CHAPTER ONE: INTRODUCTION

1.1 Introduction

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. DM threatens to become a global health crisis; treating diabetes and its complications is going to dominate future health care expenditures. Some 425 million people worldwide, or 8.8% of adults 20-79 years, are estimated to have diabetes and out of these 79% live in low and middle-income countries.[40] This value increases to 451 million if we expand the age to 18-99years and at this rate, by 2045, 693 million people 18-99 years, or 629 million of people 20-79 years, will have diabetes.[40] Type 2 diabetes mellitus (T2DM) accounts for about 90% of the total diabetic population, and coronary artery disease (CAD) is the most common cause of morbidity and mortality in patients with diabetes.[1] Cardiovascular deaths are increased up to fourfold in patients with diabetes compared with their nondiabetic counterparts.[1]

Cardiovascular disease, the major cause of mortality and morbidity in modern societies, is set to overtake infectious diseases in the developing world as the most common cause of death. The increasing prevalence of major and emerging cardiovascular risk factors accounts for the growing burden of cardiovascular disease in the world.[14] Diabetes is one of the main cardiovascular risk factors. Two out of three diabetic patients will die as a result of cardiovascular complications, and approximately 30% of patients treated in cardiovascular intensive care units have diabetes.[14]

Several clinical trials (such as United Kingdom Prospective Diabetes Study (UKPDS) as well as a metanalysis done in 2015 by Kelly et al) have demonstrated the benefit of tight control of risk factors on the incidence and mortality from cardiovascular disease.[23] However, in clinical practice, few patients achieve the therapeutic goals. The current diagnostic procedures for subclinical cardiovascular disease in T2DM patients have not been shown to improve prognosis or mortality, probably because they do not categorize cardiovascular risk. Thus, clinical practice guidelines by The American Diabetes Association (ADA) “Standards of Medical Care in Diabetes” 2018, do not systematically recommend screening for subclinical atherosclerosis in these patients, although it is known that patients with extra-coronary atherosclerosis, microangiopathy and poorly-controlled cardiovascular risk factors are at high risk for cardiovascular disease. Improvements in the reliability of diagnostic tests, with fewer side

effects and better cost efficiency, may better help to stratify cardiovascular risk in this group of patients, and further evaluation on this topic should be considered.[27]

However, given the poor risk factor control in clinical practice, it is essential to evaluate strategies for early diagnosis of cardiovascular disease in T2DM patients, especially since the disease is often asymptomatic and has worse prognosis in these subjects than in non-patients with diabetes.[28] A substantial percentage of patients with T2DM have silent myocardial ischemia, and these patients are at greater risk for cardiovascular events such as cardiomyopathy, heart failure, recurrent myocardial infarction.[29] Therefore, the diagnosis of silent coronary disease may help to identify subjects at very high risk and consequently aid the implementation of more aggressive risk reduction strategies in this subgroup of patients.[27]

Diabetes is a prime risk factor for cardiovascular disease (CVD). Vascular disorders of diabetes include retinopathy and nephropathy, peripheral vascular disease (PVD), stroke, and coronary artery disease (CAD). Hyperglycemia affects the heart muscle, causing both systolic and diastolic heart failure.[2] There is convincing evidence from epidemiological and pathophysiological studies that hyperglycemia has a detrimental effect on cardiovascular risk profile.[41] It is well known that among patients with type 2 diabetes, those with higher levels of blood glucose and HbA1c are at greater risk for CVD.[23] Glycemic fluctuations and chronic hyperglycemia are triggers for inflammatory responses via increased endoplasmic reticulum stress and mitochondrial superoxide production.[41] The molecular pathways underlying hyperglycemia, low-grade inflammation, and oxidative stress have been widely recognized in the pathogenesis of endothelial dysfunction, which represents the first step of atherogenesis.[41] Through this pathway, hyperglycemia-induced early atherogenesis may lead to an increased probability of cardiovascular events later in life. Direct effects of glucose toxicity, oxidative stress, and low-grade inflammation act in a vicious cycle that determines impaired insulin sensitivity, β-cell loss, and endothelial dysfunction, thus leading to micro- and macrovascular complications.[41]

Screening for peripheral arterial disease (PAD) in patients with diabetes can identify subclinical cardiovascular disease. Ninety per cent of patients with established PAD (determined using Ankle Brachial Index) have coronary atherosclerosis on angiography.[27] In accordance with this observation, the presence of PAD is a predictor of symptomatic coronary artery disease, as established in a meta-analysis done in 2014 by Chillaron et al.[27] Studies in patients who have suffered a stroke showed an 18%-38% prevalence of asymptomatic heart disease.[42, 43] Thus,

patients with extra-coronary atherosclerosis are at high risk of coronary involvement, and therefore screening strategies should be considered along with aggressive treatment of cardiovascular risk factors.[42]

Microalbuminuria and chronic kidney disease are clearly associated with cardiovascular disease as the incidence of coronary heart disease or cardiac death 5 years after kidney failure diagnosis is 40%,[31] and the age-adjusted hazard ratio for the development of coronary heart disease is 1.66 (95%CI: 1.24-1.92) when microalbuminuria is present, and may rise to 2.84 (95%CI: 1.80-4.46) in the case of macroalbuminuria.[32] Although the pathophysiologic explanation for this association is not fully understood, factors associated with the development of microalbuminuria or renal failure, such as a nocturnal rise in blood pressure, increased lipoprotein(a) and homocysteine levels or elevation of inflammatory markers and insulin resistance could play a role.[2]

In any event, multiple observational studies[31,32,41] confirmed this association, and thus patients with T2DM and any renal impairment stage should be considered at high risk for asymptomatic coronary artery disease.

Closely linked to type 2 diabetes is the metabolic syndrome (the clustering of several metabolic risk factors). These risk factors of metabolic syndrome are associated with insulin resistance, which is related to coronary heart disease and diabetes. Cardiovascular risk factors often seen in conjunction with the metabolic syndrome include hypertension, atherogenic dyslipidemia, a prothrombotic state, and in many patients, glucose intolerance.[3]

Recent studies suggest that the absolute risk for major coronary events in patients with type 2 diabetes approaches that of nondiabetic patients with established coronary heart disease. Also, once patients with diabetes develop clinical coronary heart disease, they have a particularly bad prognosis, both acutely in the post infarction period and over the long term.[6] Consequently, it is necessary that most patients with diabetes deserve the aggressive intervention on risk factors typically reserved for patients with clinically established coronary disease. It is important to recognize that the pathogenesis of diabetes-associated CVD is only partially understood and that expanded basic and clinical research is needed to determine the best and most efficacious ways to reduce cardiovascular complications in these high-risk patients. In addition, more needs to be learned about factors relatively unique to type 1 and type 2 diabetes, such as autoimmune

inflammatory and immunological responses, and the clustering of CVD risk factors in type 1 and type 2 patients, respectively, which may contribute to the increased risk for CVD.[4]

One reason for the poor prognosis in patients with both diabetes and ischemic heart disease seems to be an enhanced myocardial dysfunction leading to accelerated heart failure (diabetic cardiomyopathy).[11] Diabetic cardiomyopathy is defined as structural and functional myocardial abnormalities without coronary artery disease, hypertension or valvular heart disease. It is characterized by diastolic dysfunction. Several factors probably underlie diabetic cardiomyopathy: severe coronary atherosclerosis, chronic hyperglycemia, microvascular disease, glycosylation of myocardial proteins, and autonomic neuropathy. The responsible mechanisms are left ventricular hypertrophy (increased left ventricular mass and concentric remodeling, myocardial lipotoxicity, increased oxidative stress, cell death, interstitial and perivascular fibrosis, impaired contractile reserve, changes in myocardial substrate and energy metabolism, altered substrate utilization and mitochondrial dysfunction.[11] Thus, patients with diabetes are unusually prone to congestive heart failure.

The lack of diagnostic facilities limits the study of CAD in sub-Saharan Africa. Coronary angiography and myocardial scintigraphy are available only in a few urban health facilities. A relatively young population, inadequate diagnostic facilities, and death before arrival at a health facility may be partly responsible for the relatively low incidence of ischemic heart disease in sub-Saharan Africa.[3]

Kuller et al[35] in 2000 did a study in USA which documented that there was a substantial increase in relative risk of death in patients with diabetes associated with subclinical disease as compared with both the risk of death associated in neither patient with diabetes nor subclinical disease. The incidence of CHD (including MI and angina) cases was higher in diabetic participants and those with impaired glucose tolerance (IGT). However, the increase in incident disease risk was largely confined to those with prevalent subclinical CVD at baseline. The risk for incident stroke (fatal and nonfatal) was elevated for diabetic participants with and without subclinical disease at baseline. Only those with IGT with prevalent subclinical CVD at baseline had increased risk of stroke. A similar pattern was seen for CHF. The study concluded that the primary determinant of the risk of clinical CVD among older patients with diabetes (prevalent and newly diagnosed) is the presence of subclinical disease.

IGT is a risk factor for clinical CVD, primarily among participants who also exhibited subclinical disease. The prevalence of subclinical disease is very high among older patients with diabetes. The measurement of subclinical disease may enhance risk stratification among diabetic patients.

No study has been done in Zambia to detect if patients develop cardiac complications despite not yet being clinically evident and the range of ScCVD that occur. If detected early, these complications could be addressed to prevent further development of cardiovascular disease and thereby improving morbidity and mortality in patients with diabetes.

1.2 Statement of Problem

About half the patients that visit hospital facilities worldwide are patients with diabetes with a vast majority of these presenting with Cardiovascular complications such as cardiomyopathy or myocardial infarction whereas others might still be asymptomatic yet already developing cardiac complications.[4] Cardiovascular complications are now the leading causes of diabetes-related morbidity and mortality worldwide. The public health impact of cardiovascular disease (CVD) in patients with diabetes is already enormous and is increasing as stated by American Heart Association. Several explanations are behind this increase.

a) The incidence of diabetes rises with advancing age, and the number of older people is growing rapidly.
b) Insulin treatment for persons with type 1 diabetes has prolonged their lives significantly, and with each additional year of life comes an increased risk for CVD complications.
c) Diabetes occurs at an earlier age in obese and overweight persons, and the prevalence of obesity is rising.

These factors will lead to an absolute increase in the number of patients who will require medical intervention to prevent the complications of diabetes.[5]

There are no published studies done in Zambia that show the spectrum of cardiovascular diseases in diabetic patients.

1.3 Research question

What are the various forms of subclinical CVD manifestations in patients with diabetes presenting to the out-patient clinic in relation to their blood glucose control?

1.4 Objectives

General

1. To describe the spectrum of CVD manifestation in asymptomatic diabetic patients

Specific

1. To document the subclinical (Sc) CVDs on ECG, ECHO
2. To correlate the various ScCVD with level of sugar control based on HbA1c including the prevalence of silent myocardial ischemia in diabetic patients
3. To determine the risk factors associated with ScCVD

1.5 Study justification

Diabetes has long been recognized to be an independent risk factor for CVD. Individuals with diabetes have twice the incident myocardial infarction (MI) rate as the general population, and survival rates are lower among individuals with diabetes once they have an adverse cardiovascular event.[48] Women with diabetes and CVD, regardless of menopausal status, have a four- to six-fold increase in the risk of developing CVD, whereas men with diabetes have a two- to threefold increased risk of CVD compared to women and men without diabetes.[6,8] Diabetes acts as an independent risk factor for several forms of CVD. To make matters worse, when patients with diabetes develop clinical CVD, they sustain a worse prognosis for survival than do CVD patients without diabetes.[6, 7, 8] Because individuals with diabetes are at higher risk for CVD events than individuals without diabetes and are at risk for future events if they have already had one, it is necessary to screen all patients with diabetes for cardiovascular complications.

The association of subclinical cardiovascular manifestations with level of glycemic control will be evaluated in this study. Early detection of these subclinical cardiovascular manifestations could help institute preventative measures to prevent progression of these cardiovascular complications.

CHAPTER TWO: LITERATURE REVIEW

2.1 Prevalence of Disease

About four hundred and fifty million people have diabetes in the world and more than 14 million people in Africa, by 2040 this figure will more than double.[36] Approximately four percent (3.94%) of the global number of patients with diabetes are in Zambia.[37] There were 218,200 cases of diabetes in Zambia in 2015 and 680,904 cases in 2016.[21]

Diabetes-related cardiovascular disease complications are considered to be rare in Africa but are on the rise and are regularly associated with classic cardiovascular risk factors.[14] Coronary heart disease may affect 5% to 8% of type 2 diabetic patients and cardiomyopathy, up to 50% of all patients.[14] Close to 15% of patients with stroke have diabetes, and up to 5% of diabetic patients present with cerebrovascular accidents at diagnosis.[14] Peripheral vascular disease prevalence varies across sites from 4% to 28%.[14]

Prospective studies, such as the Framingham, Honolulu, and San Antonio Heart Studies, as well as numerous more recent population studies in the United States and other countries, have documented the excess CVD risk in patients with diabetes from multiple racial and ethnic groups. The adverse influence of diabetes extends to all components of the cardiovascular system: the microvasculature, the larger arteries, and the heart, as well as the kidneys. Because of the increasing prevalence of diabetes in our society, it now rivals cigarette smoking, hypertension, and cholesterol disorders as a major risk factor for CVD. It is a particularly strong risk factor among women and among the growing elderly population.[21]

In the Multiple Risk Factor Intervention Trial (MRFIT), men with diabetes had a threefold higher absolute risk of cardiovascular death than non-diabetic men (160 vs 53 cardiovascular deaths per 10 000 person-years) even after controlling for age, race, income, cholesterol levels, blood pressure and smoking.[10]

The Framingham Study 20-year follow-up similarly demonstrated that patients with diabetes not only had a higher mortality with their index event; they also had a higher incidence of reinfarction and heart failure in the acute and post infarction periods.[9]

The risk of a first cardiovascular event in patients with diabetes is as high as in non-diabetic patients who have already had a cardiovascular event.[11] The American Heart Association as

well as the European Cardiology association guidelines reflect this concept by treating diabetes without overt coronary disease as a "post infarct" equivalent.

Diabetes doubles the risk for ACS with an additional doubling of the clinical risk once the event has occurred. Patients with diabetes present acutely more often with heart failure or non-ST elevation ACS than ST elevation MI.[12]

2.2 Glucose levels and Cardiovascular Complications

In the Europe and Diabetes (EURODIAB) study[3] on diabetic individuals with a normal QTc at baseline, female sex and higher values of hemoglobin A1c and systolic blood pressure were associated with increased risk of prolonged QTc, whereas physical activity and normal body mass index were protective factors.

In type 1 diabetes as compared to type 2 diabetes, the relationship of hyperglycemia with microangiopathy as well as macroangiopathy seems to be more significant.[18] According to the results of a large Finnish database, CVD mortality in patients with type 1 diabetes aged from 45–64 years at baseline increases by about 50% with every 1% increase in glycosylated hemoglobin (HbA1c).[18]

An important reason to become more aggressive about the cardiovascular complications of diabetes resides in the positive results achieved in recent clinical trials. Recent controlled trials[48-50] of cholesterol-lowering therapy, particularly secondary prevention trials, showed that reducing low-density lipoprotein cholesterol levels results in a striking decrease in major coronary events in patients with type 2 diabetes. Blood pressure–lowering trials, such as the Systolic Hypertension in the Elderly Program (SHEP) and the United Kingdom Prospective Diabetes Study (UKPDS), likewise have shown a reduction in cardiovascular events in patients with diabetes comparable to benefits found in those without diabetes. The Diabetes Control and Complication Trial (DCCT) showed that improved glycemic control can prevent or reduce microvascular disease and may reduce macrovascular disease in patients with type 1 diabetes. The UKPDS demonstrated similar benefits in decreasing microvascular disease by controlling hyperglycemia in patients with type 2 diabetes and reported that glycemic control probably reduces macrovascular disease. These positive results call for aggressively treating the cardiovascular risk factors often seen in people with diabetes as well as to ensure that their patients with diabetes are supported in their efforts to maintain tight control of their blood

glucose. Overall, results of these trials provide strong evidence that comprehensive risk factor control with drugs and other methods available today will substantially reduce the macrovascular complications of diabetes.

2.3 Cardiovascular Changes

Okin et al., 2004 also found that both QTc prolongation and ST depression predicted all-cause mortality in patients with type 2 diabetes mellitus.[15] Hyperinsulinemia-induced hypoglycemia prolong the QTc interval and decrease T-wave area and amplitude.[16]

Fibrotic changes, especially in the basal area of the left ventricle, have frequently been observed in diabetic patients, even when cardiac involvement is clinically not yet evident.[13]

The EURODIAB Insulin-Dependent Diabetes Mellitus Complications Study (EURODIAB IDDM)[17] investigated 3250 type 1 diabetes patients with an average diabetes duration of >30 years; the prevalence of left ventricular hypertrophy was found to be 3 times greater than that reported in the general population of similar age.

Myocardial ischemia is more often painless in patients with diabetes mellitus. Resting ECG abnormalities as well as cardiac autonomic dysfunction are predictors of silent ischemia in asymptomatic persons with T1D.[6, 7, 8]

Both type 1 diabetes and type 2 diabetes are independent risk factors for CHD. Moreover, myocardial ischemia due to coronary atherosclerosis commonly occurs without symptoms in patients with diabetes.[19] As a result, multivessel atherosclerosis often is present before ischemic symptoms occur and before treatment is instituted.[19] A delayed recognition of various forms of CHD undoubtedly worsens the prognosis for survival for many diabetic patients.[25]

CHAPTER THREE: METHODOLOGY

3.1 Study design and site

A cross sectional descriptive study at the Medical Outpatient Department (Clinic 5) of the University Teaching Hospital, Lusaka, Zambia.

3.2 Study population

All patients presenting to the Out-Patient department with a diagnosis of Diabetes Mellitus without documented CVD, who came for their regular scheduled clinic visits, were screened for eligibility for recruitment into the study. The recruitment was done over a period of four (4) months. All consenting patients that presented during this time period were recruited into the study.

3.3 Eligibility

Inclusion Criteria

All patients who were:

- Known to have Diabetes
- Age of either sex above 18 years (age at which patients get seen in the Adult Out Patient Clinic)
- Willing to participate in the study

Exclusion Criteria

- Known cardiac patients
- Pregnant women

3.4 Study procedure

Patients were screened weekly. Informed signed consent was sought, and enrolment was done of every third patient screened. All patients in this study were able to give individual consent without requirement for a surrogate. A face- to- face questionnaire was administered to the

eligible participants. Blood samples were collected from each participant by vein puncture. Spot urine samples were collected, and a urinalysis done on the spot.

Tests were divided to assess the cardiac function, the control of the blood glucose and any other risk factors

1. Cardiac Function:
   A) ECHO
   B) ECG
   C) ANKLE BRACHIAL INDEX

2. Blood Glucose Control
   A) HbA1c
   B) Fundoscopy – was done by 2 Ophthalmic nurses, trained by Ophthalmologists
   C) Urine albumin

3. Other Risk Factors
   a) Fasting lipid profile
   b) Blood pressure – was measured using a Mckesson Adult Sphygmomanometer with two cuff sizes to account for the obese and the slim participants. The participant was requested to seat in the chair and rest for at least 15 minutes with legs not crossed, before recording the blood pressure. Blood pressure was measured on both arms with calf 2 cm above the elbow. The average blood pressure for the two readings was recorded.
   c) BMI – was calculated from the formula: BMI= Weight (Kg/height $(m)^2$
   d) Height was measured with the patient standing against a wall and then measuring from heel to top of the head with a scale drawn up on the wall.
   e) Weight was measured using the Equinox BR-9808 Mechanical personal scale. Participant was in light clothing, without shoes on

A Beckman Coulter AU 480 chemistry analyzer was used for all the chemistry samples which was collected in a green (Lithium heparin) specimen bottle while the Tosoh G8 HbA1c analyzer was used for HbA1c, collected in a purple (EDTA) specimen bottle.

ECHOCARDIOGRAPHY

Echo was done using the Philips Model HD11XE Echo Machine by a trained radiographer under the supervision of a cardiologist. The participant was placed in the left lateral position with the chest exposed and left arm tucked under the head. Left ventricular systolic function was measured from the left parasternal long axis or short axis views using the Teicholz method in M-Mode; any abnormal result was verified using the 2-dimensional Simpsons biplane method in the 4-chamber apical view. Chamber sizes and wall thicknesses were measured in 2-dimensional mode. Pulsed wave, continuous wave and color flow Doppler studies were used in determining flow velocities and pressures across the mitral valve, left ventricular outflow tract (LVOT), aortic valve, tricuspid and pulmonic valves. The pericardium and the Inferior vena cava were assessed from the subcostal view. A print out of all the measurements was obtained and attached to a standard reporting sheet.

ECG

Twelve-lead ECG measurements were conducted on each patient using the EDAN SE-1200 ECG Machine. The Minnesota Code (Appendix IV) was used for interpretation of the ECG tracings.

Ankle Brachial Index

This was calculated as a ratio of the systolic BP at the ankle (Dorsalis pedis artery) to the systolic BP at the arm (Brachial artery). The participants were required to expose their arms and legs. The legs were kept warm with a blanket to avoid low readings from cold-induced vasoconstriction. Systolic blood pressures were obtained using a standard analogue sphygmomanometer and BT-200 vascular Doppler machine.

All the above procedures were conducted on the same day. Participants found with severely elevated blood pressures were admitted for BP control. Health education was given to all participants found with any traditional cardiovascular risk factors (smoking, alcohol, increased BMI) in terms of lifestyle modifications, adherence to medications and regular clinic visits.

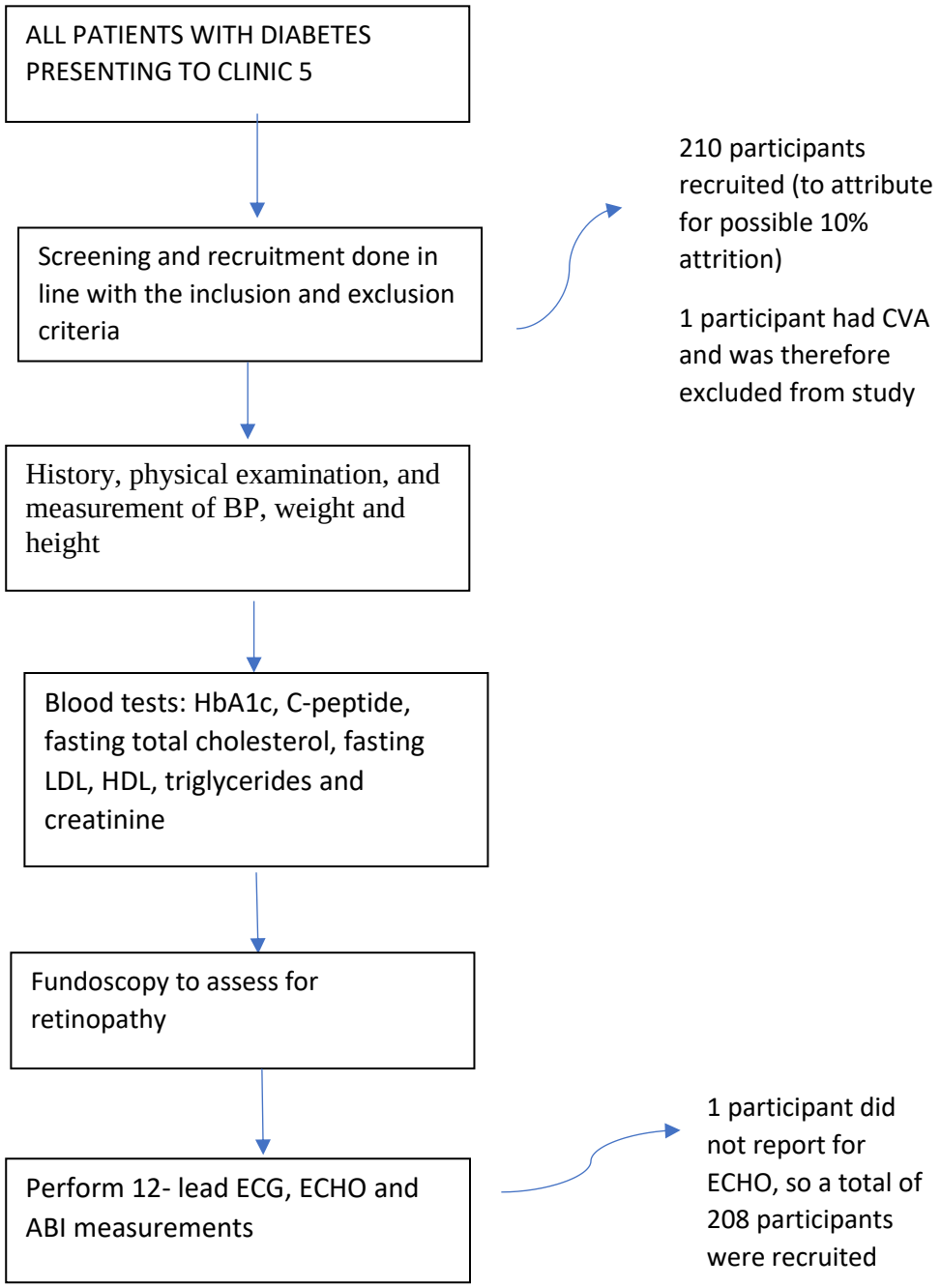

Figure 1. Patient flow chart

3.5 Outcomes

Dependent Variables:

Subclinical cardiovascular disease diagnosed from abnormalities found on either/or ECG, ECHO and ABI.

Independent Variables:

These included:

- Age
- Sex
- Duration of diabetes diagnosis,
- Regimen for sugar control (insulin versus oral hypoglycemic agents)
- Blood pressure
- BMI
- HbA1c
- Known smoker
- Fasting lipid profile
- Abnormal urinalysis
- Retinopathy

3.6 Sample size

The Prevalence formula was used to calculate sample size

$$N = \frac{Z^2 \times P(1-P)}{(E)^2}$$

Where

N = sample required

Z =Z statistic =1.96 (95% C I)

P= expected prevalence

E= confidence interval 0.05

The expected prevalence of cardiac diseases in outpatient patients with diabetes was estimated to between 11% - 22.5% based on earlier studies and sample size calculated was 195 patients.[20] To account for a possible 10% attrition, 210 patients were recruited.

3.7 Data entry

Data from each participant was collected on a hard copy data entry sheet. Each participant was assigned a participant identification number (PIN) which was double entered onto an electronic data entry excel 2016 spread sheet. No participant's names were used, to ensure confidentiality.

Routine monitoring of data collection tools by means of once daily spot checks for completeness and errors was carried out.

3.8 Statistical analysis

The data was analyzed using STATA MP Version 14.

Continuous variables with a Gaussian distribution pattern were expressed as means and standard deviation. A student t-test was used to compare the means. Non-Gaussian type of data was expressed as medians and comparisons were made using the Mann-Whitney U (Kruskal Wallis) test. Categorical variables were expressed as percentages and a Chi square test was used to analyze dichotomous variables.

Step down Logistic Regression was used to determine the relationship among variables traditionally leading to ScCVD.

Cardiovascular outcomes of interest were re-defined as dichotomized categorical variables where "normal" was evaluated against other categories. To determine the association of HbA1c to cardiovascular abnormalities of interest, we dichotomized the variable as On Target (normal) with HbA1c $\leq$ 7% and Raised (High) with HbA1c $\geq$ 7%. Other continuous variables that were dichotomized include blood pressure, total cholesterol and triglycerides. Multivariate logistic regression models were constructed to determine the association between various clinical factors (e.g. age, sex, hypertension, smoking, duration of diabetes, type of regimen) with the CVD outcomes of interest (abnormal EGC, ECHO and ABI), and the backward elimination method to derive the final adjusted odds ratio starting with variables with the highest p values were used.

A p-value of less than or equal to 0.05 was considered statistically significant.

3.9 Ethical Issues

All procedures were done under aseptic conditions by competent staff members. Ethical clearance was sought and given from the UNZA Research Ethics Committee. Permission was also granted from the University Teaching Hospital administration as well as the department of Internal Medicine. The purpose and procedures of the study was fully explained and a written informed consent obtained from the care givers. It was emphasized that participation in the study was purely voluntary and that participants may withdraw from the study at any point. The risks and benefits were fully explained to the participants as described in the consent form. Patient results were treated as strictly confidential. All data entry forms were identified by coded numbers only. The data entry sheets were locked in a secure cabinet and all electronic entries were password protected.

3.10 Study Limitations

This was a single center study; therefore, findings cannot be generalized to the entire Zambian diabetic population. Most of our blood tests were limited to routine tests done on patients with diabetes attending the out-patient clinic at UTH. We were unable to do myocardial perfusion scan, or angiography, or stress ECG studies screening for coronary artery disease, as well d-dimers, BNP or microalbuminuria screening, due to lack of both budgetary constraints and lack of equipment.

Another important limitation was that we did not divide the study group based on the duration of hypertension, alcohol consumption or years of smoking.

CHAPTER FOUR: RESULTS

From November 2017 to February 2018, 208 asymptomatic out-patients with diabetes were recruited in the study from Clinic 5 of the University Teaching Hospital in Lusaka, Zambia.

4.1 Baseline characteristics of the participants

The baseline characteristics of the participants are shown in Table 1. The mean age was 54 years; with the most common age range of 40-65 years and majority were females (77%). About 75.96 % of the participants had poorly controlled diabetes based on their raised HbA1c (mean was 9.6%) which ranged from 7.1%- 16.4%, with 50% of patients having an average fasting blood glucose of more than 7.8 mmol/L.

About 50.48% of participants had diabetes for more than 5 years with most of them being on oral hypoglycemic, mostly Metformin and Glibenclamide. A few of them (49.04%) were on Glipizide. About 45.67% of them were on insulin therapy. From history, hypertension was the commonest traditional CVD risk factor. About 61.54% of the participants had both diabetes and hypertension. Smoking was not a common risk factor, unlike alcohol (13.95% and 49.52%, respectively). On laboratory review, serum Total cholesterol and triglyceride levels were mostly normal (60.98% and 85.03% respectively).

Table 1. Baseline Characteristics of screened patients

Characteristic	Participants n=208	Percentage (%)
Age in years –mean (SD)	54.2	±2.99*
No. of females	160	76.92
Duration since Diabetes diagnosis > 5 years	105	50.48
Drug Type: Insulin	95	45.67
Oral Hypoglycemic	102	49.04
Both	11	5.29
Diagnosed Hypertension	128	61.54
Ever smoked	29	13.94
Ever taken alcohol	103	49.52
Waist mean (SD)cm	95.8	±13.86*
BMI mean (SD)	27.0	±5.09*
P.R – mean (SD) bpm	90.0	±9.40*
Systolic BP mean (SD) mmHg	146.0	±20*
Diastolic BP mean (SD) mmHg	87.0	±12*
HbA1c mean (%)	9.6	±2.99*
High HbA1c (>7%)	158	75.96
Average Fasting blood sugar was > 7.8 mmols/L	104	50
Total Cholesterol mean (SD) mmols/L	4.9	±1.31*
High cholesterol	80	38.46
Triglycerides mean (SD) mmols/L	1.5	±0.95*
High triglycerides	31	14.9

*****_standard deviation_

Table 2. Demographic characteristics of screened patients against level of sugar control (HbA1c)

DEMOGRAPHIC CHARACTERISTICS OF DM PATIENTS AT UTH			
		Number of patients (% of the total)	
HbA1c		**Normal**	**High**
SEX*	Female	32 (15.38)	128 (61.54)
	Male	18 (8.65)	30 (14.42)
AGE (years)*	<25	1 (0.48)	3 (1.44)
	25-39	4 (1.92)	18 (8.65)
	40-65	27 (12.98)	112 (53.85)
	>65	18 (8.65)	25 (12.02)
MARITAL STATUS	Single	2 (0.96)	11 (5.29)
	Married	25 (12.02)	101 (48.56)
	Divorced	5 (2.40)	7 (3.37)
	Widowed	18 (8.65)	39 (18.75)
EMPLOYMENT*	Unemployment	21 (42.00)	74 (46.84)
	Retired	14 (28.00)	22 (13.92)
	Professional	8 (16.00)	22 (13.92)
	Self Employed	7 (14.00)	40 (25.32)
EDUCATION	No Education	2 (4.00)	17 (10.76)
	Primary	19 (38.00)	55 (34.81)
	Secondary	25 (50.00)	77 (48.73)
	College/ University	1 (2.00)	3 (1.90)
BMI CAT	Underweight (<18.5)	0 (0.00)	9 (5.70)
	Normal (18.5-24.9)	14 (28.00)	43 (27.22)
	Overweight (25-29.9)	18 (36.00)	64 (40.51)
	Obese Class (≥30.0)	18 (36.00)	42 (26.58)
AVG FBS (mmols/L)*	<4	5 (10.00)	4 (2.55)
	4-7.8	40 (80.00)	54 (34.39)
	>7.8	5 (10.00)	100 (48.02)
ALCOHOL	No	27 (54.00)	78 (49.37)
	Ever Taken	23 (46.00)	80 (50.63)
HYPERTENSION	No	17 (34.00)	63 (39.87)
	Yes	33 (66.00)	95 (60.13)
SMOKER	No	44 (88.00)	135 (85.44)
	Ever Smoked	6 (12.00)	23 (14.56)
DURATION OF TX	< 1 YEARS	9 (18.00)	22 (13.92)
	1 – 5 YEARS	19 (38.00)	53 (33.54)
	5 YEARS	22 (44.00)	83 (52.53)

* statistically significant

Table 2 elucidates how employment plays an important role in glucose control. Participants who were unemployed had high levels of HbA1c, which could mean failure to comply to treatment as a result of their inability to afford the cost of the medications, or transport fares to and from the hospital for review. Medication noncompliance may also be an issue if patients

that cannot afford regular meals. The higher the average fasting blood glucose, the higher the HbA1c, as expected. Participants aged 25-39 years had the worst glycemic control, which may be due to treatment noncompliance resulting from work related problems; some participants in this age group may miss their doses because they are afraid to carry their drugs to their workplaces. Treatment noncompliance would also result from suboptimal medication prescription by the prescriber.

4. 2 Noncardiac complications

Table 3 shows that 80.29% of the patients had normal urinalysis with no proteinuria, glycosuria or ketonuria. About 57.77% of the participants had a normal right eye fundoscopy and 55.82% had a normal left eye fundoscopy. Age, drug type, duration of treatment and average fasting blood sugar did not show any trend for the urinalysis or fundoscopy changes.

Table 3. Noncardiac Complications

NON - CARDIAC COMPLICATIONS							
		URINALYSIS		**RIGHT FUNDOSCOPY**		**LEFT FUNDOSCOPY**	
		Normal n (%)	**Abnormal n (%)**	**Normal n (%)**	**Abnormal n (%)**	**Normal n (%)**	**Abnormal n (%)**
SEX	**M**	41 (19.71)	7 (3.37)	27 (13.10)	20 (9.71)	34 (16.50)	13 (6.31)
	F	126 (60.58)	34 (16.35)	60 (29.13)	99 (48.06)	81 (39.32)	78 (37.86)
		P = 0.31		P = 0.02		P = 0.01	
AGE (YEARS)	**<25**	3 (1.44)	1 (0.48)	2 (0.97)	2 (0.97)	2 (0.97)	2 (0.97)
	25-39	15 (7.2)	7 (3.37)	8 (3.88)	13 (6.31)	11 (5.34)	10 (4.85)
	40-65	113 (54.33)	26 (12.50)	59 (28.64)	79 (38.35)	75 (36.41)	63 (30.58)
	>65	36 (17.31)	7 (3.37)	18 (8.74)	25 (12.14)	27 (13.11)	16 (7.77)
		P = 0.47		P = 0.97		P = 0.77	
DRUG REGIMEN	**INSULIN**	75 (36.06)	20 (9.62)	37 (17.96)	57 (27.67)	46 (22.33)	48 (23.30)
	ORAL HYPOGLYCEMICS	86 (41.35)	16 (7.69)	46 (22.33)	55 (26.70)	61 (29.61)	40 (19.42)
	BOTH	6 (2.88)	5 (2.40)	4 (1.94)	7 (3.40)	8 (3.88)	1 (1.46)
		P = 0.05		P = 0.63		P = 0.14	
DURATION OF TX	**<1 YEAR**	26 (12.50)	5 (2.40)	12 (5.83)	18 (8.74)	17 (8.25)	13 (6.31)
	1-5 YEARS	56 (26.92)	16 (7.69)	29 (14.08)	43 (20.87)	43 (20.87)	29 (14.08)
	>5 YEARS	85 (40.87)	20 (9.62)	46 (22.33)	58 (28.16)	55 (26.70)	49 (23.79)
		P = 0.75		P = 0.84		P = 0.67	
HbA1c	**Normal**	45 (21.63)	5 (2.40)	23 (11.17)	27 (13.11)	30 (14.56)	20 (9.71)
	High	122 (58.65)	36 (17.31)	64 (31.07)	92 (44.66)	85 (41.26)	71 (34.47)
		P = 0.04		P = 0.54		P = 0.50	
AVG FBS (mmols/L)	**<4**	8 (3.86)	1 (0.48)	2 (0.98)	7 (3.41)	4 (1.95)	5 (2.44)
	4-7.8	79 (38.16)	15 (7.25)	44 (21.46)	49 (23.90)	56 (18.05)	37 (27.32)
	>7.8	79 (38.16)	25 (12.08)	40 (19.5)	63 (30.73)	54 (26.34)	49 (23.90)
		P = 0.29		P = 0.23		P = 0.43	

Figure 2 illustrates the distribution of noncardiac microvascular complications in participants with diabetes mellitus in relation to HbA1c. The abnormalities noted were presence of glycosuria and proteinuria. None of the patients had ketonuria. High HbA1c was associated with abnormal urinalysis. This is probably an underestimate as microalbuminuria was not investigated. The same findings applied to the fundoscopy examination. Fundoscopy findings ranged from Non-Proliferative diabetic retinopathy to Proliferative diabetic retinopathy. A few patients had glaucoma and cataracts.

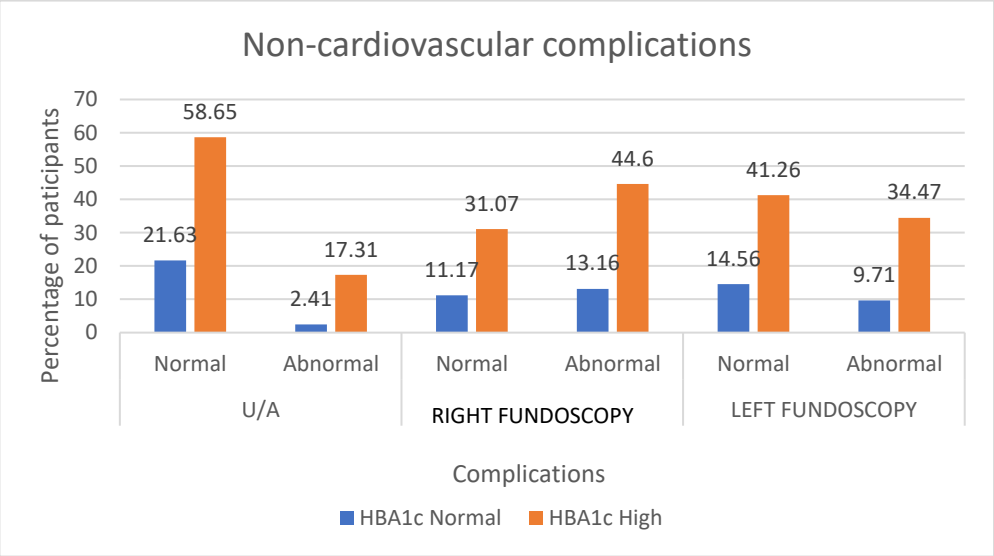

Figure 2. Non-cardiac complications against glycosylated hemoglobin A1c

4.3 ECG ABNORMALITIES

Figure 3 gives a visual representation of the distribution of various abnormalities seen on ECG in this population. The clinical characteristics against the overall ECG abnormality has been shown in Table 4 while the important ECG changes that occur in diabetes were looked at in detail as shown in Table 5.

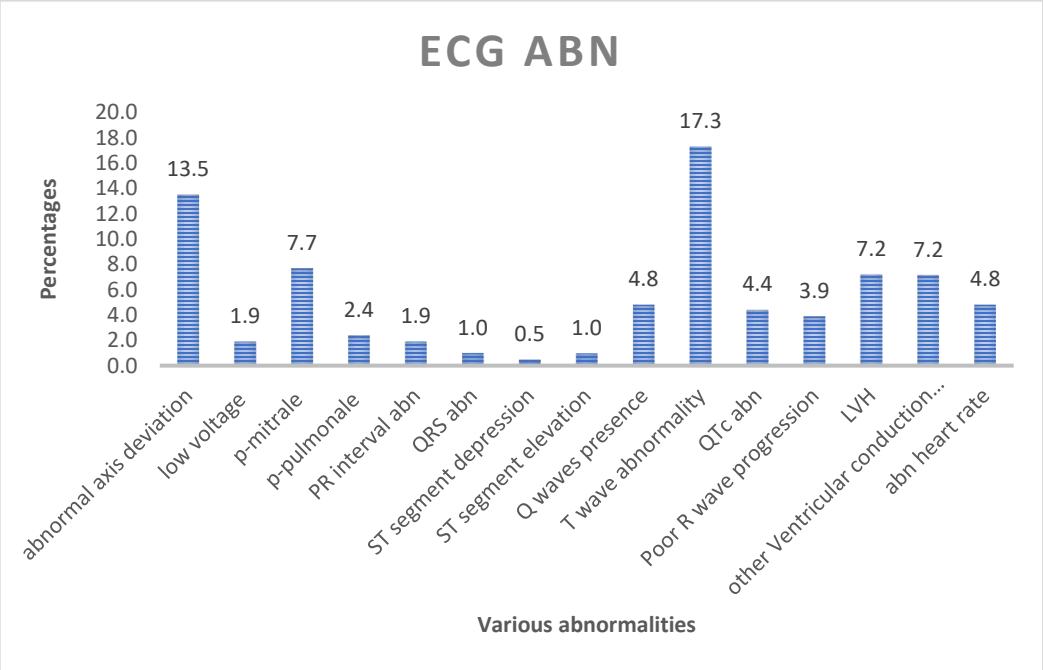

Figure 3. ECG Abnormalities

T wave abnormality was the commonest abnormality seen, followed by abnormal axis and Left ventricular hypertrophy (LVH). Other abnormalities included short and prolonged QRS waves, ST depression and elevation, presence of Q waves, premature ventricular conduction, right bundle branch block, poor R wave progression and QT prolongation. The low voltage was noted in patients with a raised BMI which is expected. T wave abnormality is often associated with increased BMI as well as can be a predictor of ST depression. While permanent negative T waves in the chronic stage of MI have indicated the presence of transmural infarction. T waves in a post-myocardial phase have been shown to be associated with the presence of viable myocardium at jeopardy. T waves should therefore be regarded as a dynamic substrate.

Based on the Figure 4 (below), it was noted that 57% of patients had only 1 abnormality (#1) on ECG predominantly T wave changes followed by axis deviation and Left Ventricular Hypertrophy. 29% had 2 abnormalities (#2). These ranged from combinations of P-wave abnormality with T wave changes or Poor R wave progression with T wave abnormality. About 13% of the participants had 3 ECG abnormalities (#3). These mostly were combinations of Left Anterior Hemiblock, axis deviation and T wave abnormalities.

Only 1% had 4 abnormalities (#4) that included RBBB, axis deviation, and prolongation of QRS wave and presence of Q waves.

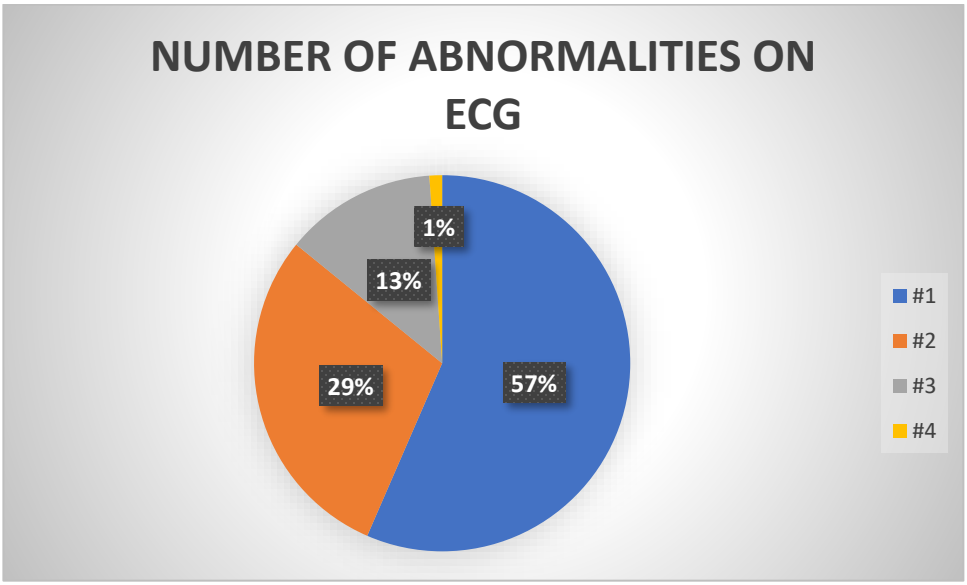

Figure 4: Number of Abnormalities on ECG

ECG abnormalities and relation to glycemic control (Poor = HbA1c ≥ 7%)

Table 4 shows how the various ECG abnormalities are related to sex, age, drug type, duration of treatment and HbA1c. Approximately a quarter of the participants had abnormal ECGs, however most of these abnormalities were not statistically significant. T-wave abnormalities were seen more commonly with increasing age; ages >65 were associated with the maximum number of abnormalities (23% with p-value <0.05).

Table 4. Clinical Characteristics for CVD on ECG

Characteristic	No ECG ABN N (%) 146 (70.19)	Yes ECG ABN N (%) 62 (29.81)	P Value
Systolic Blood Pressure			
High (≥ 140mmHg) *	93 (44.71)	38 (18.27)	0.742
Normal (100-139mmHg) *	53 (25.48)	24 (11.54)	
Diastolic Blood Pressure			
High (≥ 90mHg)	59 (28.37)	25 (12.02)	0.991
Normal (60-89mmHg)	87 (41.83)	37 (17.79)	
Average Blood Sugar (RBS)			
>4mmols/L	5 (2.42)	4 (1.93)	
4-7.8mmols/L	66 (31.88)	28 (13.53)	0.618
>7.8mmols/L	74 (35.5)	30 (14.49)	
Hypertension			
Not Hypertensive	60 (75)	20 (25)	0.231
Hypertensive	86 (67.19)	42 (32.81)	
Pulse			
Bradycardia	0 (0)	1 (100)	
Normal	140 (70.71)	58 (29.29)	0.296
Tachycardia	6 (66.67)	3 (33.33)	
Sex			
Female	111 (53.37)	41 (23.56)	0.638
Male	35 (16.83)	13 (6.35)	
Age (Years)			
<25	2 (0.96)	2 (0.4)	
25-39	15 (7.21)	7 (3.37)	0.156
40-65	104 (50)	35 (16.83)	
>65	25 (12.02)	18 (8.65)	
Drug Type			
Insulin	65 (31.25)	30 (14.4)	
Oral hypoglycemics	72 (34.62)	30 (14.4)	0.65
Both	9 (4.35)	2 (0.96)	
Duration of treatment			
<1 year	22 (10.58)	9 (4.33)	
1-5 years	49 (23.56)	23 (11.06)	0.886
>5 years	75 (36.06)	30 (4.42)	
HbA1c			
On target (≤7%)	32 (15.38)	18 (8.65)	0.272
High (>7%)	114 (54.81)	44 (21.15)	
Left Fundoscopy			
Normal	84 (40.78)	31 (15.05)	0.269
Abnormal	60 (29.13)	31 (15.05)	
Right Fundoscopy			
Normal	64 (31.07)	23 (11.17)	0.327
Abnormal	80 (38.83)	39 (18.93)	

*based on the 2016 ACC/AHA guidelines

4. 4 ECHO ABNORMALITIES

The distribution of ECHO abnormalities is depicted in Figure 5. Impaired diastolic dysfunction was noted to be the commonest abnormality (49% of patients) followed by concentric LVH (35.44%) and MV abnormality. Mitral valve abnormality was predominately in the elderly (age), in keeping with degenerative valvular calcification. The age groups 40-65 years had the most common ECHO abnormality with participants on oral hypoglycemic drugs having more cases of diastolic dysfunction and overall ECHO abnormalities as compared to patients on insulin.

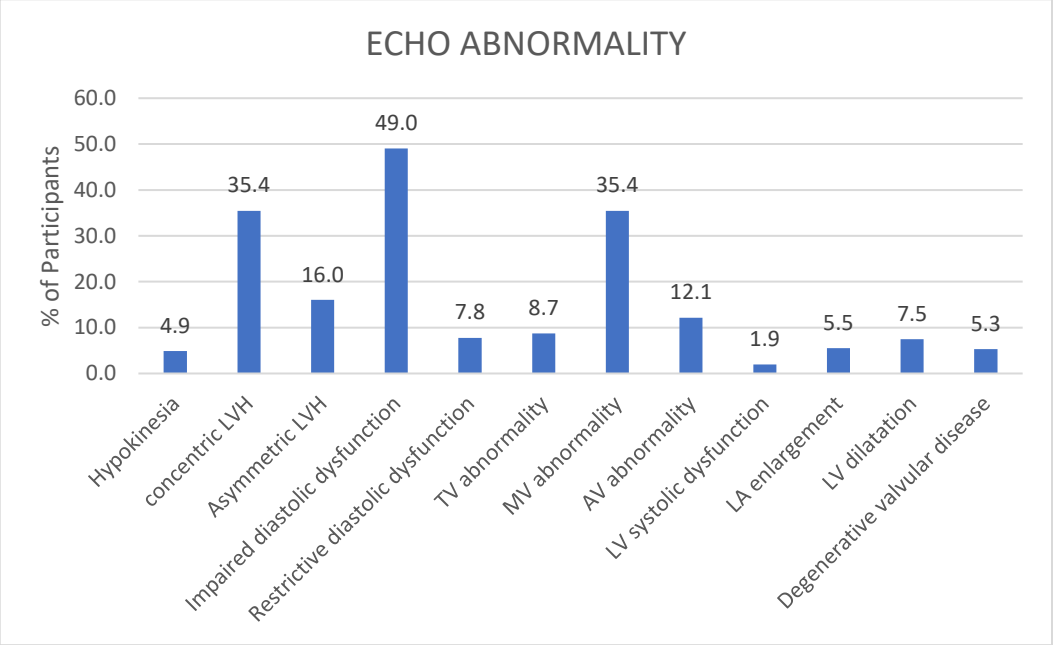

Figure 5: ECHO Abnormality

About 5% of patients were noted to have global hypokinesia despite no previous cardiac problems. Other notable abnormalities were LA enlargement, degenerative valvular disorders, systolic dysfunction and pericardial effusion in minimal population.

ECHO abnormalities and relation to glycemic control (Poor = HbA1c ≥ 7%)

Table 5 shows how the various ECHO abnormalities are related to sex, age, drug type, duration of treatment and HbA1c. It was noted that female diabetic patients had abnormal diastolic dysfunction as compared to men with mostly impaired relaxation, but some cases of restrictive diastolic function were also noted. Another thing of note was as the age increased the greater number of patients had impaired diastolic dysfunction. Oral drug hypoglycemic agents were commonly associated with increased detection of diastolic dysfunction as compared to insulin

therapy. Most participants on oral hypoglycemic agents received Metformin in combination form with Glibenclamide, which made it difficult to pinpoint the responsible drug for the diastolic dysfunction between the two. The level of blood glucose control on the other hand did not have any effect on ECHO findings.

TABLE 5: Clinical Characteristics for CVD on ECHO

Characteristic	**No** **N (%) 63(30.58%)**	**Yes** **N (%) 143 (69.42%)**	**P Value**
Systolic Blood Pressure			
High (≥ 140mmHg) *	26 (12.62)	105 (50.97)	**0.000**
Normal (100-139mmHg) *	34 (16.50)	41 (19.90)	
Diastolic Blood Pressure			
High (≥ 90mHg)	13 (6.31)	71 (34.47)	**0.000**
Normal (60-89mmHg)	47 (22.82)	75 (36.41)	
Hypertension			**<0.0001**
Not Hypertensive	43 (55.13)	35 (44.87)	
Hypertensive	20 (15.62)	108 (84.38)	
Pulse			0.794
Bradycardia	0 (0)	1 (100)	
Normal	60 (30.46)	137 (69.54)	
Tachycardia	3 (37.5)	5 (62.5)	
SEX			
Male	21 (10.19)	27 (13.11)	**0.011**
Female	39 (18.93)	119 (57.77)	
Age			
<25	4 (1.94)	0 (0)	
25-39	15 (7.28)	6 (2.91)	**0.000**
40-65	38 (18.43)	100 (48.54)	
>65	3 (1.46)	40 (19.42)	
Drug Type			
Insulin	36 (17.48)	58 (28.16)	**0.029**
Oral hypoglycemics	22 (10.68)	79 (49.03)	
Both	2 (0.97)	9 (4.37)	
Duration of treatment			
<1 year	10 (4.85)	20 (9.71)	0.123
1-5 years	26 (12.62)	45 (21.84)	
>5 years	24 (11.65)	81 (39.32)	
HbA1c			
On target (≤7%)	12 (5.83)	58 (18.45)	0.359
High (>7%)	48 (23.30)	108 (52.43)	
Average Glucose (mmols/L)			
<4	4 (1.94)	5 (2.43)	
4-7.8	20 (9.71)	73 (35.44)	0.076
>7.8	36 (17.98)	68 (33.01)	
Left Fundoscopy			
Normal	74 (36.27)	40 (19.61)	0.068
Abnormal	68 (33.33)	22 (10.78)	
Right Fundoscopy			
Normal	58 (28.43)	28 (13.73)	0.336
Abnormal	84 (41.18)	34 (16.67)	

*based on the 2016 ACC/AHA guidelines

Also noted from Table 5 was diastolic dysfunction was impaired more in women than in men (41.26% as compared to 7.77% respectively, p value < 0.05). Age was also noted to be an important factor, with more patients having impaired diastolic dysfunction and LVH with age >65years (15.05% and 13.1% respectively). Oral hypoglycemic agents had 49.03% participants with diastolic dysfunction as compared to insulin which had 45.63%.

4. 5 Abnormal ABI

Peripheral artery disease as defined by the presence of an abnormal ABI was divided into 2 groups: Patients with ABI of less than 0.9 (which was interpreted as occlusive arterial disease) and patients with an ABI of more than 1.3 (indicating calcified vessel).[39]

The negative effects of elevated blood glucose on blood vessel integrity was observed using HbA1c levels. High HbA1c was associated with calcified and occlusive arterial disease as illustrated in Table 6

TABLE 6. Vascular Complications

VASCULAR COMPLICATIONS							
		ABI RIGHT			**ABI LEFT**		
		>0.91 - 1.3 (Normal)	≤0.9 Occlusive Arterial Disease	>1.3 (Calcified Vessels)	>0.91 - 1.3 (Normal)	≤0.9 Occlusive Arterial Disease	>1.3 (Calcified Vessels)
SEX	**M**	34 (16.35)	4 (1.92)	10 (4.81)	33 (15.87)	6 (2.88)	9 (4.33)
	F	114 (54.81)	12 (5.77)	34 (16.35)	115 (55.29)	8 (3.85)	37 (17.79)
		P = 0.982			P = 0.178		
AGE	**<25**	4 (1.92)	0 (0)	0 (0)	4 (1.92)	0 (0)	0 (0)
	25-39	16 (7.69)	2 (0.96)	4 (1.92)	14 (6.73)	1 (0.48)	7 (3.37)
	40-65	99 (47.60)	9 (4.33)	31 (14.90)	97 (46.63)	10 (4.81)	32 (15.38)
	>65	29 (13.94)	5 (2.40)	9 (4.33)	33 (15.87)	3 (1.44)	7 (3.37)
		P = 0.799			P= 0.693		
DRUG TYPE	**INSULIN**	71 (34.13)	6 (2.88)	18 (8.65)	66 (31.73)	9 (4.33)	20 (9.62)
	ORAL	70 (33.65)	9 (4.33)	23 (11.06)	75 (36.06)	4 (1.92)	23 (11.06)
	BOTH	7 (3.37)	1 (0.48)	3 (1.44)	7 (3.37)	1 (0.48)	3 (1.44)
		P = 0.863			P = 0.601		
DURATION OF TX	**<1 YEAR**	20 (9.62)	3 (1.44)	8 (3.85)	24 (11.54)	1 (0.48)	6 (2.88)
	1-5 YRS	48 (23.08)	7 (3.37)	17 (8.17)	53 (25.48)	4 (1.92)	15 (7.21)
	>5 YRS	80 (38.46)	6 (2.88)	19 (9.13)	71 (34.13)	9 (4.33)	25 (12.02)
		P = 0.586			P = 0.744		
HbA1c	**Normal**	35 (16.75)	5 (2.39)	10 (4.78)	40 (19.23)	3 (1.44)	7 (3.37)
	High	114 (54.55)	11 (5.26)	34 (16.27)	108 (51.92)	11 (5.29)	39 (18.75)
		P = 0.770			P = 0.255		
AVG GLC	**<4**	5 (2.42)	1 (0.48)	3 (1.45)	7 (3.38)	1 (0.48)	1 (0.48)
	4-7.8	64 (30.92)	6 (2.90)	24 (11.59)	66 (31.88)	5 (2.42)	23 (11.11)
	>7.8	78 (37.68)	9 (4.35)	17 (8.21)	74 (35.75)	8 (3.86)	22 (10.63)
		P = 0.445			P = 0.825		

Figure 6 shows that 71.16% of the patients had normal Right and Left ABI. 4% of patients had Right, 3% had Left and 4% having both right and left occlusive arterial disease. On the other hand, 12% of patients had right calcified vessel, 13% left and 10% had both sides calcified vessels. Also noted from the figure was that patients with normal HbA1c had a markedly decreased prevalence of occlusive arterial disease.

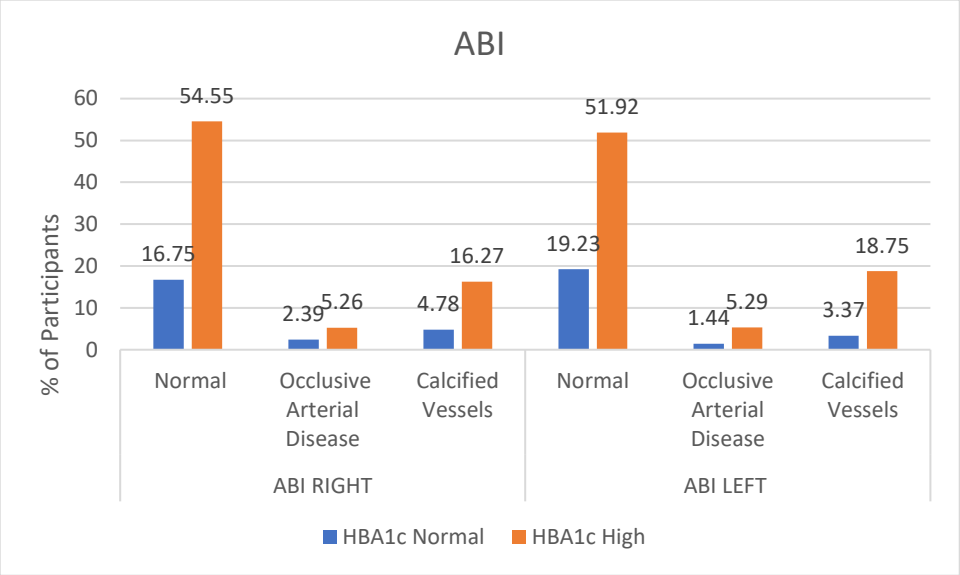

FIGURE 6. Abnormal ABI in relation to HbA1c

4.6 Clinical correlates of subclinical CVD on logistic regression

Table 7 shows the clinical correlates of subclinical CVD on logistic regression. From the table, it can be noted that alcohol, tobacco smoking and abnormal lipids (low HDL, raised LDL, raised TG and raised total cholesterol), which are the other known traditional CVD risk factors, were not associated with any abnormal findings on ECG, ECHO, or ABI.

The other non-traditional CVD risk factors particularly applied to diabetic patients such as sex, duration of diabetes, education, type of type also did not show any association in this population.

Age and diastolic Hypertension accounted for three and two-fold increased risk respectively in subclinical cardiovascular diseases in diabetic patients.

Table 7. Clinical correlates of subclinical CVD with regard to abnormal ECG, ECHO, ABI Right and ABI Left side

CLINICAL CORRELATES								
ABNORMAL ECG					ABNORMAL ECHO			
PARAMETER	CRUDE OR	CI	ADUJUSTED OR	CI	CRUDE OR	CI	ADUJUSTED OR	CI
Sex	0.84	0.41-1.73	0.6	0.23-1.55	0.42*	0.21-0.83	0.37*	0.13-1.06
Age	0.34	0.05-2.48	1.31	0.69 - 2.5	0.19*	0.06-0.68	3.13*	1.34-7.34
Education	2.25	0.12-40.66	1.9	0.54-1.37	0.08*	0.11-0.52	0.95	0.56-1.63
Duration of Treatment	0.97	0.40-2.37	0.86	0.54-1.37	1.69	0.70-4.09	1.14	0.67-1.93
Drug Type	0.9	0.49-1.66	0.73	0.40-1.31	2.23*	1.19-4.18	1.24	0.63-2.45
Ever smoked	0.71	0.29-1.78	0.92	0.65-1.32	0.90	0.38-2.11	1.24	0.85-1.82
Ever taken alcohol	0.86	0.47-1.55	0.92	0.45-1.89	0.83	0.45-1.51	1.21	0.5-2.91
HbA1c	0.69	0.35-1.35	0.64	0.27-1.5	0.71	0.34-1.48	0.55	0.19-1.6
Average Glc	0.51	0.13-2.02	1.18	0.62-2.23	1.51	0.38-5.98	1.41	0.66-2.99
s-TG	1.87	0.85-4.11	2.02	0.82-4.97	2.38	0.87-6.54	3.2	0.84-12.16
s-CHO	0.73	0.39-1.36	0.61	0.3-1.25	1.39	0.74-2.61	0.86	0.36-2.06
Dx of HTN	1.47	0.78-2.74	1.58	0.73-3.43	7.13*	3.66-13.91	4.19	1.78-9.84
SBP > 140mmHg	0.9	0.49-1.66	0.8	0.35-1.8	3.35*	1.79-6.26	0.91	0.36-2.28
DBP >90mmHg	0.99	0.54-1.83	1.05	0.49-2.23	3.42*	0.54-1.83	2.52*	1.98-6.53
ABNORMAL ABI RIGHT					ABNORMAL LEFT ABI			
PARAMETER	CRUDE OR	CI	ADUJUSTED OR	CI	CRUDE OR	CI	ADUJUSTED OR	CI
Sex	1.02	0.50-2.08	1.07	0.41-2.83	1.16	0.58-2.34	1.99	0.76-5.21
Age	0.84	0.4-1.75	1.2	0.6-2.37	1.43	0.65-3.16	0.96	0.48-1.89
Education	0.39	0.06-2.42	0.86	0.53-1.39	0.49	0.08-3.04	1.39	0.87-2.22
Duration of Treatment	0.57	0.24-1.35	0.68	0.43-1.08	1.64	0.64-4.19	1.34	0.82-2.19
Drug Type	1.35	0.72-2.52	1.39	0.78-2.48	0.82	0.44-1.52	0.96	0.54-1.71
Ever smoked	1.62	0.71-3.68	1.3	0.92-1.84	1.13	0.48-2.64	1.05	0.73-1.5
Ever taken alcohol	0.94	0.51-1.7	0.82	0.39-1.71	0.71	0.39-1.29	0.46	0.21-0.99
HbA1c High	0.92	0.46-1.85	1.12	0.46-2.69	1.85	0.86-4	2.57	1-6.6
Average Glc	0.42	0.1-1.67	0.73	0.39-1.36	1.42	0.28-7.23	0.83	0.44-1.57
s-TG	1.98	0.9-4.36	1.89	0.77-4.64	1	0.43-2.32	0.69	0.27-1.78
s-CHO	1.34	0.73-2.48	1.08	0.53-2.18	1.48	0.80-2.73	1.48	0.73-3.01
Dx of HTN	1.51	0.80-2.85	1.22	0.56-2.66	1.11	0.6-2.07	0.69	0.31-1.51
SBP > 140mmHg	1.55	0.81-2.94	1.09	0.46-2.58	1.72	0.9-3.30	1.11	0.46-2.67
DBP >90mmHg	2.11*	1.45-3.88	1.98*	0.92-4.27	2.56*	1.39-4.74	2.58*	0.01-0.89

CHAPTER FIVE: DISCUSSION

The prevalence and distribution of subclinical CVD among asymptomatic stable diabetic patients attending their routine out-patient clinic reviews and the relationship of HbA1c (as a proxy of sugar control) with the various outcomes were assessed and analyzed, respectively. The study population had a wide range of age groups with the mean age of 54 years ± 3 (median 53). The majority of the participants were females (76.9%).

The average HbA1c in the study participants was 9.6 ± 2.99. Poor glycemic control was noted in 75.96% of these patients. This is quite a significant prevalence and thus treatment practices need to be investigated. Poor glycemic control was also in concordance to a study done in 2014 by Musenge et al at UTH.[34] Similar poor glycemic control has been noted in various other countries, such as in China[34], where 80% of the patients had poor glycemic control. In Brazil and Nigeria, poor glycemic control of values greater than 55mmol/mol was noted in 24% and 64 %, respectively[34].In these studies dietary modification and weight loss were associated with the best glycemic control, possibly due to improved insulin sensitivity. In contrast, good glycemic control status reported in Japan and Germany (45% and 65% respectively) may be due to the prevailing higher literacy levels and therefore probable better knowledge of diabetes in these developed countries.

Resting ECHO, ECG and ABI were done on all these patients to screen for ScCVD and silent MI. Subclinical CVD was highly prevalent on ECG, an observation also registered in many studies across Africa.[12,25]

5.1 ECG Abnormalities

The study noted that all the patients had a regular rhythm. Q waves were noted in about 5% of the population with T wave changes in about 18%. These findings have also been recorded in various other studies, where diabetic patients are reported to have early T wave changes.[44,45,46] However, unlike the Europe and Diabetes (EURODIAB) study on diabetic individuals which noted female sex and higher values of hemoglobin A_{1C} and systolic blood pressure were associated with increased risk of prolonged QTc, whereas physical activity and normal body

mass index were protective factors, this study showed no correlation between QTc and sex, age, drug type, duration of treatment, level of sugar control. Genetic variants in previously identified candidate genes may be associated with QT interval duration in individuals with diabetes mellitus.[3]

T wave changes were noted more in older participants. This finding has also been reported in various other studies and may be due to the increased coronary atherosclerotic burden associated with the advancing age.[13, 20, 25]

Studies have found that the presence of major abnormalities on ECG were associated with an increased risk of incidental heart failure[4]. In this study, some of the abnormalities found were poor R wave progression, left ventricular hypertrophy, complete left and right bundle branch blocks, major QT prolongation, Right Bundle Branch Block, Premature ventricular contractions and hemi -blocks.

The high prevalence of hypertension in this study population may explain most of the ECG abnormalities especially left ventricular hypertrophy. Systolic arterial hypertension has been associated with the development of pathological left ventricular hypertrophy, which is a risk factor for ventricular arrhythmias and sudden cardiac death.[7]

5.2 Echo abnormalities

Echo abnormalities in about 71% of the study population were noted, and this was driven mainly by the presence of myocardial abnormalities – including impaired relaxation, diastolic dysfunction and left ventricular hypertrophy.

In this study, there was a sex difference in echocardiographic abnormalities with more women than me having more echo abnormalities (76% versus 56%, respectively). The reason for this difference is unknown but could be due to the higher number of female than male participants in the study. fact Similar sex differences in cardiac structure and function have been reported previously. In a study of 2016 by Jørgensen et and the Framingham cohort, women with diabetes had increased left ventricular mass compared to men and the inverse was noted for decreased fractional shortening (a measure of systolic function).[26] These findings, however,

were not confirmed in the Strong Heart Study, where both men and women had increased left ventricular mass and decreased fractional shortening.[27] For both sex, the most common echo abnormality was impaired diastolic dysfunction followed by left ventricular hypertrophy (concentric hypertrophy was more common than the asymmetric hypertrophy). Left ventricular diameter and left atrial diameter were noted not to be significant when compared between the 2 sexes. The sex of the patient was noted to also determine the level of glycemic control, with more females than males having a higher HbA1c, 80% versus 63 %, respectively.

Left ventricular hypertrophy is a well-established precursor both of systolic dysfunction and overall cardiovascular disease[4]. Though typically associated with hypertension, its prevalence increases with increasing age, body mass index and presence of hypertension and diabetes; Hence, left ventricular hypertrophy is a very relevant concern in this population, and in accordance, we found a prevalence of 55% in women and 40% in men. Hypertension may be responsible for these abnormalities. However, further research is needed to determine the isolated effect of diabetes in this population.

Also, besides sex differences, we have shown that the prevalence of abnormal echo findings increases sharply with age and that it has a very high prevalence in patients >65 years of age, driven mainly by impaired diastolic dysfunction followed by LVH. Hence, our study confirms that increasing age is a very important determinant of cardiac abnormalities, and further research is needed to address the specific effect of diabetes on cardiac structure and function in the ageing population.[35]

Hypokinesia was also noted in about 5% of the screened population of patients with diabetes. It was predominantly global with a few having septal hypokinesia. This percentage is considerably high considering these patients did not present with any cardiac symptoms and could present ultimately in refractory heart failure due to dilated cardiomyopathy. It is in this regard that the patients with cardiac hypokinesia are recommended to do angiography to evaluate for coronary artery disease. Restrictive cardiomyopathy was noted in about 8% of the patients.

As expected, the type of drug type played an essential role in echo abnormalities with patients being on oral hypoglycemics having more diastolic dysfunction as compared to patients on insulin. The higher the BMI the more the risk of having echo abnormalities.

Duration of treatment and level of glycated hemoglobin showed no statistical significance when compared to ECHO abnormalities. In type 2 diabetes, small-sized populations have reported considerable variations in the prevalence of diastolic dysfunction, ranging from 40% to 75%. One study has reported no differences in diastolic function of healthy subjects compared to patients with type 2 diabetes that are free from hypertension, coronary artery disease and microangiopathic complications.[31] In a recent study Boonman de-Winter et al. assessed both the prevalence of systolic and diastolic dysfunction in a primary care setting and found a prevalence of 0.7% and 25.1%, respectively. This study was conducted in 581 patients with type 2 diabetes without known heart failure. They also estimated the prevalence of cardiologist-confirmed heart failure in this population and found that 96.3% of the patients with newly detected heart failure had diastolic dysfunction.[4] The discrepancy in prevalence between the previous and present studies lies in the differences in the criteria for establishing the presence of diastolic dysfunction. In our study, we used the ratio of early mitral valve inflow velocity to septal early diastolic tissue Doppler velocity (E/e′). In previous studies of patients with type 2 diabetes, diastolic left ventricular dysfunction was been linked to poor prognosis.[23] This measure, however, is more conservative as it will only classify patients with definitely abnormal diastolic function and not the patients with borderline abnormal diastolic function. This makes our estimates of prevalence more conservative, but on the other hand identifies a subgroup with verified increased risk.

ECHO is an important tool for assessing both cardiac structure and function. However, due to its non-availability in most Zambian hospitals and that it requires expertise, using it as a screening tool might be a challenge, notwithstanding the cost implications. However, from this study it can be noted that most diabetic patients develop impaired diastolic dysfunction in them without them having overt cardiac symptoms.

Smoking was not noted to be very prevalent in our diabetic patients. About 13.94% of the study population said to have smoked. On the other hand, alcohol was noted to have been taken in about 50% of our population. Both these risk factors are more common in males than females. Average BMI was in the range of 27 ± 5.09. However, on logistic regression none of these factors contributed to the ECG, ECHO or ABI.

5.3 Non-Cardiac Complications

Poor glycemic control was noted to be associated with abnormal urinalysis results and abnormal fundoscopy findings.

This was also true for drug regimens; more patients on insulin had higher abnormal urinalysis results compared to patients on oral hypoglycemic. This can be explained by the fact that patients were put on insulin after metabolic control with oral hypoglycemic agents had been lost.

Peripheral artery disease has been shown to be associated with future incidents of cardiovascular events, particularly ischemic strokes and myocardial infarction.[26] Peripheral artery disease can be screened for using Ankle Brachial Index (ABI). Our study population showed a similar prevalence of abnormal ABI as other major studies (20.1% vs. 19%).[26]

ABI is a cheap tool that has been validated by many population studies; [26] it can be easily administered by caregivers at a primary health care level with minimal expertise. As such, all patients with type 2 diabetes mellitus and those with type 1 diabetes for 5 years or longer may benefit from a routine measurement of the ABI.

5.4 Risk factors

According to the Framingham heart study of 1961, traditional CVD risk factors are hypertension, diabetes mellitus, high serum cholesterol and smoking. These risk factors have been associated with increased risk of future CVD events.[5] In our study population, the commonest traditional CVD risk factor was hypertension, whose occurrence on physical examination was two-fold increased among the participant. This finding may suggest most participants had undiagnosed hypertension. Furthermore, hypertension was the only traditional CVD risk factor which showed a significant association with abnormalities on the ECG, ECHO and ABI assessments. Alcohol and tobacco smoking did appear give any abnormalities on ECG, ECHO and ABI assessments. However, there was a very low prevalence of smoking and tobacco use among our study participants. This finding is important in that it draws attention to hypertension as being the most important traditional CVD risk factor in our study population, and that more effort is required to screen for hypertension and adequately treat it at every opportunity.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Subclinical CVD is quite common among clinically healthy diabetic patients attending their regular out-patient clinic visits at UTH, demonstrated from the tools utilized in the study. Echocardiography showed the highest prevalence of subclinical CVD abnormalities. Hypertension is the most common traditional CVD risk factor in our study population. Alcohol, BMI and smoking are least prevalent. Level of glycemic control was poor among relatively healthy individuals (75.96% of participants) with mean HbA1c of 9.6% (7.1%- 16.4%).

6.2 Recommendations

The following recommendations are being made:

- The level of glucose control in patients with diabetes at UTH is poor and needs re-enforcing
- Screening for and treatment of hypertension must be conducted at each clinic visit.
- All patients with abnormal ECG findings, particularly left ventricular hypertrophy, major QT prolongation, Q waves, major arrhythmias (complete bundle branch blocks, 2^{nd} and 3^{rd} degree heart blocks, atrial flutter/fibrillation) must undergo a routine baseline ECHO. All the patients with hypokinesia on ECHO need full evaluation for coronary artery disease.
- To evaluate the cost effectiveness of using ECG, ECHO and ABI as screening tools for CVD across Zambia.
- A long-term prospective study should to be conducted to determine the outcomes in patients with subclinical CVD abnormalities.
- A study is needed to correlate the level of glycemic control with the incidence and progression of cardiovascular disease.

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APPENDIX I - Participant Information Sheet

SPECTRUM OF SUB-CLINICAL CARDIOVASCULAR DISEASE AMONG DIABETIC PATIENTS PRESENTING TO OUT PATIENT CLINIC AT UNIVERSITY TEACHING HOSPITAL IN LUSAKA

Introduction

I, Meenakshi Gupta, an MMED student in Internal Medicine of the School of Medicine at the University of Zambia, kindly ask for your participation in the above study. The purpose of the study is in partial fulfilment of the requirements for the award of a Master of Medicine in Internal Medicine. Before you decide whether to participate in the study or not, I would like to explain to you the purpose of the study and what is expected of you. If you agree to take part, you will be asked to sign this consent form in the presence of a witness.

Purpose of the study

This study is being conducted to determine the various types of cardiovascular diseases in diabetic patients who have not yet developed clinically evident cardiac problems. This is important because it will help us identify patients at risk of developing serious cardiac conditions and to help in putting in prevention measures.

Study procedure

You have been selected to participate in the study after meeting the inclusion criteria. If you agree to participate in this study, I will put your information on a data entry sheet; your name will not be included. We will ask for information regarding the history of your illness, then perform a physical examination that will include checking your blood pressure, pulse, weight and a general physical exam, in strict privacy. Some blood samples will be drawn which will be sent to the laboratory for various tests. You will then be asked to undergo other tests, namely; Electrocardiography (ECG), Echocardiography (ECHO) and Ankle Brachial index.

Risks and discomforts

You will not be exposed to any risks when participation in this study. However, you will experience discomfort from a needle prick during drawing of the blood samples. You may

also feel some discomfort during the ECHO test as you may be required to lie down for up to 30 minutes. All the costs for the procedures have been covered by the researcher.

Benefits

This study will help us identify various forms of heart diseases in their early stages and thereby give us information that will help set up measures to prevent these diseases from progressing into more serious form.

Confidentiality

All information will be kept strictly confidential. Your name will not be used, but you will be given a study number. Therefore, any data obtained will not be traced back to you.

Consent

Participation in this study will be voluntary, with no expectation of payment. Should you decide to withdraw from the study for any reason, you will not suffer any consequences.

Thank you for considering participating in this study. For any questions or concerns, please feel free to contact Dr. Meenakshi Gupta or the UNZABREC office on the following addresses;

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APPENDIX II - Consent Form

I, _____ (Full Names of Participant) hereby confirm that the nature of this clinical study has been sufficiently explained to me. I am aware that my personal details will be kept confidential and I understand that I may voluntarily, at any point, withdraw my participation without suffering any consequences. I have been given sufficient time to ask questions and seek clarifications, and of my own free will declare my participation in this research.

_____	_____	_____
Name of Participant (Print)	Participant's Signature or thumbprint	Date

_____	_____	_____
Name of Witness (Print)	Witness (Signature)	Date

Interviewer

I have explained this research study to the subject. I am available to answer any questions now or in the future regarding the study and the subject's rights.

_____	_____	_____
Name (Print)	Signature	Date

For any questions or concerns, please feel free to contact:

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APPENDIX III - Data Collection Sheet

SPECTRUM OF SUB-CLINICAL CARDIOVASCULAR DISEASES AMONG DIABETIC PATIENTS PRESENTING TO CLINIC 5, UNIVERSITY TEACHING HOSPITAL IN LUSAKA

Participant study number: …….

Instructions: Please put a cross (X) where applicable

Part I: Demographics

1. Age: ……. Years
2. Sex: i) Male ii) Female
3. Marital status: i) Single ii) Married iii) Divorced iv) Widowed
4. Educational level: i) Primary ii) Secondary iii) University Graduate iv) Postgraduate studies
5. Employment: i) Unemployed ii) Retired iii) Student iv) Professional v) Self-employed
6. Are you a smoker? i) Yes (currently smoker) ii) No (never smoked) iii) Ex-smoker

   If you answered "Yes" or "NO" to Q6 skip to Q9
7. If you are a past smoker, when did you stop smoking?

i) Less than 6 months ago ii) in the last 6-12 months iii) more than 12 months ago

8. How long did you smoke for prior to stopping?
   i) less than 15 years ii) 15 to 20 years iii) more than 20 years
9. Do you drink alcohol? i) Yes ii) No (never) iii) Stopped (when……)
10. Do you have any allergies: i) Yes ii) No?
11. Have any of your immediate family members been diagnosed with a cardiovascular disease? (Mother, father – stroke, heart attack) i) Yes ii) No
12. PMHX

    …HTN …. HIV …. CVA ……. Asthma OTHERS.....
13. How long have you known to be diabetic: i) less than 1 year ii)1-5years
    iii)5-10years iv)10-20years v) more than 20years

14. How long before diagnosis did the symptoms of diabetes begin (polyuria, polydipsia, polyphagia): ……
15. Are you on treatment? i) Yes ii) No
16. Duration of treatment: i) <1yr ii) 1 -5 yrs. iii) >5yrs
17. Compliant: i) Regular reviews ii) Self adherence iii) Regular RBS Profile
18. How conversant are you with your condition? I) None ii) Aware iii) Fully understand
19. Hypoglycemic type i) Insulin ii) Oral Hypoglycemic iii) Both
20. ORAL HYPOGLYCEMIC DRUGS
    i. Metformin
    ii. Glibenclamide (Daonil)
    iii. Glimepiride
    iv. Glipizide
    v. Meglitinides
    vi. Thiazolidinediones (Pioglitazone)
    vii. Alpha-glucosidase inhibitors (Acarbose)
    viii. DPP-IV inhibitor (Sitagliptin, vildagliptin)

OTHER DRUGS …….

21. Do you ever have any pain in your chest: i) Yes ii) No?
    - If YES, where is the pain situated…….
    - Does the pain occur when walking: i) Yes ii) NO?
    - If yes, Is the pain relieved at rest: i) Yes ii) No
22. Do you ever feel numbness or tingling in your legs: i) Yes ii) No?
23. Do you ever feel muscle pain while walking: i) Yes ii) No?
    - If yes, is the pain relieved at rest: i) Yes ii) No
24. Do you have blurred vision: i) Yes ii) No

Section 2: Physical examination

Weight .....Kgs Height .....meters Waist……cm

BMI Kg/m2

Blood Pressure .....mm/Hg

Pulse ..... bpm

Pulse i) regular ii) irregular

Fundoscopy i) Normal ii) Retinopathy

ABI ……. I) less than 1 ii) 1- 1.4 iii) more than 1.4

Section 3: Laboratory tests

1. HbA1c _____%
2. Fasting Total cholesterol _____mmol/l
3. Triglycerides _____mmol/l
4. Fasting HDL _____mmol/l
5. Fasting LDL _____mmol/l
6. C-peptide _____
7. Creatinine _____umol/l
8. CrCl _____ml/min

SECTION 4: ECG[26]

Rhythm	Sinus	Non-sinus		
Axis	Normal	Left	Right	
voltage	Normal	Low		
P - wave	Normal	p-mitrale	p-pulmonale	
PR interval	Normal (120-200ms)	Short (<120ms)	Prolonged (>200ms)	
QRS	Normal (60 – 120ms)	Short (<60)	Prolonged (>120)	
ST Segment	Normal	Depressed (>1mm limbs, >2mm chest)	Elevated (>1mm limbs, >1mm chest)	
Q – waves	Absent	Present		
T - wave	Normal	Flat	peaked	inverted
QTc	Normal	Short	prolonged	
AV conduction	Normal	Abnormal (specify)		
Ventricular conduction	Normal	Abnormal (specify)		
Miscellaneous				

SECTION 5: ECHO[26]

Date of ECHO.....

Study ID No.....

Age/Sex..... Height .....meters Weight.....Kgs

1) M-Mode 2D Measurements

IVSd: _____(mm)

LVPWd: _____(mm)

LVIDd: _____(mm)

LVIDs: _____(mm)

Fractional Shortening: _____ (%)

LV Mass_____ (grams)

Biplanes Simpson EF _____ (%)

Teich EF_____ (%)

Aortic root diameter_____(mm)

Left Atrial diameter _____(mm)

Right atrial diameter (short axis) _____(mm)

Right ventricular diameter (basal)_____(mm)

Pulmonary artery diameter_____(mm)

Valvular Disease

Mitral Valve	Normal	☐
	Stenosis	☐
	Regurgitation	☐
	Unable to assess	☐
Aortic Valve	Normal	☐
	Stenosis	☐
	Regurgitation	☐
	Unable to assess	☐

Tricuspid Valve	Normal	☐
	Stenosis	☐
	Regurgitation	☐
	Unable to assess	☐
Pulmonic Valve	Normal	☐
	Stenosis	☐
	Regurgitation	☐
	Unable to assess	☐

Doppler Measurements and Calculations

E max vel: _____(cm/sec)

A max vel: _____(cm/sec)

Mitral Valve DT _____ (msec)

Mitral valve PHT_____(msec)

Mitral valve mean gradient_____mmHg

MVOA_____ cm2

Diastolic Function	Normal	☐
	Impaired Relaxation	☐
	Pseudonormal	☐
	Restrictive	☐
	Unable to Assess	☐
	Indeterminate	☐

AoV mean gradient: _____(mmHg)

AoV PHT_____(ms)

AVOA_____(cm2)

TR max vel: _____(m/s)

PV acc. time_____(ms)

Color Flow Doppler comments

_____

IVC_____cm

IVC collapse with respiration_____%

Pericardial Effusion None ☐

Small ☐

Moderate ☐

Large ☐

Overall Test Results: Normal ☐ Abnormal ☐

If Abnormal Clinically Significant: No ☐

Yes ☐

Echo Comments

_____

_____

Echo done by_____

Verified by_____

Name of doctor: ……. Signature: …….

Data Entry Date: ……. /……/…….

Data Entry Number ☐

APPENDIX IV - The Minnesota Code Classification System* for Electrocardiographic Findings

Article II. Q and QS Patterns

(Do not code in the presence of WPW code 6-4-1.) To qualify as a Q- or QS-wave, the deflection should be at least 0.1 mV (1 mm in amplitude).

Section 2.01 Anterolateral site (leads I, aVL, V6)

1-1-1 Q/R amplitude ratio ≥ 1/3, plus Q duration ≥ 0.03 sec in lead I or V_6.

1-1-2 Q duration ≥ 0.04 sec in lead I or V_6.

1-1-3 Q duration ≥ 0.04 sec, plus R amplitude ≥ 3 mm in lead aVL.

1-2-1 Q/R amplitude ratio ≥ 1/3, plus Q duration ≥ 0.02 sec and < 0.03 sec in lead I or V_6.

1-2-2 Q duration ≥ 0.03 sec and < 0.04 sec in lead I or V_6.

1-2-3 QS pattern in lead I. Do not code in the presence of 7-1-1.

1-2-8 Initial R amplitude decreasing to 2 mm or less in every beat (and absence of codes 3-2, 7-1-1, 7-2-1, or 7-3

between V_5 and V_6. (All beats in lead V_5 must have an initial R > 2 mm.)

1-3-1 Q/R amplitude ratio ≥ 1/5 and < 1/3, plus Q duration ≥ 0.02 sec and < 0.03 sec in lead I or V_6.

1-3-3 Q duration ≥ 0.03 sec and < 0.04 sec, plus R amplitude 3 mm in lead aVL.

Section 2.02 Posterior (Inferior) site (leads II, III, aVF)

1-1-1 Q/R amplitude ratio ≥ 1/3, plus Q duration ≥ 0.03 sec in lead II.

1-1-2 Q duration ≥ 0.04 sec in lead II.

1-1-4 Q duration ≥ 0.05 sec in lead III, plus a Q-wave amplitude ≥ 1.0 mm in the majority of beats in lead aVF.

1-1-5 Q duration ≥ 0.05 sec in lead aVF.

1-2-1 Q/R amplitude ratio ≥ 1/3, plus Q duration ≥ 0.02 sec and < 0.03 sec in lead II.

1-2-2 Q duration ≥ 0.03 sec and < 0.04 sec in lead II.

1-2-3 QS pattern in lead II. Do not code in the presence of 7-1-1.

1-2-4 Q duration ≥ 0.04 sec and < 0.05 sec in lead III, plus a Q-wave ≥ 1.0 mm amplitude in the majority of beats in aVF.

1-2-5 Q duration ≥ 0.04 sec and < 0.05 sec in lead aVF.

1-2-6 Q amplitude ≥ 5.0 mm in leads III or aVF.

1-3-1 Q/R amplitude ratio ≥ 1/5 and < 1/3, plus Q duration ≥ 0.02 sec and < 0.03 sec in lead II.

1-3-4 Q duration ≥ 0.03 sec and < 0.04 sec in lead III, plus a Q-wave ≥ 1.0 mm amplitude in the majority of beats in lead aVF.

1-3-5 Q duration ≥ 0.03 sec and < 0.04 sec in lead aVF.

1-3-6 QS pattern in each of leads III and aVF. (Do not code in the presence of 7-1-1.)

Section 2.03 Anterior site (leads V1, V2, V3, V4, V5)

1-1-1 Q/R amplitude ratio ≥ 1/3 plus Q duration ≥ 0.03 sec in any of leads V_2, V_3, V_4, V_5.

1-1-2 Q duration ≥ 0.04 sec in any of leads V_1, V_2, V_3, V_4, V_5.

1-1-6 QS pattern when initial R-wave is present in adjacent lead to the right on the chest, in any of leads V_2, V_3, V4, V5, V6.

1-1-7 QS pattern in all of leads V_1-V_4 or V_1-V_5.

1-2-1 Q/R amplitude ratio ≥ 1/3, plus Q duration ≥ 0.02 sec and < 0.03 sec, in any of leads V_2, V_3, V_4, V_5.

1-2-2 Q duration ≥ 0.03 sec and < 0.04 sec in any of leads V_2, V_3, V_4, V_5.

1-2-7 QS pattern in all of leads V_1, V_2, and V_3. (Do not code in the presence of 7-1-1).

1-2-8 Initial R amplitude decreasing to 2.0 mm or less in every beat (and absence of codes 3-2, 7-1-1, 7-2-1, or 7-3) between any of leads V_2 and V_3, V_3 and V_4, or V_4 and V_5. (All beats in the lead immediately to the right on the chest must have an initial R > 2 mm.)

1-3-1 Q/R amplitude ratio ≥ 1/5 and < 1/3 plus Q duration ≥ 0.02 and < 0.03 sec in any of leads V_2, V_3, V_4, V_5.

1-3-2 QS pattern in lead V_1 and V_2. (Do not code in the presence of 3-1 or 7-1-1.)

Article III. QRS Axis Deviation

(Do not code in presence of low-voltage QRS, code 9-1, WPW 6-4-1, ventricular conduction defects, or 7-1-1, 7-2-1, and 7-4.)

2-1 Left. QRS axis from -30^0 through -90^0 in leads I, II, III. (The algebraic sum of major positive and major negative QRS waves must be zero or positive in I, negative in III, and zero or negative in II.)

2-2 Right. QRS axis from $+120^0$ through -150^0 in leads I, II, III. (The algebraic sum of major positive and major negative QRS waves must be negative in I, and zero or positive in III, and in I must be one-half or more of that in III.)

2-3 Right (optional code when 2-2 is not present). QRS axis from $+90^0$ through $+119^0$ in leads I, II, III. (The algebraic sum of major positive and major negative QRS waves must be zero or negative in I and positive in II and III.)

2-4 Extreme axis deviation (usually S1, S2, S3 pattern). QRS axis from -90^0 through -149^0 in leads I, II, and III (The algebraic sum of major positive and major negative QRS waves must be negative in each of leads I, II, and III.)

2-5 Indeterminate axis QRS axis approximately 90^0 from the frontal plane. (The algebraic sum of major positive and major negative QRS waves is zero in each of leads I, II and III, or the information from these three leads is incongruous.)

Article IV. High Amplitude R Waves

3-1 Left: R amplitude > 26 mm in either V_5 or V_6, or R amplitude > 20.0 mm in any of leads I, II, III, aVF, or R amplitude > 12.0 mm in lead aVL. (All criteria measured only on second to last complete normal beat.)

3-2 Right: R amplitude ≥ 5.0 mm and R amplitude ≥ S amplitude in the majority of beats in lead V_1, when S amplitude is > R amplitude somewhere to the left on the chest of V_1 (codes 7-3 and 3-2, if criteria for both are present).

3-3 Left (optional code when 3-1 is not present): R amplitude > 15.0 mm but ≤ 20.0 mm in lead I, or R amplitude in V_5 or V_6, plus S amplitude in V_1 > 35.0 mm. (Measured only on second to last complete normal beat.)

3-4 Criteria for 3-1 and 3-2 both present.

Article V. ST Junction (J) and Segment Depression

(Do not code in the presence of codes 6-4-1, 7-1-1, 7-2-1 or 7-4. When 4-1, 4-2, or 4-3 is coded, then a 5-code must also be assigned except in lead V_1.)

Section 5.01 Anterolateral site (leads I, aVL, V6)

4-1-1 STJ depression ≥ 2.0 mm and ST segment horizontal or downward sloping in any of leads I, aVL, or V_6.

4-1-2 STJ depression ≥ 1.0 mm but < 2.0 mm, and ST segment horizontal or downward sloping in any of leads I, aVL, or V_6.

4-2 STJ depression ≥ 0.5 mm and < 1.0 mm and ST segment horizontal or downward sloping in any of leads I, aVL, or V_6.

4-3 No STJ depression as much as 0.5 mm but ST segment downward sloping and segment or T-wave nadir ≥ 0.5 mm below P-R baseline, in any of leads I, aVL, or V_6.

4-4 STJ depression ≥ 1.0 mm and ST segment upward sloping or U-shaped, in any of leads I, aVL, or V_6.

Section 5.02 Posterior (inferior) site (leads II, III, aVF)

4-1-1 STJ depression ≥ 2.0 mm and ST segment horizontal or downward sloping in lead II or aVF.

4-1-2 STJ depression ≥ 1.0 mm but < 2.0 mm and ST segment horizontal or downward sloping in lead II or aVF.

4-2 STJ depression ≥ 0.5 mm and < 1.0 mm and ST segment horizontal or downward sloping in lead II or aVF.

4-3 No STJ depression as much as 0.5 mm, but ST segment downward sloping and segment or T-wave nadir ≥ 0.5 mm below P-R baseline in lead II.

4-4 STJ depression ≥ 1.0 mm and ST segment upward sloping, or U-shaped, in lead II.

Section 5.03 **Anterior site (leads V_1, V_2, V_3, V_4, V_5)**

(continued)

4-1-1 STJ depression ≥ 2.0 and ST segment horizontal or downward sloping in any of leads V_1, V_2, V_3, V_4, V_5.

4-1-2 STJ depression ≥ 1.0 mm but < 2.0 mm and ST segment horizontal or downward sloping in any of leads V_1,

V2, V3, V4, V5

4-2 STJ depression ≥ 0.5 mm and < 1.0 mm and ST segment horizontal or downward sloping in any of leads V_1,

V2, V3, V4, V5.

4-2 No STJ depression as much as 0.5 mm, but ST segment downward sloping and segment or T-wave nadir ≥ 0.5 mm below P-R baseline in any of leads V_2, V_3, V_4, V_5.

4-4 STJ depression ≥ 1.0 mm and ST segment upward sloping or U-shaped in any of leads V_1, V_2, V_3, V_4, V_5.

Article VI. T-Wave Items

(Do not code in the presence of code 6-4-1, 7-1-1, 7-2-1 or 7-4.)

Section 6.01 Anterolateral site (leads I, aVL, V6)

5-1 T amplitude negative 5.0 mm or more in either of leads I, V_6, or in lead aVL when R amplitude is ≥ 5.0 mm.

5-2 T amplitude negative or diphasic (positive-negative or negative-positive type) with negative phase at least 1.0 mm but not as deep as 5.0 mm in lead I or V_6, or in lead aVL when R amplitude is ≥ 5.0 mm.

5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type only) with less than 1.0 mm negative phase in lead I or V_6, or in lead aVL when R amplitude is ≥ 5.0 mm.

5-4 T amplitude positive and T/R amplitude ratio < 1/20 in any of leads I, aVL, V_6; R wave amplitude must be ≥ 10.0 mm.

Section 6.02 Posterior (inferior) site (leads II, III, aVF)

5-1 T amplitude negative 5.0 mm or more in lead II, or in lead aVF when QRS is mainly upright.

5-2 T amplitude negative or diphasic with negative phase (negative-positive or positive-negative type) at least 1.0 mm but not as deep as 5.0 mm in lead II, or in lead aVF when QRS is mainly upright.

5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type only) with less than 1.0 mm negative phase in lead II; not coded in lead aVF.

5-4 T amplitude positive and T/R amplitude ratio < 1/20 in lead II; R wave amplitude must be ≥ 10.0 mm.

Section 6.03 Anterior site (leads V2, V3, V4, V5)

5-1 T amplitude negative 5.0 mm or more in any of leads V_2, V_3, V_4, V_5.

5-2 T amplitude negative (flat), or diphasic (negative-positive or positive-negative type) with negative phase at least 1.0 mm but not as deep as 5.0 mm, in any of leads V_2, V_3, V_4, V_5.

5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type only) with less than 1.0 mm negative phase, in any of leads V_3, V_4, V_5.

5-4 T amplitude positive and T/R amplitude ratio < 1/20 in any of leads V_3, V_4, V_5; R wave amplitude must be ≥ 10.0 mm.

Article VII. A-V Conduction Defect

6-1 Complete (third degree) A-V block (permanent or intermittent) in any lead. Atrial and ventricular complexes independent, and atrial rate faster than ventricular rate, with ventricular rate < 60.

6-2-1 Mobitz Type II (occurrence of P-wave on time with dropped QRS and T).

6-2-2 Partial (second degree) A-V block in any lead (2:1 or 3:1 block).

6-2-3 Wenckebach's Phenomenon (P-R interval increasing from beat to beat until QRS and T dropped).

6-3 P-R (P-Q) interval ≥ 0.22 sec in the majority of beats in any of leads I, II, III, aVL, aVF.

6-4-1 Wolff-Parkinson-White Pattern (WPW), persistent. Sinus P-wave. P-R interval < 0.12 sec, plus QRS duration ≥ 0.12 sec, plus R peak duration ≥ 0.06 sec, coexisting in the same beat and present in the majority of beats in any of leads I, II, aVL, V_4, V_5, V_6. (6-4-1 suppresses 1-2-3, 1-2-7, 1-2-8, 1-3-2, 1-3-6, all 3, 4, 5, 9-2, 9-4, 9-5 codes.)

6-4-2 WPW Pattern, intermittent. WPW pattern in ≤ 50% of beats in appropriate leads.

6-5 Short P-R interval. P-R interval < 0.12 sec in all beats of any two of leads I, II, III, aVL, aVF.

6-6 Intermittent aberrant atrioventricular conduction. P-R > 0.12 sec (except in presence of 6-5 or heart rate greater than 100); wide QRS complex > 0.12 sec; normal P-wave when most beats are sinus rhythm. (Do not code in the presence of 6-4-2.) 6-8 Artificial pacemaker.

Article VIII. Ventricular Conduction Defect

7-1-1 Complete left bundle branch block (LBBB). (Do not code in presence of 6-1, 6-4-1, 6-8, 8-2-1 or 8-2-2.) QRS duration ≥ 0.12 sec in a majority of beats in any of leads I, II, III, aVL, aVF, *plus* R peak duration ≥ 0.06 sec in a majority of beats (of the same QRS pattern) in any of leads I, II, aVL, V_5, V_6. (7-1-1 suppresses 1-2-3, 1-2-7, 1-

2-8, 1-3-2, 1-3-6, all 2, 3, 4, 5, 9-2, 9-4, 9-5 codes. If any other codable Q-wave coexists with the LBBB pattern, code the Q and diminish the 7-1-1 code to a 7-4 code.)

7-1-2 Intermittent left bundle branch block. Same as 7-1-1 but with presence of normally conducted QRS complexes of different shape than the LBBB pattern.

7-2-1 Complete right bundle branch block (RBBB). (Do not code in the presence of 6-1, 6-4-1, 6-8, 8-2-1 or 8-2-2.) QRS duration ≥ 0.12 sec in a majority of beats in any of leads I, II, III, aVL, aVF, *plus*: R' > R in V_1 or V2; or QRS mainly upright, with R peak duration ≥ 0.06 sec in V_1 or V_2; or S duration >R duration in all beats in lead I or II. (7-1 suppresses 1-2-3, 1-2-7, 1-2-8, 1-3-2, 1-3-6, all 2, 3, 4, 5, 9-2, 9-4, 9-5 codes.

7-2-2 Intermittent right bundle branch block. Same as 7-2-1 but with presence of normally conducted QRS complexes of different shape than the RBBB pattern.

7-3 Incomplete right bundle branch block. QRS duration < 0.12 sec in each of leads I, II, III, aVL, aVF, and R' > R in either of leads V_1, V_2 .(Code as 3-2 in addition if those criteria are met. 7-3 suppresses code 1-2-8.)

7-4 Intraventricular block. QRS duration ≥ 0.12 sec in a majority of beats in any of leads I, II, III, aVL, aVF. (7-4 suppresses all 2, 3, 4, 5, 9-2, 9-4, 9-5 codes.)

7-5 R-R' pattern in either of leads V_1, V_2 with R' amplitude ≥ R.

7-6 Incomplete left bundle branch block. (Do not code in the presence of any codable Q- or QS-wave.) QRS duration ≥ 0.10 sec and < 0.12 in the majority of beats of each of leads I, aVL, and V_5 or V_6.

7-7 Left anterior hemiblock (LAH). QRS duration < 0.12 sec in the majority of beats in leads I, II, III, aVL, aVF, plus Q-wave amplitude ≥ 0.25 mm and < 0.03 sec duration in lead I, plus left axis deviation of -45^0 or more negative.

(In presence of 7-2, code 7-8 if axis is < -45^0 and the Q-wave in lead I meets the above criteria.) 7-8 Combination of 7-7 and 7-2.

Article IX. Arrhythmias

8-1-1 Presence of frequent atrial or junctional premature beats (10% or more of recorded complexes).

8-1-2 Presence of frequent ventricular premature beats (10% or more of record complexes).

8-1-3 Presence of both atrial and/or junctional premature beats and ventricular premature beats (so that individual frequencies are < 10% but combined premature beats are ≥ 10% of complexes).

8-1-4 Wandering atrial pacemaker.

8-1-5 Presence of 8-1-2 and 8-1-4.

8-2-1 Ventricular fibrillation or ventricular asystole.

8-2-2 Persistent ventricular (idioventricular) rhythm.

8-2-3 Intermittent ventricular tachycardia. Three or more consecutive ventricular premature beats occurring at a rate ≥100. This includes more persistent ventricular tachycardia.

8-2-4 Ventricular parasystole (should not be coded in presence of 8-3-1).

8-3-1 Atrial fibrillation (persistent).

8-3-2 Atrial flutter (persistent).

8-3-3 Intermittent atrial fibrillation (code if 3 or more clear-cut, consecutive sinus beats are present in any lead).

8-3-4 Intermittent atrial flutter (code of 3 or more clear-cut, consecutive sinus beats are present in any lead).

8-4-1 Supraventricular rhythm persistent. QRS duration < 0.12 sec; and absent P-waves or presence of abnormal Pwaves (inverted or flat in aVF); and regular rhythm.

8-4-2 Supraventricular tachycardia intermittent. Three consecutive atrial or junctional premature beats occurring at a rate ≥ 100.

8-5-1 Sinoatrial arrest. Unexpected absence of P, QRS and T, plus a R-R interval at a fixed multiple of the normal interval, ± 10%.

8-5-2 Sinoatrial block. Unexpected absence of P, QRS and T, preceded by progressive shortening of P-P intervals. (RR interval at a fixed multiple of the normal interval, ± 10%.

8-6-1 A-V dissociation with ventricular pacemaker (without capture). Requires: P-P and R-R occur at variable rates with ventricular rate as fast as or faster than the atrial rate, plus variable P-R intervals, plus no capture beats.

8-6-2 A-V dissociation with ventricular pacemaker (with capture).

8-6-3 A-V dissociation with atrial pacemaker (without capture).

8-6-4 A-V dissociation with atrial pacemaker (with capture).

8-7 Sinus tachycardia (over 100/min).

8-8 Sinus bradycardia (under 50/min).

8-9 Other arrhythmias. Heart rate may be recorded as a continuous variable.

ST Segment Elevation

Anterolateral site (leads I, aVL, V_6)

9-2 ST segment elevation ≥ 1.0 mm in any of leads I, aVL, V_6.

Posterior (inferior) site (leads II, III, aVF)

9-2 ST segment elevation ≥ 1.0 mm in any of leads II, III, aVF.

Anterior site (leads V1, V2, V3, V4, V5)

9-2 ST segment elevation ≥ 1.0 mm in lead V5 or ST segment elevation ≥ 2.0 mm in any of leads V_1, V_2, V_3, V_4.

Article X. Miscellaneous Items

9-1 Low QRS amplitude. QRS peak-to-peak amplitude < 5 mm in all beats in each of leads I, II, III, or < 10 mm in all beats in each of leads V_1, V_2, V_3, V_4, V_5, V_6. (Check calibration before coding.)

9-3 P-wave amplitude ≥ 2.5 mm in any of leads II, III, aVF, in a majority of beats.

9-4-1 QRS transition zone at V_3 or to the right of V_3 on the chest. (Do not code in the presence of 6-4-1, 7-1-1, 7-2-1 or 7-4.)

9-4-2 QRS transition zone at V_4 or to the left of V_4 on the chest. (Do not code in the presence of 6-4-1, 7-1-1, 7-2-1 or 7-4.)

9-5 T-wave amplitude > 12 mm in any of leads I, II, III, aVL, aVF, V_1, V_2, V_3, V_4, V_5, V_6. (Do not code in the presence of 6-4-1, 7-1-1, 7-2-1 or 7-4.)

9-8-1 Technical problems which interfere with coding.

9-8-2 Technical problems which do not interfere with coding.

* Prineas R, Crow R, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings. John Wright-PSG, Inc. Littleton, MA, June 1982.