.64±15.73mmHg respectively. Mean PP and MAP were 63.29±16.92mmHg and 106.74±17.06mmHg respectively. Eighty three of the patients had MAP ≥110mmHg while 162 patients had wide PP (>50mmHg).

One hundred and twenty-four (49.6%) of hypertensive patients were either overweight or obese compare to 83 (33.2%) among non-hypertensive group (table Ib). Hypertensive patients were significantly heavier than non-hypertensive patients (Mean BMI=25.66±4.08kg/m² versus 24.64±3.90kg/m², p= 0.004) as listed in table Ic. Abdominal obesity was significantly commoner among hypertensive patients than in non-hypertensives. One hundred and fifty (60%) and 176 (70.4%) of the patients had WC and WHR, respectively; above referenced cut-off values
As listed in table Ic, the mean values of WC and WHR were higher among hypertensive patients than in controls. This was statistically significant only with WHR among females (p=0.003). Forty five (18%) hypertensive patients were diabetic, out which 22 (48.8%) had fasting plasma glucose ≥7 mmol/l and 10 (22.2%) had good glycemic control (table Ib).

**Table Ib: Comparisons of clinical characteristics among the participants.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HT (N = 250)</th>
<th>Control (N = 250)</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤139/89</td>
<td>61 (24.4)</td>
<td>250 (100.0)</td>
<td>385.25</td>
</tr>
<tr>
<td>140/90 to 159/99</td>
<td>84 (33.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>160/100 to 179/109</td>
<td>71 (28.4)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>≥180/110</td>
<td>34 (13.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Pulse Pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;50)</td>
<td>162 (64.8)</td>
<td>0 (0.0)</td>
<td>305.51</td>
</tr>
<tr>
<td>Normal (≤50)</td>
<td>88 (35.2)</td>
<td>250 (100.0)</td>
<td></td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>HT (N = 250)</td>
<td>Control (N = 250)</td>
<td>Independent t</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>56.36±9.83</td>
<td>54.76±13.19</td>
<td>1.545</td>
</tr>
</tbody>
</table>

**Legends:** HT - Hypertensives; M - Male; F - Female; DM - diabetes mellitus; $X^2$ - Chi square, F - Fisher’s Exact. Bold figures indicate statistical significance.

Classification: BMI$^{79}$, waist circumference and waist-hip ratio$^{80}$-WHO criteria; Pulse pressure and MAP( mean arterial pressure)$^{83}$; Fasting plasma glucose$^{84}$-WHO criteria; Lipid profile$^{85}$- Adult treatment panel III.

**Table Ic:** Mean comparisons of clinical characteristics among the participants.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (Kg/m²)</td>
<td>25.66±4.08</td>
<td>24.64±3.90</td>
<td>2.872</td>
<td>0.004</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>148.93±23.80</td>
<td>118.24±12.46</td>
<td>18.061</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WC (male, cm)</td>
<td>85.59±15.23</td>
<td>84.00±5.55</td>
<td>0.935</td>
<td>0.351</td>
</tr>
<tr>
<td>WC(female, cm)</td>
<td>91.01±11.13</td>
<td>90.04±7.19</td>
<td>0.926</td>
<td>0.355</td>
</tr>
<tr>
<td>WHR (male)</td>
<td>0.88±0.17</td>
<td>0.86±0.06</td>
<td>0.961</td>
<td>0.338</td>
</tr>
<tr>
<td>WHR(female)</td>
<td>0.91±0.10</td>
<td>0.88±0.05</td>
<td>2.974</td>
<td>0.003</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>85.64±15.76</td>
<td>68.42±9.18</td>
<td>14.923</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse Pressure (mmHg)</td>
<td>63.29±16.92</td>
<td>49.82±10.46</td>
<td>10.706</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>106.74±17.06</td>
<td>85.03±9.14</td>
<td>17.737</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Legends: HT- Hypertensives; BMI- Body mass index; BP- blood pressure; WC- waist circumference; WHR- waist-hip ratio; MAP- mean arterial pressure; Bold figures indicate statistical significance.
Table I showed the breakdown of lipid profile of the participants. TC, TG and LDL-c were significantly higher among hypertensive patients than in controls. Desirable serum TC (<5.17 mmol/l) were present in 153 out of 250 (61.2%) hypertensive patients and normal serum TG was found in 215 (86%) hypertensive patients. Abnormal level of LDL-c (high and near optimal) was found in 157 (62.8%) and 122 (48.8%) hypertensive patients and controls, respectively. One hundred and fifty three (61.2%) hypertensive patients had low HDL-c (<1.30 mmol/l) compared with 85 (34%) non-hypertensive adults.

Table I: Comparisons of lipid profile among the participants.
<table>
<thead>
<tr>
<th>Variable</th>
<th>HT (N = 250)</th>
<th>Control (N = 250)</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TC (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High ($\geq$6.2)</td>
<td>46 (18.4)</td>
<td>6(2.4)</td>
<td>87.42</td>
</tr>
<tr>
<td>Borderline high (5.17 to &lt; 6.2)</td>
<td>51 (20.4)</td>
<td>5 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Desirable(&lt;5.17)</td>
<td>153 (61.2)</td>
<td>239 (95.6)</td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>4.83±1.77</td>
<td>3.88±0.82</td>
<td>7.729</td>
</tr>
<tr>
<td><strong>TG (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;2.25)</td>
<td>25 (10.0)</td>
<td>2 (0.8)</td>
<td>22.97</td>
</tr>
<tr>
<td>Borderline high (1.69 to 2.25)</td>
<td>10 (4.0)</td>
<td>5 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Normal (&lt;1.69)</td>
<td>215 (86.0)</td>
<td>243 (97.2)</td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>1.13±0.93</td>
<td>0.67±0.32</td>
<td>7.383</td>
</tr>
<tr>
<td><strong>LDL-c (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;3.35)</td>
<td>80 (32.0)</td>
<td>40 (16.0)</td>
<td>19.03</td>
</tr>
<tr>
<td>Near optimal (2.57 to 3.35)</td>
<td>77 (30.8)</td>
<td>82 (32.8)</td>
<td></td>
</tr>
<tr>
<td>Normal (&lt;2.57)</td>
<td>93 (37.2)</td>
<td>128 (51.2)</td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>3.21±1.48</td>
<td>2.58±0.81</td>
<td>5.922</td>
</tr>
<tr>
<td><strong>HDL-c (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;1.30)</td>
<td>153 (61.2)</td>
<td>85 (34.0)</td>
<td>37.07</td>
</tr>
<tr>
<td>High ($\geq$1.30)</td>
<td>97 (38.8)</td>
<td>165 (66.0)</td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>1.14±0.38</td>
<td>1.36±0.41</td>
<td>-6.242</td>
</tr>
</tbody>
</table>

Legends: HT- Hypertensives; TC- total cholesterol; TG- triglycerides; LDL-c- low density lipoprotein cholesterol; HDL-c- high density lipoprotein cholesterol; * Independent t test; $X^2$- Chi square; Bold figures indicate statistical significance. Lipid profile86- Adult treatment panel III.
PREVALENCE, PATTERN OF ECG-LVH AND ELEVATED SERUM CRP AMONG PATIENTS WITH HYPERTENSION.

Table II showed breakdown of elevated CRP and ECG abnormalities among participants. It described the prevalence and pattern of elevated CRP among hypertensive patients using the set cut off value of ≥2mg/l. Serum CRP was significantly higher (p=<0.001) among hypertensive patients (3.02±1.26mg/l) than non-hypertensives (1.95±0.22mg/L). One hundred and twenty-eight (51.2%) hypertensive patients had elevated serum CRP (≥ 2mg/l) while 122 (48.8%) had CRP <2mg/l. In control group 97(38.8%) adults had elevated CRP while 153 (61.2%) normotensive adults had low CRP (<2mg/l).

Seven participants had complete bundle branch block and were not included in analysis for ECG-LVH. Therefore 245 and 248 ECG tracings, of hypertensive patients and non-hypertensive controls respectively, were analysed for ECG-LVH. Pattern of ECG-LVH and its prevalence among hypertensive adults were also shown in table II. ECG-LVH was more (54.3%) among hypertensive patients than (43.1%) in non-hypertensive
participants (p=0.02). One hundred and twelve (45.7%) hypertensive patients did not have ECG-LVH. QTc was significantly higher among hypertensive patients than in controls (0.43±0.03 versus 0.42±0.02, p<0.001). QRS duration was significantly longer among hypertensive patients than in controls (0.10±0.08 versus 0.09±0.01, p=0.044).

Table II: Comparisons of CRP, QTc, QRS duration and LVH among participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HT (N = 250)</th>
<th>Control (N = 250)</th>
<th>χ²</th>
<th>p – value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated (≥2mg/l)</td>
<td>128 (51.2)</td>
<td>97 (38.8)</td>
<td>7.766</td>
<td>0.005</td>
</tr>
<tr>
<td>Normal (&lt;2mg/l)</td>
<td>122 (48.8)</td>
<td>153 (61.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>3.02±1.26*</td>
<td>1.95±0.22*</td>
<td>4.400*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged</td>
<td>118 (47.2)</td>
<td>96 (38.4)</td>
<td>3.954</td>
<td>0.047</td>
</tr>
<tr>
<td>Normal</td>
<td>132 (52.8)</td>
<td>154 (61.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.43±0.03*</td>
<td>0.42±0.02*</td>
<td>5.406*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QRS Duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;0.12)</td>
<td>5 (2)</td>
<td>2 (0.8)</td>
<td>1.304</td>
<td>0.253</td>
</tr>
<tr>
<td>Normal (≤0.12)</td>
<td>245 (98)</td>
<td>248 (99.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SOCIODEMOGRAPHIC CHARACTERISTICS AND ELEVATED SERUM CRP.

Figure 2 showed the association between age and elevated CRP among participants. In each age category, except 45-54 years, the number and percentage of hypertensive patients with elevated CRP (blue) were higher than that of controls with elevated CRP (green). There was a significant association between age and elevated CRP among subjects and controls. However, the strength of association between age and CRP was lesser among hypertensives (p=0.002 versus <0.001). The mean age
of adult hypertensive patients with elevated CRP was significantly higher than those without elevated CRP (57.87±9.23 versus 54.79±7.9; p=0.013). There was no statistical difference between the mean age of hypertensive patients with elevated CRP and that of non-hypertensives adults with elevated CRP (57.87±9.23 vs 55.56±10.34; p = 0.079).

Figure 2: Association between age and CRP among hypertensives and non-hypertensives.

- Hypertensives Elevated CRP
- Hypertensives Not Elevated CRP
- NonHypertensives Elevated CRP
- NonHypertensives Not Elevated CRP

χ² = 16.861 vs 25.788
p = 0.002 vs <0.001
Legends: CRP- C reactive protein; Elevated CRP- ≥2mg/l; Not elevated CRP < 2mg/l. HT- hypertensives; Non-HT- Non-hypertensives.

Figure 3 showed relationship between CRP and three variables (gender, cigarette smoking and family history of hypertension) among participants. Ninety-two (56%) out of 164 hypertensive females had elevated CRP compared to 36 (42%) out of 86 hypertensive males. Similarly, there were more (83) non-hypertensive females with elevated CRP than non-hypertensive males (14) with elevated CRP. In both hypertensive and non-hypertensive groups there were association between elevated CRP and gender, the strength of association was lesser among hypertensive group (p= 0.032 vs <0.001). There were 10 participants who smoked cigarette, majority of them were hypertensive patients (9 vs 1). Eight (89%) hypertensive patients had elevated CRP compared to 120 (50%) hypertensive adults who were non-smokers who had elevated CRP. There was a slight significant association between
elevated CRP and cigarette smoking among hypertensive adults, but none among controls (p=0.048 vs 0.818). Percentage of hypertensives with family history of HT and elevated CRP (46%) was similar to that of hypertensives without family history of HT who had elevated CRP (45%). This was similar to the finding among controls. There was no association between family history of HT and elevated CRP in both groups (p= 0.899 vs 0.952).
Figure 3: Association between CRP, gender, smoking and family history of hypertension among hypertensives and non-hypertensives

<table>
<thead>
<tr>
<th></th>
<th>Hypertensives Elevated CRP</th>
<th>Hypertensives Not Elevated CRP</th>
<th>Non-Hypertensives Elevated CRP</th>
<th>Non-Hypertensives Not Elevated CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>50</td>
<td>77</td>
<td>72</td>
<td>76</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>0</td>
<td>121</td>
<td>153</td>
</tr>
<tr>
<td>Cigarette Smoker</td>
<td>HT</td>
<td>Non-HT</td>
<td>HT</td>
<td>Non-HT</td>
</tr>
<tr>
<td>FHH Present</td>
<td>27</td>
<td>35</td>
<td>110</td>
<td>111</td>
</tr>
<tr>
<td>FHH Absent</td>
<td>50</td>
<td>77</td>
<td>72</td>
<td>76</td>
</tr>
</tbody>
</table>

\[ p = 0.032 \text{ vs } <0.001 \]
\[ X^2 = 4.577 \text{ vs } 33.037 \]

\[ p = 0.048 \text{ Yates vs } 0.818 \text{ Yates} \]
\[ X^2 = 4.858 \text{ vs } 0.053 \]
\[ p = 0.899 \text{ vs } 0.952 \]
\[ X^2 = 0.016 \text{ vs } 0.004 \]

Legends: CRP- C reactive protein; Yates- continuity correction; FHH- family history of hypertension; Elevated CRP- ≥2mg/l; Not elevated CRP < 2mg/l. HT- Hypertensives; Non-HT- Non-hypertensives.
ASSOCIATION BETWEEN SYSTEMIC HYPERTENSION AND ELEVATED CRP

Table III described the association between systemic HT and elevated CRP (≥2mg/l) among hypertensive patients. The percentage of hypertensives with elevated CRP was higher than those without elevated CRP in BP group ≥ 160/100mmHg compared to those with good BP control and mild HT. This was significant statistically (p<0.001). The mean SBP of hypertensive patients with elevated CRP was statistically different (higher) than those without elevated CRP (152.67±23.15 versus 145.00±23.94 mmHg, t=2.576, p= 0.011). In contrast, there was no statistical difference between mean DBP of hypertensive patients with CRP ≥2mg/l and those below 2mg/l (86.86±15.66 versus 84.36±15.83, t=1.254, p=0.211). As shown in table III, mean values of PP and MAP was statistically higher among patients with high CRP (≥2mg/l) compared to patients without elevated CRP (65.81±17.72 versus 60.64±16.69 mmHg, t=2.440, p=0.015 and 108.80±16.51 versus 104.57±17.42 mmHg, t=1.968, p=0.050) respectively.
Table III: Association between blood pressure and CRP among hypertensive patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Elevated (n = 128)</th>
<th>Not elevated (n = 122)</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
</table>

HT- Hypertension; CRP- C reactive protein; Elevated- CRP≥ 2mg/l; Not elevated- CRP < 2mg/l; $\chi^2$- chi square; *- Independent t test; SBP/DBP- systolic/diastolic blood pressure; PP- Pulse pressure; MAP- Mean arterial pressure; Bold figures- statistically significant; Elevated CRP- ≥2mg/l; Not elevated CRP < 2mg/l.

INDICES OF OBESITY, SERUM LIPID AND ELEVATED SERUM CRP

Figure 4 showed the association between waist circumference (WC), waist-hip ratio (WHR) and elevated CRP among the participants. Using WC, abdominal obesity was found in 150 hypertensive patients and
66.7% of them had elevated CRP. Twenty eight (28%) hypertensive patients with normal WC had elevated CRP (p<0.001). However, 48.8% of 127 non-hypertensive controls with abdominal obesity had elevated CRP and 35 (28.4%) non-hypertensive controls had normal WC with elevated CRP (p=0.001). Female hypertensive patients with elevated CRP had significantly higher mean WC than those with low CRP (93.29±13.14 versus 88.10±6.90cm, t=3.042, p=0.003). The mean WC of female

<table>
<thead>
<tr>
<th>HT (mmHg)</th>
<th>SBP Mean ± SD</th>
<th>DBP Mean ± SD</th>
<th>PP (mmHg)</th>
<th>MAP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤139/89</td>
<td>152.67±23.15</td>
<td>145.00±23.94</td>
<td>19 (31.1)</td>
<td>59 (71.1)</td>
</tr>
<tr>
<td>140/90 to 159/99</td>
<td>36 (42.9)</td>
<td>48 (57.1)</td>
<td>72 (44.4)</td>
<td>24 (28.9)</td>
</tr>
<tr>
<td>160/100 to 179/109</td>
<td>52 (73.2)</td>
<td>19 (26.8)</td>
<td>38 (43.2)</td>
<td>69 (41.3)</td>
</tr>
<tr>
<td>≥180/110</td>
<td>21 (61.8)</td>
<td>13 (38.2)</td>
<td>50 (56.8)</td>
<td>98 (58.7)</td>
</tr>
</tbody>
</table>

SBP Mean ± SD 152.67±23.15 145.00±23.94  2.576*
DBP Mean ± SD 86.86±15.66 84.36±15.83  1.254*
PP (mmHg)
High (>50) 90 (55.6) 72 (44.4) 3.494
Normal (≤50) 38 (43.2) 50 (56.8) 
Mean ± SD 65.81±17.72 60.64±16.69  2.440*
MAP (mmHg)
High (>110) 59 (71.1) 24 (28.9) 19.662
Normal (≤110) 69 (41.3) 98 (58.7) 
Mean ± SD 108.80±16.51 104.57±17.42  1.968*
hypertensive patients with elevated CRP was not significantly higher than the corresponding female non-hypertensive controls with elevated CRP (93.29±13.14 vs 90.35±7.351, p=0.067). Among male hypertensive patients, WC of those with elevated CRP were not significantly higher than those with low CRP (88.44±11.51 versus 83.54±17.24cm, t=1.484, p=0.142). Mean WC of male hypertensive patients with elevated CRP was also not significantly higher than that of non-hypertensive male controls with elevated CRP (88.44±11.51 vs 81.00±1.038, p= 0.074).

One hundred and fourteen (64.8%) hypertensive patients with high WHR had elevated CRP and 14 (18.9.1%) hypertensive patients with normal WHR had low CRP. Mean WHR was significantly higher in (particularly female) hypertensive patients with elevated CRP than those without elevated CRP (0.94±0.12 vs 0.87±0.06, t=3.042, p=0.003). Mean WHR of hypertensive male with elevated CRP was significantly higher than that of hypertensive male with low CRP (0.93±0.08 versus 0.85±0.20; p=0.019). The strength of association between WC, WHR and CRP was stronger among hypertensives than in non-hypertensives \{(WC: X^2 = 35.903 vs 10.912), (WHR: X^2 = 43.838 vs 11.653)\}. 
Figure 4: Association between WHR, WC and CRP among hypertensives and non-hypertensives.

Legends: WC - waist circumference; WHR - waist-hip ratio; CRP - C reactive protein; P-value and chi-square = hypertensives vs non-hypertensives. WHR (M) high >0.90; (F) high >0.85; WC High (M)≥94cm, high (F)≥80cm; Elevated CRP - ≥2mg/l; Not elevated CRP < 2mg/l. HT - hypertensives; Non-HT - Non-hypertensives.
Figure 5 showed association between BMI and CRP. Forty two (36%) hypertensive patients with normal BMI had elevated CRP. Whereas 56 (63.6%) and 25 (69.4%) hypertensive patients who were overweight and obese respectively had elevated CRP. This was statistically significant (p<0.001). There were higher percentages of hypertensive patients with elevated CRP than non-hypertensives with elevated CRP in each BMI category. This was more prominent among participants who were underweight. Association between CRP and BMI was stronger among non-hypertensives than in hypertensive patients ($X^2 = 33.677$ vs 20.685). Hypertensive patients with elevated CRP were significantly heavier than hypertensive patients with low CRP (26.60±4.06 versus 24.68±3.89 kg/m², t=3.808, p<0.001), likewise among the non-hypertensives (25.73±4.24 versus 23.95±3.51; p<0.001).
Legends: BMI - Body mass index; CRP - C reactive protein; $P$-value and chi square value = hypertensive vs non-hypertensive. Underweight $<=$ 18.50 kg/m$^2$; Normal $=$ 18.50 - 24.99 kg/m$^2$; overweight $=$ 25.00 - 29.99 kg/m$^2$; obese $=$ 30.00 - 34.99 kg/m$^2$; Elevated CRP $\geq$ 2mg/l; Not elevated CRP $<$ 2mg/l. HT-hypertensives; Non-HT- Non-hypertensives.

Figure 5: Association between BMI and CRP among hypertensives and non-hypertensives

<table>
<thead>
<tr>
<th></th>
<th>Hypertensives Elevated CRP</th>
<th>Hypertensives Not elevated CRP</th>
<th>Non-hypertensives Elevated CRP</th>
<th>Non-hypertensives Not elevated CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Normal</td>
<td>42</td>
<td>44</td>
<td>56</td>
<td>38</td>
</tr>
<tr>
<td>Overweight</td>
<td>55</td>
<td>25</td>
<td>74</td>
<td>11</td>
</tr>
<tr>
<td>Obese</td>
<td>25</td>
<td>11</td>
<td>44</td>
<td>74</td>
</tr>
</tbody>
</table>

$p < 0.001$ vs $< 0.001$

$X^2 = 20.685$ vs $33.677$
Figure 6 showed association between total cholesterol (TC), high density lipoprotein-cholesterol (HDL-c) and elevated CRP among patients with hypertension (HT) and non-hypertensive. It was found that 31(67.4%) hypertensive patients with high TC (≥6.2mmol/l) had elevated CRP whereas 19(37.3%) hypertensives with borderline high TC (5.17-<6.2mmol/l) had elevated CRP. There was an association between elevated CRP and TC among hypertensives and non-hypertensives. The strength of association was lesser among hypertensive patients (p= 0.012 vs 0.005). Mean TC of hypertensive patients with elevated CRP was higher compared to those with CRP <2mg/l but not significant (4.97±2.00 versus 4.69±1.47 mmol/l, t=1.230, p=0.220). In contrast, mean TC of non-hypertensive controls with elevated CRP was significantly higher than that of non-hypertensive controls without elevated CRP (4.09±0.92 vs 3.75±0.72 mmol/l, p=0.001).

Among hypertensive and non-hypertensive participants, there was significant association between low HDL-c and CRP. This was stronger among hypertensive patients (X²,p =47.933, <0.001 vs 16.935, <0.001). Hypertensive patients who had low serum HDL-c (<1.30mmol/l) with elevated CRP were more (68.6%) than (56.5%) non-hypertensive controls.
with low serum HDL-c and elevated CRP. This was reverse with regard to high HDL-c (≥1.30mmol/l). Mean HDL-c of hypertensive patients with elevated CRP was extremely lower than that of non-hypertensive controls with elevated CRP (1.03±0.35 versus 1.29±0.23; p<0.0001). Likewise, mean HDL-c of hypertensive patients without elevated CRP was very lower than that of non-hypertensive controls without elevated CRP (1.25±0.38 versus 1.40±0.49; p=0.0058) respectively.
Figure 6: Association between TC, HDL-c and CRP among hypertensives and non-hypertensives

Legends: TC- Total cholesterol; HDL-c – high density lipoprotein cholesterol; CRP- C reactive protein; P-value= hypertensives vs non-hypertensives. TC<5.17mmol/l=Desirable, 5.17-<6.2mmol/l=borderline high, ≥6.2mmol/l=high; HDL-c<1.30mmol/l=low, ≥1.30mmol/l=high;
Elevated CRP - ≥2mg/l; Not elevated CRP < 2mg/l; HT- hypertensives; Non-HT- Non-hypertensives.

Elevated CRP was present in 23 (92%), 6 (60%) and 99 (46%) hypertensive patients with high serum TG (≥2.25mmol/l), borderline high TG (1.69- <2.25mmol/l) and normal serum TG (<1.69mmol/l) respectively (figure 7). There was significantly higher TG mean value in hypertensive patients with elevated CRP compared to hypertensive patients without elevated CRP (1.31±1.21 versus 0.94±0.41mmol/l, t=3.192, p=0.002). There was association between TG and CRP among hypertensive patients but none among non-hypertensive controls (p<0.001 vs 0.583) respectively. Among hypertensive patients who had normal LDL-c (<2.57mmol/l), 47 (50.5%) had elevated CRP whereas 50 (62.5%) hypertensive patients had high LDL-c (>3.35mmol/l) with elevated CRP (figure 6). Mean LDL-c was significantly higher among hypertensive patients with elevated CRP compared to hypertensive patients with low CRP (3.47±1.77 versus 3.00±1.06; p=0.024). The strength of association between LDL-c and CRP was lesser in hypertensive patients than in non-hypertensives (p= 0.020 vs 0.005).
**Legends:** LDL-c – Low density lipoprotein cholesterol; TG – triglyceride; CRP – C reactive protein; P-value= hypertensives vs non-hypertensives. LDL-c High >3.35mmol/l, Near optimal=2.5-3.35mmol/l, normal <2.57mmol/l; TG high >2.25mmol/l, borderline high=1.69-2.25mmol/l, normal <1.69mmol/l; Elevated CRP- ≥2mg/l; Not elevated CRP <2mg/l; HT-hypertensives; Non-HT- non-hypertensives.

**Figure 7:** Association between TG, LDL-c and CRP among hypertensives and non-hypertensives

- **Hypertensives Elevated CRP**
- **Hypertensives Not elevated CRP**
- **Non-hypertensives Elevated CRP**
- **Non-hypertensives Not elevated CRP**

- **X²** for TG:
  - Hypertensives Elevated CRP vs Non-Hypertensives Not elevated CRP: X²= 19.251 vs 1.081
  - Hypertensives Not elevated CRP vs Non-Hypertensives Not elevated CRP: X²= 10.723 vs 7.793

- **X²** for LDL-c:
  - Hypertensives Elevated CRP vs Non-Hypertensives Not elevated CRP: X²= 7.793 vs 10.723
  - Hypertensives Not elevated CRP vs Non-Hypertensives Not elevated CRP: X²= 0.020 vs 0.583

- **p-values**:
  - X² for TG: 0.583 vs <0.001
  - X² for LDL-c: 0.005 vs 0.020
ASSOCIATION BETWEEN CRP AND DIABETES MELLITUS AMONG PATIENTS WITH HYPERTENSION

Figure 8 showed association between CRP and diabetes mellitus among hypertensive patients. There were 45 hypertensive patients that were diabetic and met other inclusion criteria into the study. Twenty seven (60%) of hypertensive-diabetic patients had elevated CRP and it was not statistically associated with CRP (p=0.192, $X^2 = 1.701$).
Figure 8: Association between CRP and Diabetes Mellitus among patients with hypertension.

Legend: CRP – C reactive protein DM - Diabetes mellitus; Elevated CRP - ≥2mg/l; Not elevated CRP < 2mg/l.
ECG ABNORMALITIES AND ELEVATED SERUM CRP

Figure 9 showed association between ECG-LVH and elevated serum CRP among participants. Among hypertensive patients with ECG determined LVH, 78 (58.6%) had elevated CRP while 46 (41.1%) hypertensive patients without ECG-LVH had elevated CRP and this difference was statistically significant ($X^2=7.513, p=0.006$). Seventy-two (67.3%) non-hypertensive controls had ECG LVH with elevated CRP while 23 (16.3%) non-hypertensive controls without ECG-LVH had elevated CRP ($X^2=66.896, p=0.000$). The association between CRP and ECG-LVH was stronger in non-hypertensive controls than in hypertensive patients ($X^2 = 66.896$ versus 7.513).
Figure 9: Association between ECG LVH and CRP among hypertensives and non-hypertensives.

<table>
<thead>
<tr>
<th></th>
<th>Hypertensives Elevated CRP</th>
<th>Hypertensives Not elevated CRP</th>
<th>Non-hypertensives Elevated CRP</th>
<th>Non-hypertensives Not elevated CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH - ve</td>
<td>46</td>
<td>23</td>
<td>78</td>
<td>72</td>
</tr>
<tr>
<td>LVH + ve</td>
<td>66</td>
<td>118</td>
<td>55</td>
<td>35</td>
</tr>
</tbody>
</table>

p = 0.006 vs 0.000
X² = 7.513 vs 66.896

Legends: ECG-LVH – electrocardiographic left ventricular hypertrophy; +ve - present; -ve - absent; CRP - C reactive protein; P-value = hypertensives vs non-
hypertensives; Elevated CRP- ≥2mg/l; Not elevated CRP < 2mg/l; HT-hypertensives; Non-HT- non-hypertensives.

In figure 10, 74(62.7%) hypertensive patients with prolonged QTc had elevated CRP while 54(40.9%) hypertensive patients with normal QTc had elevated CRP ($X^2=11.854$, p=0.001). Among non-hypertensive controls (green bar), there was no association between CRP and QTc ($X^2=0.004$, p=0.947). Five hypertensive patients had complete bundle branch block while 2 controls had complete right bundle branch block. Four (80%) hypertensive patients with bundle branch block had elevated CRP, out of which 3(75%) had left bundle branch block and 1(25%) had right bundle branch block. There was no association between QRS duration and CRP among hypertensive and non-hypertensive participants (p= 0.193 vs 0.744).
Figure 10: Association between QRS duration, QTc and CRP among hypertensives and non-hypertensives

<table>
<thead>
<tr>
<th></th>
<th>Hypertensives Elevated CRP</th>
<th>Hypertensives Not elevated CRP</th>
<th>Non-hypertensives Elevated CRP</th>
<th>Non-hypertensives Not elevated CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS≤0.12</td>
<td>124</td>
<td>96</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>QRS&gt;0.12</td>
<td>1</td>
<td>1</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>Normal QTc</td>
<td>78</td>
<td>94</td>
<td>44</td>
<td>59</td>
</tr>
<tr>
<td>Prolonged QTc</td>
<td>121</td>
<td>152</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

p=0.193 vs 0.744
$X^2 = 1.692$ vs 0.107
p=0.001 vs 0.947
$X^2 = 11.854$ vs 0.004

Legends: CRP - C reactive protein; Normal QTc <0.43 (M), < 0.44 (F); QRS Normal ≤0.12s, Prolonged QRS - >0.12s; Elevated CRP - ≥2mg/l; Not elevated CRP < 2mg/l; HT - hypertensives; Non-HT - Non-hypertensives.
DETERMINANTS OF ELEVATED CRP

In table IV shown below using binary logistic regression, it was found that increasing age, TG, QTc, and decreasing HDL-c were determinants of elevated CRP. High MAP, WC, WHR and presence of ECG-LVH were also determinants of elevated CRP. Increasing age, TG and QTc were all found to be associated with an increased likelihood of exhibiting elevated CRP (p = 0.027, 0.001 and < 0.001 respectively). However, decrease in HDL-c was significantly associated with increase in likelihood of displaying elevated CRP (p<0.001).

In addition, patients with high MAP (>110mmHg) were about 6.3 times more likely to exhibit elevated CRP than patients with normal MAP (p=0.012). Those with high WC (>94cm for male, >80cm for female) were found to be about 4.3 times more likely to possess elevated CRP than those whose WC were normal (p=0.006). Moreover, patients with high WHR (>0.90 for male, >0.85 for female) had 13 times the likelihood of displaying elevated CRP than patients with normal WHR (p=0.000). Finally, patients with ECG-LVH were twice at risk of exhibiting elevated CRP than patients without ECG-LVH (p=0.014).
Table IV: A binary logistic regression for determinants of elevated CRP (Adjusted Odd Ratio)

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value</th>
<th>AOR</th>
<th>95% C.I. for AOR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Age*</td>
<td>0.027</td>
<td>1.058</td>
<td>1.006 1.112</td>
</tr>
<tr>
<td>BMI*</td>
<td>0.128</td>
<td>1.097</td>
<td>0.974 1.237</td>
</tr>
<tr>
<td>SBP*</td>
<td>0.395</td>
<td>0.981</td>
<td>0.937 1.026</td>
</tr>
<tr>
<td>PP*</td>
<td>0.201</td>
<td>1.030</td>
<td>0.984 1.077</td>
</tr>
<tr>
<td>TC*</td>
<td>0.500</td>
<td>1.088</td>
<td>0.851 1.390</td>
</tr>
<tr>
<td>TG*</td>
<td>0.001</td>
<td>2.272</td>
<td>1.430 3.611</td>
</tr>
<tr>
<td>LDL-c*</td>
<td>0.119</td>
<td>1.277</td>
<td>0.939 1.737</td>
</tr>
<tr>
<td>HDL-c*</td>
<td>&lt;0.001</td>
<td>0.065</td>
<td>0.017 0.243</td>
</tr>
<tr>
<td>QTc*</td>
<td>&lt;0.001</td>
<td>14.236</td>
<td>4.991 40.503</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.837</td>
<td>1.117</td>
<td>0.389 3.202</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>1.000</td>
<td></td>
</tr>
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*Variable entered as a continuum; AOR- adjusted odd ratio; BMI-body mass index; SBP- systolic blood pressure; PP- pulse pressure; TC- total cholesterol; TG- triglyceride; LDL-c- low density lipoprotein cholesterol; HDL-c- high density lipoprotein cholesterol; QTc- corrected QT interval l(Bazet's); MAP- mean arterial pressure, High>110mmHg; WC- waist circumference, High ≥94cm(M),≥80cm(F); WHR- waist hip ratio, High >0.90(M), >0.85(F); LVH- left ventricular hypertrophy.

**CHAPTER FIVE**
**DISCUSSION**

This study showed association between serum CRP and ECG-LVH among hypertensive patients attending MOPC at FMC, Ido-Ekiti. It also described prevalence and pattern of elevated hsCRP, ECG-LVH and association between elevated CRP and conventional cardiovascular risk factors among hypertensive adults.

Five hundred participants including 250 hypertensive patients were recruited in this study with male to female ratio of 1: 1.9 among the
patients. The demographic distribution showed that 70% of the hypertensive patients were 55 years and above. This finding is similar to that of Ogunmola et al\textsuperscript{94} among people in the same rural community of Ekiti state. This reflected the population characteristic of the community with higher number of older people due to retirement to their country home after years of active service and migration of the young adults to the city in search of a better future. The female preponderance may be due to the good health seeking attitude of women in contrast to men who probably present late in the hospital with complications.\textsuperscript{94}

The prevalence of elevated CRP was higher among hypertensive patients compared to normotensive control (51.2\% versus 38.8\%, p=0.005, while 48.8\% of hypertensive patients had CRP <2mg/l. The prevalence of elevated CRP among hypertensives was similar to the finding (54.1\%) in EURIKA study (European study on cardiovascular risk prevention and management in usual daily practice)\textsuperscript{95} using CRP cut-off value of \(\geq 2\)mg/l. The prevalence in this study could perhaps have been higher if hypertensive patients were not on statins in contrast to participants in EURIKA study. Iwashima et al found a prevalence of 21\% among Japanese with HT using similar cut-off value.\textsuperscript{77} The difference might be explained by racial differences suggesting that Blacks have higher level of CRP compare to other races.\textsuperscript{96} This study suggests that despite being
on antilipemic and antihypertensive medications, majority of the hypertensive patients still had moderate CV risk based on the prevalence of elevated CRP. Adverse CV risk may be prevented or minimised in the majority of hypertensive group with intensification of treatment. Ninety seven (38.8%) non-hypertensive group had elevated CRP and therefore had moderate CV risk based on the set cut-off value. This could be explained by high prevalence of central obesity among the non-hypertensive group (51-56%). Being a rural community, undetected subclinical infection, autoimmune disease or occult malignancy among the selected non-hypertensive group might contribute to high prevalence. The high prevalence (38.8%) of elevated CRP among non-hypertensive adults (using cut off value of ≥2mg/l) was lower than 52% documented among general US adults population. The difference could be explained by the facts that US study involved multiple ethnics/races and individuals with multiple co-morbidities. To the best knowledge of the author, this is the first study in Africa that used this CRP threshold.

Mean serum CRP among adults with HT was 3.02mg/l while it was 1.95mg/l for normotensive control (p<0.001). This might signify that hypertension was associated with inflammation and hypertensive patients were at higher cardiovascular risk. This value was higher than the finding of Idemudia et al26 (1.8 mg/l) but lower than the finding (9.07mg/l) of
Oboh et al among hypertensive patients in Benin. The subjects in Idemudia’s study were younger compared to those recruited in this study. Participants in Oboh’s study were older, heavier and had higher level of BP compared to the hypertensive adults in this study. Highlighted reasons might explain the difference in mean values of CRP among the studies.

Using one criterion, 54.3% of hypertensive patients had ECG LVH. This is similar to the findings of Katibi et al (56.7-71.7%, using Araoye’s and Sokolow-Lyon criteria) and Dada et al (48-51%, using Sokolow-Lyon and Araoye’s criteria) among hypertensive patients in Ilorin and Ibadan respectively. The import of this finding is that the hypertensive group had severe hypertension for a prolonged period (for those with a voltage criteria only) and at higher risk of cardiovascular (CV) death (for those with more than one voltage criteria or LV strain pattern) from likely severe degrees of left ventricular enlargement. Among the hypertensives, 45.7% did not have ECG LVH. The closeness in prevalence of presence and absence of ECG LVH among hypertensives reflects documented low sensitivity of ECG voltage criteria for LVH. In addition, this could be due to remodelling effect of antihypertensive medications which perhaps had reduced the prevalence of ECG LVH and increase prevalence of absence of ECG LVH among hypertensives. The prevalence of ECG LVH among non-hypertensive (43.1%) was higher than the finding (30%) of Katibi
among non-hypertensive in Ilorin using automated programme. The difference could be due to the fact that only one criterion (Sokolow-Lyon) was applied, whereas presence of at least a criterion in Araoye’s code system or Sokolow-Lyon was applied in this study. This study suggests that using more than one ECG criteria might improve sensitivity of ECG in diagnosing LVH.

ELEVATED CRP AND ECG ABNORMALITIES AMONG PATIENTS WITH HYPERTENSION

This study showed association between ECG-LVH and elevated CRP (inflammation) among hypertensive and non-hypertensive groups. However, the association was lesser among hypertensive group than non-hypertensive group (p=0.006 versus 0.000) respectively. This could be explained by the effects of antihypertensive medications in hypertensive patients that has reduced level/degree of inflammation in them. In a binary logistic regression, ECG- LVH was one of the determinant factors of elevated CRP. Hypertensive patients with ECG LVH were twice likely to have elevated CRP considering all other factors are constant. Studies had documented relationship between echo-LVH, particularly concentric hypertrophy, and CRP. The present study extended the observation by using ECG-LVH. ECG- LVH determination is faster, cheaper, higher reproducibility and readily available compare to echo LVH.
CRP may play a direct role in promoting LVH via increasing vasoconstriction, endothelial dysfunction and phosphatidylinositol-3-kinase activity.\textsuperscript{77} Perhaps inflammation may be an epiphenomenon to the process of ventricular hypertrophy.\textsuperscript{19} Lastly, it has been proposed that other metabolic disorders (for instance obesity), associated with raised CRP can simultaneously promote increase in left ventricular mass.\textsuperscript{77} Identifiable risk factors - age, obesity, gender, race, for the development of LVH can be seen among non-hypertensive.\textsuperscript{101} These may be the reasons LVH is present in certain proportion of adults without hypertension. Elevated CRP and ECG LVH are independent CV risk factors and had prognostic importance.\textsuperscript{18, 20} Presence of these risk factors in a patient increase their CV risk burden. The result of the study suggests that their effects were collaborative if not additive. Intensive treatment regime will be better in adult hypertensive with ECG-LVH and elevated CRP than individuals with either of these risk factors. Further research is needed to determine the role of inflammation in ventricular hypertrophy.

This study found that 47.2\% of hypertensive patients had prolonged QTc. This is similar to the finding of Familoni \textit{et al} of 43.8\% among hypertensive adults who had stroke.\textsuperscript{102} However, it was lower than 52.14\% reported by Akintunde \textit{et al} among hypertensive patients in LAUTECH Osogbo.\textsuperscript{103} The difference might be due to higher proportion
of obese participants in later study as prolonged QTc is associated with obesity which increase cardiac workload and burden of inflammation. Prolonged QTc has been linked to increase ventricular myocardial in homogeneity as a result of fibrosis, scar and LVH. This predisposes to cardiac arrhythmia and CV death. Chang et al documented that CRP was associated with prolonged QTc among hypertensives, as found in this study. There was no association between CRP and QTc among non-hypertensives. Thus, suggesting that hypertension contributes to association between CRP and prolonged QTc. Prolonged QTc strongly determined elevated CRP in multivariate analysis. CRP link with prolonged QTc has been explained or hypothesized to be due to low grade inflammation in the in homogeneous ventricular myocardium, associated hypertension, obesity or LVH. This study suggests that low grade inflammation in adults with systemic HT was associated with prolongation of ventricular repolarisation and may promote arrhythmogenesis.

ELEVATED CRP AND SOCIODEMOGRAPHIC CHARACTERISTICS AMONG PATIENTS WITH HYPERTENSION

The study showed significant association between elevated CRP and increasing age, similar to previous findings. The stronger
association between age and CRP among non-hypertensive than hypertensive (p<0.001 vs 0.002 respectively) group could be due to treatment effects that perhaps has reduced the level of inflammation among hypertensive patients. Increasing age was one of the determinants of elevated CRP in multivariate analysis, and however, the clinical effect is likely to be minimal. There is an increasing load of inflammation as one grows older; due to expected gradual decline in renal function as one grows older.

The relationship between elevated CRP and gender has been controversial. This study demonstrated association between elevated CRP and female gender among hypertensive and non-hypertensives, though stronger among non-hypertensives. This could be due to the fact that larger participants were female who were overweight or obese and possibly treatment effects. Higher oestrogen level in female may have contributed to greater subcutaneous fat accumulation than in male and could partially account for differences in CRP level among gender. Contrary to finding in this study; Idemudia et al found no difference in CRP level between male and female hypertensive patients. However both studies agreed to the fact that gender is not a determinant of elevated CRP as binary logistic regression showed in this study.
This study showed slight association between cigarette smoking and elevated CRP in univariate analysis \((p=0.048)\) among hypertensive patients but not among non-hypertensive group\((p=0.818)\); this has been documented by studies.\(^9\) However, the number of hypertensive adults who smoke was very low and in multivariate analysis it did not determine elevated CRP. Therefore the finding on cigarette smoking could not be generalised considering low number of smokers among the participants. Smoking directly increases serum CRP and it is one of numerous pathways of higher CV morbidity and mortality associated with cigarette smoking.\(^9\) There was no association between CRP and family history of hypertension among the hypertensives and non-hypertensives. This could be explained by poor sensitivity of family history of hypertension in determining vascular inflammation. This study found that family history of HT was commoner among non-hypertensive than hypertensive group. This might be the motivating factor among non-hypertensive group in participating in the study. This difference could also be due to the fact that hypertensive patients who participated in this study were not aware of hypertension in their siblings who often resides in another far away town.

**ELEVATED CRP AND HYPERTENSION**

As previously documented in various studies\(^{113}\), this study agreed to association between HT and elevated CRP. Sixty one \((25\%)\) hypertensive
patients on treatment had their BP controlled. This is similar to the finding of Akpa et al in Port Harcourt. However; it is higher than 9% by Ekwunife et al in a community study and 12.4% by Oyati et al. The difference may be due to differences in populations studied (community versus hospital based study) and sampling method. The population in this study was hypertensive patients attending both specialist and general clinics where regular health education is given to patients. Blood pressure control among adult hypertensive patients range from 9% to 53.3%, according to published studies.

There was association between elevated CRP and mean SBP, PP and MAP but not with mean DBP. In binary logistic regression analysis only the effect of MAP persisted. The association between elevated CRP and increasing BP, SBP, DBP and MAP independent of other associated study factors has been documented by Blake et al in women health study. The lack of association between DBP and CRP in this study could be explained by lower mean DBP among hypertensives compare to that in Blake’s study. Elderly tends to have reduced elasticity of their arteries, contributing to lower DBP commonly seen in them compared to younger age group. Pulsatile blood flow modulates biomechanical stimuli within vascular wall, therefore promoting vascular inflammation.
Elevated BP lead to generation of reactive oxygen species and increase oxidative stress which promotes CRP production.\textsuperscript{114} Alternatively, CRP reduces production of nitric oxide (vasodilator) by endothelial cells. This invariably leads to vasomotor tone disturbance and unopposed vasoconstriction.\textsuperscript{65} CRP may also up regulates angiotensin I receptor mediated events in vascular smooth muscle cells encouraging vasoconstriction.\textsuperscript{59} Both elevated CRP and HT are cardiovascular risk factors and this study suggests that their cardiovascular effects may be additive. Strategies targeted at both factors may improve hypertensive patients’ management.

MAP portrays organ perfusion pressure and higher organ perfusion pressure in hypertensive population may increase end organ damage. Increasing level of CRP has been associated with end organ damage.\textsuperscript{115} In multivariate analysis; patients with elevated MAP (≥110mmHg) were 6.3 times likely to have elevated CRP. With increasing value of serum CRP, the probability of multiple end organ damage increases. Thus, this study suggested that hypertensive patients with elevated MAP may be at higher risk of multiple subclinical end organ damage (LVH inclusive). Also that vascular inflammation (CRP) may contribute to damaging effects of HT on end organs thereby increasing their CV risk.
ELEVATED CRP AND MEASURES OF OBESITY AMONG PATIENTS WITH HYPERTENSION

Several studies had demonstrated association between anthropometric indices of obesity (BMI, WC and WHR) and HT.\textsuperscript{116} This also reflected in this study as obesity was present in 14\%, 60\% and 70\% of hypertensive adults using BMI, WC and WHR respectively as against 8.8\%, 50.8\% and 55.6\% respectively among non-hypertensives. This was similar to the finding of Soyoye et al.\textsuperscript{117} However the prevalence of abdominal obesity was higher than 50.8\% Iloh et al documented in the eastern part of Nigeria. The difference might be due to ethnic difference and increasing incidence of obesity in Nigeria.

This study demonstrated association between elevated CRP and measures of obesity, similar to what Soyoye et al found\textsuperscript{117}. Association between high CRP and BMI was stronger among non-hypertensives than among hypertensives ($X^2=33.677$ vs $20.685$, $p<0.001$). This could be due to treatment benefit among hypertensive patients attending specialists’ clinics. Association between measures of central/peripheral obesity (WC and WHR) and elevated CRP were stronger among hypertensive patients despite being on antihypertensive medications than in non-hypertensives ($WC: X^2=35.903$ vs 10.912; WHR: $X^2=43.839$ vs 11.653). This suggests that antihypertensive medications might not have significant effects on
mitigating degree of inflammation associated with central/peripheral obesity among hypertensives. The finding also suggests that hypertensive patients with central/peripheral obesity are likely to have higher burden of inflammation and therefore, at higher cardiovascular risk compare to hypertensive patients with generalised obesity as shown by greater association between elevated CRP and WC/WHR than between CRP and BMI.

The contribution of higher WC and WHR to elevated CRP were highly significant in multivariate analysis. Azevedo et al posited that CRP concentration represents an intermediate step between obesity and HT if we consider that inflammatory activity (adipocytes secretes IL-6 which modulates CRP production and regulates insulin resistance) is the mechanism through which obesity increases risk of HT.118 Thus, higher WC and WHR are indicators (both in hypertensives and non hypertensives) of likely elevated CRP and both participated in a complex pathways to increase CV risk. Determination of these (WC and WHR) will not cause extra financial burden for the patients, likewise, determination of serum CRP is relatively cheaper. Therefore they can be easily incorporated into routine clinical evaluation of hypertensive patients.
ELEVATED CRP AND LIPID PROFILE AMONG PATIENTS WITH HYPERTENSION

The study demonstrated association between elevated CRP and TC, LDL-c, TG and low HDL-c as previously documented among hypertensive patients and non-hypertensive individuals by Ding et al.\textsuperscript{115} and Salam NZ.\textsuperscript{119} Association between TC, LDL-c and CRP were stronger among non-hypertensives than in hypertensive patients (p=0.005 vs 0.012 and 0.005 vs 0.020) respectively. This could be explained by antilipemic effects of statins among hypertensive which lowers TC and LDL-c by 30\% and 40\% respectively, thereby reducing association between CRP and these sub-fractions of blood lipids among hypertensive patients. Similar effect was also observed between association of CRP and HDL-c but less obvious (p=0.001 vs <0.001). Statins increase serum HDL-c by 6\%.

In contrast to stronger association between CRP and TG among hypertensive (p<0.001), there was no association among non-hypertensives. This suggests that hypertension contributed to the association. However contribution of obesity could not be rule out. In binary logistic regression, elevated TG and low HDL-c were among factors that determine elevated CRP. However, Ding \textit{et al} found HDL-c to be a dominated factor for CRP level in stepwise regression analysis.
Higher level of TG is accompanied by TG-rich lipoproteins enriched with apo-protein C III which activate NF-Kβ (nuclear factor kappa beta). Activation of NFKβ leads to increase in inflammatory molecules, including interleukin 6, which modulate CRP secretion. Considering high prevalence of central obesity among the study group, this appeared to modulate the pathophysiology of elevated TG. Elevated TG often is accompanied by low HDL-c and other lipid abnormalities that promote atherosclerosis. This study suggests that vascular inflammation may exacerbate the pro-atherogenic effects of dyslipidemia and hypertension contributes to effects of inflammation hypothesis of obesity on dyslipidemia seen among obese individuals. Thus measures that address obesity (central/peripheral obesity in particular), dyslipidemia, hypertension and low grade vascular inflammation will likely go a long way in improving clinical management of hypertensive patients.

**ELEVATED CRP AND DIABETES MELLITUS AMONG PATIENTS WITH HYPERTENSION**

There was no association between elevated CRP and diabetes mellitus among hypertensive patients in this study, in contrast to the finding of Baba *et al.* This could be due to small number of hypertensive-diabetic patients that met inclusion criteria in this study and this finding could not be generalised. Higher percentage (51.1%) of hypertensive-diabetic had
fair glycemic control (FPG<7.0mmol/l) and this may also attenuates association between CRP and DM among hypertensive patients.

**POTENTIAL PATHWAYS LINKING DETERMINANTS OF ELEVATED CRP**

There is a complex interplay among the factors that contribute to or determine elevated CRP. The relationship between inflammation and these CV risk factors may be direct or indirect. Determinants of elevated CRP in this study were increasing age, high TG, low HDL-c, QTc prolongation, high MAP, high WC, high WHR and presence of ECG-LVH. Adipocytes secrete interleukin 6 (IL-6) which modulates CRP production by hepatocytes.\(^{118}\) Both local and systemic inflammation produce similar response via inflammatory mediators. CRP activities in atherothrombosis\(^{57,58}\) and vasoconstriction\(^{59,60,64-66}\) have been mentioned earlier, promoting CAD and systemic HT.

Elevated TG and low HDL-c are associated with obesity. Elevated TG has been linked to activation of NF-Kβ, with associated production of inflammatory molecules that increase hepatic production of CRP.\(^{120}\) During inflammation, inflammatory molecules (like IL-6 and TNF-α) increase central sympathetic outflow from the brain. Through this pathway, systemic HT may be initiated and maintained.\(^{121}\) Also, sympathetic-induced modulations of cardiomyoctes ion currents occur,
promoting delayed ventricular repolarisation. The link between obesity, LVH and inflammation was mentioned earlier. Thus, the complex interplay among these factors show that CRP, a marker of inflammation, could also serve as marker of other CV risk factors. CRP is an independent CV risk factor; its assay along with assessment of other CV risk factors (ECG-LVH in particular), is likely to improve their clinical performance in patient’s management.

CHAPTER SIX
CONCLUSION
This study among patients with HT, showed association between elevated CRP (≥2mg/l), sociodemographic characteristic (age, gender and cigarette smoking). There was association between elevated CRP and SBP, PP, MAP, but not with DBP. Elevated CRP was associated with fractions of serum lipid (low HDL-c, LDL-c, TC and TG). Association existed between elevated CRP and anthropometric indices of obesity in both genders. Central and peripheral obesity seemed to play major link between elevated CRP and other cardiovascular risk factors including ECG LVH.
Elevated CRP was significantly associated with ECG LVH (with or without HT) and prolonged QTc. There is high prevalence of elevated CRP (≥2mg/l) among adult Nigerians with HT (51.2%) and ECG LVH (54.3%) despite that they are on treatment. Significant determinant factors of elevated CRP among hypertensive patients in this study are increasing age, increasing serum TG, low serum HDL-c, QTc prolongation, high MAP, WC, WHR and presence of ECG LVH.
RECOMMENDATIONS

1. Health education in terms of regular community health campaign, should be given a priority in the community on the identification and reduction of cardiovascular risk factors (central and peripheral obesity in particular). This will go a long way in reducing the number of people that may develop CVD.

2. Adequate health education of patients and relatives (during health talk) on prevention/treatment of cardiovascular risk factors should be an integral part of every clinic visit.

3. At a relatively cheaper cost, serum hsCRP should be added to biochemical panel requested for during initial work up of patients with systemic HT to fully characterise their cardiovascular risk.
LIMITATIONS OF THE STUDY:

1. Some of the factors that influence serum CRP like occult infections could not be ruled out among participants because of limited time and financial constraint.

2. Inadequate availability of ambulatory BP monitors to improve characterisation of BP of participants.
**DURATION OF STUDY:** The study was carried out between April 2015 and June 2016.

**ETHICAL CONSIDERATION:**

Ethical approval was obtained from the hospital’s Ethics and Research committee. Informed verbal and written consent was obtained from participants. A copy of the ethical clearance is attached as appendix V and a sample of the informed consent attached as appendix II.
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APPENDIX I.

QUESTIONNAIRE

ASSOCIATION BETWEEN SERUM C-REACTIVE PROTEIN AND ECG DETERMINED LEFT VENTRICULAR HYPERTROPHY IN ADULT HYPERTENSIVE PATIENTS IN FEDERAL MEDICAL CENTRE IDO EKITI.

Name (initials only)..........................................................

Age...... Gender..............

Religion............. Marital status.......... Weight......

Ht....... BMI........

Waist circumference.......... 

1. Are you known to have hypertension? Yes/No 

2. Duration of hypertension

3. Are you on medication(s)? 

4. List of medications..........................................................................................................................

............... 

5. Are you regular on your medications? Yes/ No

6. If no, give reason(s).

7. Do you have diabetes mellitus? Yes/no
8. If Yes, duration.............
9. Do you have family history of hypertension?
10. Any family history of diabetes mellitus?
11. Do you have wound in any parts of you body, toothache, cough, painful micturition, ear ache or discharge?
12. Any history of early facial swelling, frothiness of urine, or reduce urine output?
13. Any history of orthopnoea, PND?

15. Result of investigations

A) TC...... LDL-C......

TG....... HDL-C......

B) ECG: R(I)------ Sv1+ RV6 or V5------ Sv2+RV6-------- Tv5 or V6

C) Urinalysis............ protein ......, glucose,....... Nitrite/Leucocyte esterase............

D) Serum hs-CRP............

E) FBS...........

F)BP............ PP.......... MAP.................
APPENDIX II

INFORMED CONSENT FORM

I, Dr. Ajayi B A of the department of Internal Medicine, Federal Medical Centre, Ido-Ekiti, Ekiti State is carrying out this study to determine the association between serum CRP and ECG determined left ventricular hypertrophy in adult hypertensive patients in this hospital.

- You will be required to respond to some questions from a questionnaire which include some clinical details, physical and laboratory examinations

- The cost of this study is on me and you will not be required to pay for anything except a little part of your time.

- All the information will be kept in confidence and will be use only for this study. Your participation is also anonymous and the information cannot be linked to you.

- Your participation in this study is voluntary. You can withdraw anytime you like.

- There is no vested interest that may prevent an objective conduct of this research.

Above information has been fully explained to ------------------------------- ---.
I have been fully informed about the purpose, methods, risks and benefits of this study in the language I understand and I know that my participation is voluntary and that if I choose not to participate my clinical treatment will not be affected. I also understand that I may freely stop being part of the research at any time. I have a copy of this form for myself.

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Participant’s signature/ thumbprint

Investigator’s signature