# STUDY ON CARDIOVASCULAR RISK FACTORS AND ITS MANAGEMENT IN TYPE II DIABETIC PATIENTS

A Dissertation submitted to
THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY
CHENNAI – 600 032

In partial fulfillment of the requirements for the award of Degree of
**MASTER OF PHARMACY**
**IN**
**BRANCH – VII- PHARMACY PRACTICE**

Submitted by
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**COIMBATORE - 641 044.**

**OCTOBER - 2017**

# CERTIFICATE

This is to certify that the M.Pharm dissertation entitled **"Study on Cardiovascualr Risk Factors and its Management in Type II Diabetic Patients"** being submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai was carried out by **Ms. ANJU LIZA THOMAS (Register No.261540102)** in the Department of Pharmacy Practice, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore which is affiliated to The Tamil Nadu Dr.MGR Medical University, Chennai, under my direct supervision and guidance to my fullest satisfaction.

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# CONTENTS

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| CVD | : | Cardiovascular disease |
| T2DM | : | Type 2 diabetic mellitus |
| HDL | : | High density lipoprotein |
| LDL | : | Low densitylipoproteins |
| DHD | : | Diabetic heart disease |
| MA | : | Microalbumin urea |
| CHD | : | Coronory heart disease |
| ADA | : | American diabetes association |
| AHA | : | American heart association |
| TT | : | Therapeutic Target |
| CCF | : | Congestive cardiac failure |
| IHD | : | Ischemic heart disease |
| ACS | : | Acute coronary syndrome |
| FRS | : | Framingham risk score |
| NSAID | : | Non-steroidal anti inflammatory drugs |
| ACE | : | Angiotensin converting enzyme |
| SBP | : | Systolic blood pressure |
| DBP | : | Diastolic blood pressure |
| CKD | : | Chronic kidney disease |
| PCI | : | Percutaneous coronary intervention |

# ABSTRACT

Changes in the human environment, behavior, and lifestyle are contributing to the upsurge in the incidence of diabetes. However, better management has resulted in a longer survival of patients with diabetes, but it is accompanied by long-term chronic complications due to hyperglycemia. Individuals with diabetes most often die of cardiovascular disease (CVD) rather than from a cause uniquely related to diabetes, such as ketoacidosis or hypoglycemia. Diabetic patients have a twofold to six fold higher incidence of cardiovascular disease than nondiabetic population. Furthermore, diabetic patients with CVD sustain a worse prognosis for survival than CVD patients without diabetes and their quality of life also depreciates .Therefore, diabetes has been considered as having a risk equivalent to a nondiabetic patient with preexisting heart disease. Identification of patients at risk for CVD could felicitate the prevention or retardation of cardiovascular events. The management of CVD prevention and the problem associated with it needs intensified monitoring by pharmacist.

The study was carried out the department of Cardiology and General Medicine to assess the risk factors of cardiovascular disease in type 2 DM patients in the study population. The result reveals that total of 103 diabetic patients 73% were diagnosed with CVD and 30% were non CVD. The 10 year risk factors were assessed by Framingham risk score for non CVD population. It was found that 63.33% patients were having >20 % of risk and 26.66 % patients had 10-20% risk for future CVD

The total number of drugs prescribed for the CVD patients 315 in which, the most frequently prescribed was anticoagulants (41.90%), followed by dyslipidemic agents (17.77%), antianginals (9.84%). CVD prevention categorized into primary and secondary there were 30 (29.1%) patients were provided with primary prevention and 73 (70.87%) patients received secondary prevention for CVD.

The result reveals that continuous monitoring should be done for the patients who were taking aspirin and clopidogrel for a prolonged period because of chance of resistance. Guidelines are prepared to monitor and manage CVD prevention therapy with aspirin and clopidogrel.

# INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of ill-health and mortality in people with type two diabetes (T2DM).Type two DM is associated with twice the risk of incident coronary heart disease (CHD) and ischemic stroke and 2–4 times increased risk of CHD and stroke mortality compared with diabetes-free individuals.[1] Changes in the human environment, behavior, and lifestyle are contributing to the upsurge in the incidence of diabetes. However, better management has resulted in a longer survival of patients with diabetes, but it is accompanied by long-term chronic complications due to hyperglycemia Individuals with diabetes most often die of cardiovascular disease (CVD) rather than from a cause uniquely related to diabetes, such as ketoacidosis or hypoglycemia[2] . Diabetic patients have a twofold to six fold higher incidence of cardiovascular disease than non-diabetic population. Furthermore, diabetic patients with CVD sustain a worse prognosis for survival than CVD patients without diabetes and their quality of life also depreciates. Therefore, diabetes has been considered as having a risk equivalent to a non-diabetic patient with preexisting heart disease. Identification of patients at risk for CVD could felicitate the prevention or retardation of cardiovascular events.[3]

**DIABETIC HEART DISEASE [4]**

The term "diabetic heart disease" (DHD) refers to heart disease that develops in people who have diabetes. Compared with people who don't have diabetes, people who have diabetes:

- Are at higher risk for heart disease
- Have additional causes of heart disease
- May develop heart disease at a younger age
- May have more severe heart disease

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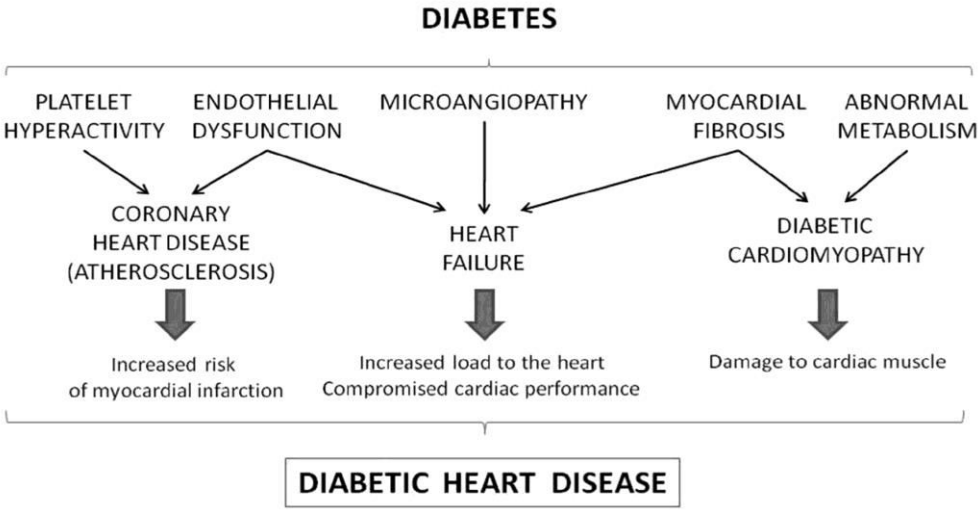


**CAUSES OF DIABETIC HEART DISEASE** [5]

At least four complex processes, alone or combined, can lead to diabetic heart disease (DHD). They include coronary atherosclerosis; metabolic syndrome; insulin resistance in people who have type 2 diabetes; and the interaction of coronary heart disease (CHD), high blood pressure, and diabetes.

1) **Coronary Atherosclerosis** [6]

Atherosclerosis is a disease in which plaque builds up inside the arteries. The exact cause of atherosclerosis isn't known. However, studies show that it is a slow, complex disease that may start in childhood. The disease develops faster as you age.

Coronary atherosclerosis may start when certain factors damage the inner layers of the coronary (heart) arteries. These factors include:[7]

- Smoking
- High amounts of certain fats and cholesterol in the blood
- High blood pressure

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- High amounts of sugar in the blood due to insulin resistance or diabetes

Plaque may begin to build up where the arteries are damaged. Over time, plaque hardens and narrows the arteries. This reduces the flow of oxygen-rich blood to your heart muscle.

Eventually, an area of plaque can rupture (break open). When this happens, blood cell fragments called platelets (PLATE-lets) stick to the site of the injury. They may clump together to form blood clots. Blood clots narrow the coronary arteries even more. This limits the flow of oxygen-rich blood to heart and may worsen angina (chest pain) or cause a heart attack.

**2) Metabolic Syndrome** [8]

Metabolic syndrome is the name for a group of risk factors that raises risk of both CHD and type 2 diabetes.

The risk factors are:

- A large waistline (a waist measurement of 35 inches or more for women and 40 inches or more for men).
- A high triglyceride level (or you're on medicine to treat high triglycerides). Triglycerides are a type of fat found in the blood.
- A low HDL cholesterol level (or you're on medicine to treat low HDL cholesterol). HDL sometimes is called "good" cholesterol. This is because it helps remove cholesterol from your arteries.
- High blood pressure (or you're on medicine to treat high blood pressure).
- A high fasting blood sugar level (or you're on medicine to treat high blood sugar).

It's unclear whether these risk factors have a common cause or are mainly related by their combined effects on the heart.

Obesity seems to set the stage for metabolic syndrome. Obesity can cause

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harmful changes in body fats and how the body uses insulin.

Chronic (ongoing) inflammation also may occur in people who have metabolic syndrome. Inflammation is the body's response to illness or injury. It may raise your risk of CHD and heart attack. Inflammation also may contribute to or worsen metabolic syndrome.

Research is ongoing to learn more about metabolic syndrome and how metabolic risk factors interact.

**3) Insulin Resistance in People Who Have Type 2 Diabetes** [9]

Type 2 diabetes usually begins with insulin resistance. Insulin resistance means that the body can't properly use the insulin it makes.

People who have type 2 diabetes and insulin resistance have higher levels of substances in the blood that cause blood clots. Blood clots can block the coronary arteries and cause a heart attack or even death.

**4) The Interaction of Coronary Heart Disease, High Blood Pressure, and Diabetes** [10]

Each of these risk factors alone can damage the heart. CHD reduces the flow of oxygen-rich blood to your heart muscle. High blood pressure and diabetes may cause harmful changes in the structure and function of the heart.

Having CHD, high blood pressure, and diabetes is even more harmful to the heart. Together, these conditions can severely damage the heart muscle. As a result, the heart has to work harder than normal. Over time, the heart weakens and isn’t able to pump enough blood to meet the body’s needs. This condition is called heart failure.

As the heart weakens, the body may release proteins and other substances into the blood. These proteins and substances also can harm the heart and worsen heart failure.

**SIGNS AND SYMPTOMS OF DIABETIC HEART DISEASE**

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Some people who have diabetic heart disease (DHD) may have no signs or symptoms of heart disease. This is called “silent” heart disease. Diabetes-related nerve damage that blunts heart pain may explain why symptoms aren't noticed. Thus, people who have diabetes should have regular medical checkups. Tests may reveal a problem before they're aware of it. Early treatment can reduce or delay related problems. Some people who have DHD will have some or all of the typical symptoms of heart disease. Treatment for a heart attack works best when it's given right after symptoms occur.

**CORONARY HEART DISEASE[11, 12]**

A common symptom of coronary heart disease (CHD) is angina. Angina is chest pain or discomfort that occurs if heart muscle doesn't get enough oxygen-rich blood. Angina may feel like pressure or squeezing chest and also may feel it in shoulders, arms, neck, jaw, or back. Angina pain may even feel like indigestion. The pain tends to get worse with activity and go away with rest. Emotional stress also can trigger the pain. Other CHD signs and symptoms include.[13, 14]

Nausea (feeling sick to your stomach)

- Fatigue (tiredness),
- Shortness of breath,
- Sweating,
- Light-headedness
- Weakness.

Some people don't realize they have CHD until they have a heart attack. A heart attack occurs if a blood clot forms in a coronary artery and blocks blood flow to part of the heart muscle. The most common heart attack symptom is chest pain or discomfort. Most heart attacks involve discomfort in the center or left side of the chest that often lasts for more than a few minutes or goes away and comes

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back. The discomfort can feel like uncomfortable pressure, squeezing, fullness, or pain. The feeling can be mild or severe. Heart attack pain sometimes feels like indigestion or heartburn. Shortness of breath may occur with or before chest discomfort.[15]

Heart attacks also can cause upper body discomfort in one or both arms, the back, neck, jaw, or upper part of the stomach. Other heart attack symptoms include nausea, vomiting, light-headedness or sudden dizziness, breaking out in a cold sweat, sleep problems, fatigue, and lack of energy.[16]

Some heart attack symptoms are similar to angina symptoms. Angina pain usually lasts for only a few minutes and goes away with rest. Chest pain or discomfort that doesn't go away or changes from its usual pattern (for example, occurs more often or while you're resting) can be a sign of a heart attack.[17]

Diabetes-related nerve damage can interfere with pain signals in the body. As a result, some people who have diabetes may have heart attacks without symptoms.

**HEART FAILURE** [18]

The most common symptoms of heart failure are shortness of breath or trouble breathing, fatigue, and swelling in the ankles, feet, legs, abdomen, and veins in your neck. As the heart weakens, heart failure symptoms worsen. People who have heart failure can live longer and more active lives if the condition is diagnosed early and they follow their treatment plans.

**DIABETIC CARDIOMYOPATHY**

Diabetic cardiomyopathy may not cause symptoms in its early stages. Later, may have weakness, shortness of breath, a severe cough, fatigue, and swelling of the legs.[19]

**RISK FACTORS FOR CVD** [20]

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Changes in the human environment, behaviour, and lifestyle are contributing to the upsurge in the incidence of diabetes. However, better management has resulted in a longer survival of patients with diabetes, but it is accompanied by long-term chronic complications due to hyperglycemia. Individuals with diabetes most often die of cardiovascular disease (CVD) rather than from a cause uniquely related to diabetes, such as ketoacidosis or hypoglycemia. Diabetic patients have a twofold to sixfold higher incidence of cardiovascular disease than nondiabetic population. Furthermore, diabetic patients with CVD sustain a worse prognosis for survival than CVD patients without diabetes and their quality of life also depreciates. Therefore, diabetes has been considered as having a risk equivalent to a nondiabetic patient with preexisting heart disease. Identification of patients at risk for CVD could felicitate the prevention or retardation of cardiovascular events. Lifetime risk estimates provide a simple conceptual basis for estimating the absolute risk of developing disease over the remaining lifespan. Presence of several risk factors among diabetic patients suffering from cardiovascular disease stresses on the assessment of the individual's total burden of risk rather than on the level of any particular risk factor. Several multivariate risk prediction algorithms have been developed to predict future CVD risk but their use has lagged in primary care**.**

Risk factors are classified into two types [21]

- **Traditional risk factors**

1. High blood pressure
2. Abnormal cholesterol and triglycerides
3. Obesity
4. Lack of physical activity
5. Poorly controlled blood sugar

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6. Smoking
7. Age
8. Cardiovascular impact in the gender
9. Metabolic syndrome
10. Unhealthy diet
11. Stress

- **Non traditional risk factors**

1. Insulin resistance and hyperinsuinemia
2. Microalbuminuria
3. Haemaatological and thrombogenic factors

**TRADITIONAL RISK FACTORS FOR CVD**

**1. High blood pressure (hypertension)**

High blood pressure has long been recognized as a major risk factor for cardiovascular disease. Studies report a positive association between hypertension and insulin resistance. When patients have both hypertension and diabetes, which is a common combination, their risk for cardiovascular disease doubles.

**2. Abnormal cholesterol and high triglycerides**

Patients with diabetes often have unhealthy cholesterol levels including high LDL ("bad") cholesterol, low HDL ("good") cholesterol, and high triglycerides. This triad of poor lipid counts often occurs in patients with premature coronary heart disease. It is also characteristic of a lipid disorder associated with insulin resistance called atherogenic dyslipidemia, or diabetic dyslipidemia in those patients with diabetes. Learn more about cholesterol abnormalities as they relate to diabetes.

**3. Obesity[22]**

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Obesity is a major risk factor for cardiovascular disease and has been strongly associated with insulin resistance. Weight loss can improve cardiovascular risk, decrease insulin concentration and increase insulin sensitivity. Obesity and insulin resistance also have been associated with other risk factors, including high blood pressure. Being overweight or obese raises your risk of heart disease and heart attack.

**4. Lack of physical activity [23]**

Physical inactivity is another modifiable major risk factor for insulin resistance and cardiovascular disease. Exercising and losing weight can prevent or delay the onset of type 2 diabetes, reduce blood pressure and help reduce the risk for heart attack and stroke. It's likely that any type of moderate and/or vigorous intensity, aerobic physical activity—whether sports, household work, gardening or work-related physical activity—is similarly beneficial.

**5. Poorly controlled blood sugars (too high) or out of normal range**

Diabetes can cause blood sugar to rise to dangerous levels. Medications may be needed to manage blood sugar.

**6. Smoking**

Smoking puts individuals, whether or not they have diabetes, at higher risk for heart disease and stroke.

**7. Age**

The impact of diabetes on risk of cardiovascular disease appears to diminish with advancing age, particularly in women. Although suggestive, this trend can not be demonstrated to be statistically significant. It suggests that late onset diabetes may have a different effect on the cardiovascular apparatus than early onset.

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**8. Cardiovascular Impact in the gender**

The relative impact of diabetes was substantially greater for women than for men. For each of the cardiovascular diseases morbidity and mortality was higher for diabetic women than nondiabetic men. Among those with diabetes, the female advantage over men as regards cardiovascular mortality is lost. After adjustment for differences in other associated cardiovascular risk factors in the two sexes, the relative impact of diabetes on coronary heart disease, peripheral vascular disease, or stroke incidence was the same in men and women, but for cardiovascular mortality and cardiac failure the impact is still greater in women. The reason for the greater susceptibility of women to these cardiovascular sequelae of diabetes is not clear.

**9. Matabolic syndrome**

Metabolic syndrome is the name for a group of risk factors that raises your risk of heart disease and type two diabetes. Metabolic syndrome also raises your risk of other health problems, such as stroke.

**10. Unhealthy diet**

An unhealthy diet can raise your risk of heart disease. Foods that are high in saturated and *trans* fats, cholesterol, sodium (salt), and sugar can worsen other heart disease risk factors.

**11. Stress**

Stress and anxiety can trigger arteries to tighten. This can raise blood pressure and risk of having a heart attack. Stress also may indirectly raise risk of heart disease if it makes more likely to smoke or overeat foods high in fat and sugar.

**NON-TRADITIONAL RISK FACTORS[27] FOR CVD**

**1) Insulin resistance and hyperinsulinemia**

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IR is a principal characteristic of T2DM and it develops in multiple organs involving the skeletal muscle, liver, adipose tissue and the heart. The onset of hyperglycaemia and diabetes is often preceded by several years of IR. Obesity plays a major role in this phenomenon and provides an important link between T2DM and the accumulation of fat. A significant section of the population with T2DM is obese.

The hyperinsulinemia, as a result of IR, occurs even before the onset of DM, and could be, by chance, related to vascular disease.

**2) Microalbuminuria**

The term microalbuminuria (MA), a urinary albumin excretion between 30 and 300 mg/24 h, has been introduced to identify subjects at increased risk of early cardiovascular death and progressive renal disease. In individuals with T2DM, MA is a prematurely clinical sign suggestive of vascular damage to the glomerulus. MA has also been currently reported as an important risk factor for CVD and remains the main and most widely used marker of diabetic renal damage in clinical practice. It is also a marker of organ dysfunction, and has been appeared to be associated with an increased risk of cardiovascular morbidity and mortality in T2DM patients. At present, an increased albumin excretion is considered to be a renal symptom of generalized endothelial dysfunction. According to different studies, the prevalence of MA is up to 19% in T2DM.

**3) Haematological and thrombogenic factors**

Atherothrombosis, defined as the formation of a thrombus on a pre-existing atherosclerotic plaque, is the leading cause of mortality in the Western world. Diabetes has been recognised as an independent risk factor and atherothrombosis accounts for the 80% of deaths in these patients. It is the result of the progression of atherosclerosis, and its major manifestations are sudden cardiac death, myocardial infarction, stroke and peripheral arterial ischemia.

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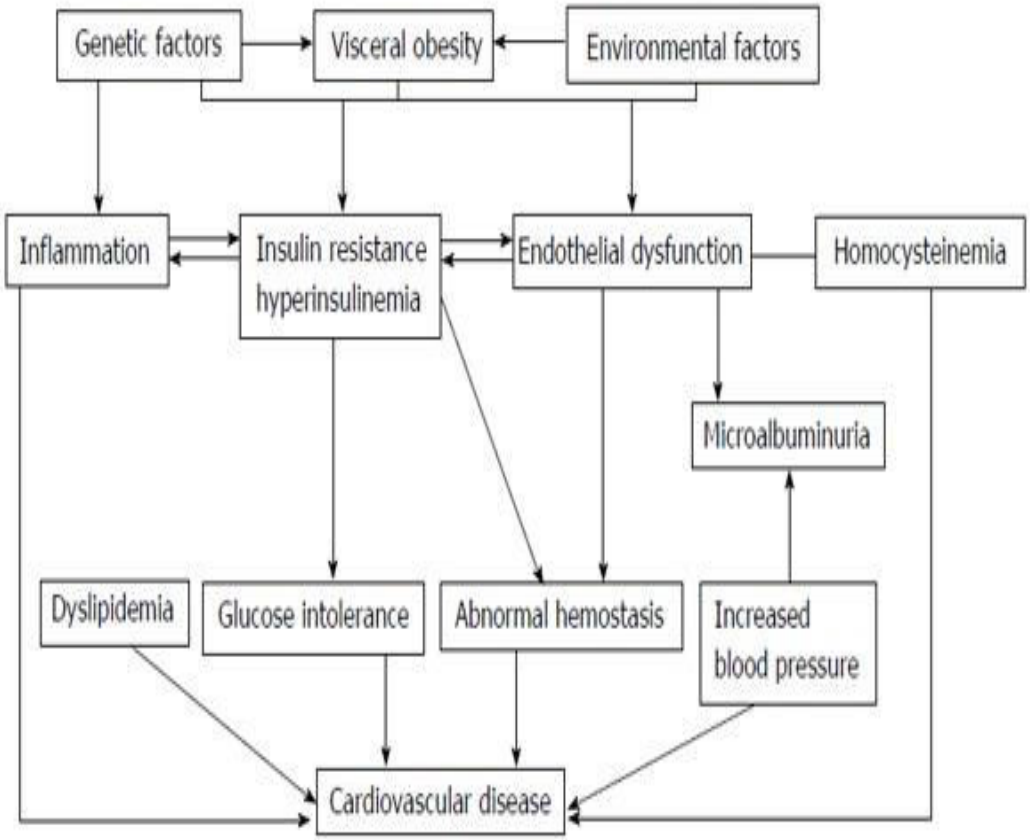
**INTERACTIONS OF TRADITIONAL AND NON-TRADITIONAL RISK FACTORS IN DIABETES MELLITUS**




**FRAMINGHAM RISK SCORE [25]**

The FRS is a risk assessment tool that has been derived from data collected in the Framingham Heart Study. The NCEP guidelines recommend that patients with two or more risk factors have their FRS calculated. The FRS consists of points that are allocated for the various degrees of risk associated with five categories: age, total cholesterol level, HDL cholesterol level, tobacco smoking status and hypertension (and whether the latter condition is treated). The

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summation of these points results in a percentage risk of having a cardiac event in the next 10 years. Although the Framingham Risk Score (FRS) is the most well known risk prediction method for the primary prevention of cardiovascular disease, other objective risk assessment options include the Reynold's Risk Score (RRS), high sensitivity C-reactive protein, total number of risk factors, and carotid ultrasound to detect atherosclerosis. . Outline FRS assessment for men and women, respectively5.

The ATP III treatment algorithm divided patients into 3 risk categories based on clinical characteristics and the Framingham 10-year risk score:

1. Established CHD and CHD risk equivalents: High risk (10-year risk higher than 20%)
2. Multiple (2 or more) risk factors: Moderately high risk (10-year risk, 10% -20%); moderate risk (10-year risk lower than 10%)
3. Zero to 1 (1 or none) risk factor: Lower risk (10-year risk lower than 10%)

**MANAGEMENT OF CVD PATIENTS HAVING DM [26]**

- The ADA (AMERICAN DIABETES ASSOCIATION) and AHA (AMERICAN HEART ASSOCIATION) each have been published guidelines for CVD prevention.
- The ADA has issued a separate recommendation for each of the cardiovascular risk factors in patients with diabetes, and AHA is shaped primary and secondary guidelines that extend to the patients with diabetes.
- Guidelines for CVD management in diabetes are based on the premise that most of the patients with diabetes are at high risk for the future CVD events. When diabetes exists in patients with established CVD, absolute risk for future events is very high.
- Even in the absence of CVD, both the ADA, and the AHA identify diabetes as a high risk of condition for macrovascular CVD.

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- Primary prevention can be individually oriented involving screening for risk factors and treatment of these risk factors by pharmacological and non-pharmacological means so called high risk approach.
- On the other hand the primary prevention can be directed towards the whole population group and secondary prevention is always directed towards in individuals.

**PRIMARY PREVENTION OF CVD IN PEOPLE WITH DIABETES[27]**

**Lifestyle management**

❖ **Weight**

Structured programs that emphasize lifestyle changes such as reduced fat (30% of daily energy) and total energy intake and increased regular physical activity, along with regular participant contact, can produce long-term weight loss on the order of 5–7% of starting weight, with improvement in blood pressure.

***Medical nutrition therapy***

To achieve reductions in LDL cholesterol:

- Saturated fats should be 7% of energy intake.
- Dietary cholesterol intake should be 200 mg/day.
- Intake of *trans* unsaturated fatty acids should be 1% of energy intake.

❖ **Physical activity**

To improve glycemic control, assist with weight loss or maintenance, and reduce risk of CVD, at least 150 min of moderate-intensity aerobic physical activity or at least 90 min of vigorous aerobic exercise per week is recommended. The physical activity should be distributed over at least 3 days per week, with no more than 2 consecutive days without physical activity.

❖ **Blood pressure**

Blood pressure should be measured at every routine diabetes visit. Patients found to have systolic blood pressure 130 mmHg or diastolic blood pressure 80

mmHg should have blood pressure confirmed on a separate day.

- Patients with diabetes should be treated to a systolic blood pressure 130 mmHg and a diastolic blood pressure 80 mmHg.

❖ **Lipids**

In adult patients, test for lipid disorders at least annually and more often if needed to achieve goals. In adults under the age of 40 years with low-risk lipid values (LDL cholesterol 100 mg/dl, HDL cholesterol 50 mg/dl, and triglycerides 150 mg/dl), lipid assessments may be repeated every 2 years.

❖ **Tobacco**

- ✓ All patients with diabetes should be asked about tobacco use status at every visit.
- ✓ Every tobacco user should be advised to quit.
- ✓ The tobacco user's willingness to quit should be assessed.
- ✓ The patient can be assisted by counseling and by developing a plan to quit.

❖ **Antiplatelet agents**

Aspirin therapy (75–162 mg/day) should be recommended as a primary prevention strategy in those with diabetes at increased cardiovascular risk, including those who are 40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).

People with aspirin allergy, bleeding tendency, existing anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease are not candidates for aspirin therapy. Other antiplatelet agents may be a reasonable alternative for patients with high risk.

❖ **Glycemic control**

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The A1C goal for patients in general is 7%.

The A1C goal for the individual patient is an A1C as close to normal (6%) as possible, without causing significant hypoglycemia.

**SECONDARY PREVENTION OF CVD IN TYPE TWO DM PATIENTS[28]**

1. Tobacco Exposure should reduce
2. Lipid Management
3. Blood pressure
4. physical activity
5. weight assessment
6. Diabetes (HbA1C>7)
7. Aspirin
8. Beta blocker

1. **Tobacco Exposure**

   Goals: Complete cessation if currently smoking; avoidance of secondhand smoke.

**2. Blood Pressure**

140/90 mm Hg or 130/80 mm Hg if patient has diabetes or chronic kidney disease. Initiate or maintain lifestyle modification—weight control; increased physical activity; alcohol moderation.

**1. PHYSICAL ACTIVITY**

**Everyday Physical Activities**

- Using stairs instead of elevator- Playing actively with children Exercise Options
- Walking

**2. WEIGHT ASSESSMENT**

- BMI Interpretation

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- <18.5 Underweight
- 18.5-24.9 Normal
- 25.0-29.9 Overweight
- >30 Obesity
- 30.0-34.9 Obesity I
- 35.0-39.9 Obesity II
- >40 Obesity III

**3. Diabetes**

Goal: HbA1c < 7%

**4. Aspirin**

Initiate aspirin, 75 to 325 mg/d, if not contraindicated.

**Aspirin Contraindications**

- Hypersensitivity to salicylates or NSAIDs- GI bleeding, unexplained GI blood loss, or hemophilia
- Use Aspirin with Caution- Anticoagulant use (warfarin/Coumadin)
- Severe nausea and vomiting or known upper GI

**5. Beta Blockers**

Start in all post-MI and acute ischemic syndrome patients at 5 to 28 days post-MI. Continue indefinitely (previous recommendation was for a minimum of six months) Use as needed to manage angina, rhythm or blood pressure

**6. ACE Inhibitors Post-MI**

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Start as early as 3 days post-MI in stable high-risk patients continue. Continue indefinitely for all patients with coronary or other vascular disease

`

**American Heart Association (AHA) and American Diabetes Association (ADA) Prevention of Cardiovascular Disease in Type 2 Diabetes 2016**

**Diabetes Diagnosis**

| Diagnostic Criteria for Diabetes and Prediabetes | | |
|---|---|---|
| | Diabetes | Prediabetes |
| HbA1C | ≥6.5% | 5.7-6.4% |
| Fasting glucose | ≥126 mg/dL | 100-125 mg/dL |
| Random glucose | ≥200 mg/dL | 140-199 mg/dL |

**Lifestyle Management**

- Lifestyle management is a cornerstone of diabetes clinical care
- It is the primary approach for weight loss
- Lifestyle management includes dietary change, increased energy expenditure and behavioral changes (eg, smoking cessation) oduce weight loss
- Reduce the need for medication to control CVD risk factors *without increasing the risk for cardiovascular events*

**Pharmacologic Therapy for Weight Management**

- Pharmacologic therapy may be considered if lifestyle interventions fail to achieve weight loss goals

**Pharmacologic Therapy Indications**

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| |
|---|
| BMI 25-30 kg/m2 with comorbidities |
| BMI >30 kg/m2 with or without comorbidities |

| **Recommendations for HbA1C Targets** |
|---|
| HbA1C ≤7.0% for most individuals with type 2 diabetes to reduce microvascular disease incidence |

| **Blood Pressure Management** |
|---|
| • High blood pressure is a major contributor to higher risk for CVD events in individuals with type 2 diabetes |

| **BP Targets** | |
|---|---|
| BP <140/90 mm Hg for most individuals with type 2 diabetes1,2 | |
| ADA recommends SBP <140 mm Hg for many A lower target (<130) may be appropriate for some if it can be achieved safely3 | |
| Pharmacologic therapy should include a regimen with an ACEI or ARB (*never together*)3 | If one class is not tolerable, switch to the other |
| Individuals with CKD should be treated with an ACEI or ARB | |

| **Cholesterol Management** |
|---|

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- Most individuals with type 2 diabetes have *diabetic dyslipidemia*
- Elevated triglycerides; decreased HDL-C; elevated, borderline, or normal LDL-C
- LDL-C is the primary target of lipid-lowering therapy
- LDL-C reduction with statins reduces the risk of major CVD events in indiviuals with or without diabetes

| **LDL-C Treatment** | |
|---|---|
| Lifestyle changes are the foundation | |
| Individuals aged 40-75 years with diabetes and LDL-C 70-189 mg/dL | Moderate-intensity statin |
| Individuals aged 40-75 years with diabetes and ≥7.5% ASCVD risk | High-intensity statin |
| Individuals aged <40 or >75 years with diabetes | Evaluate the benefit of statin therapy |
| Evaluate and treat individuals with fasting TG >500 mg/dL | |

**Aspirin Therapy**

- Aspirin therapy for CVD primary prevention in individuals with diabetes is controversial.
- Aspirin reduces CVD events in patients with known CVD (secondary prevention)
- It is effective for primary prevention of myocardial infarction in men The net effect of aspirin therapy depends on baseline risks of CVD and GI bleeding

| | |
|---|---|
| Low-dose | Reasonable for individuals with a ≥10% 10-year CVD risk and without increased bleeding risk |

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| | |
|---|---|
| aspirin (75-162 mg/d) | Reasonable for adxults with diabetes who are at intermediate CVD risk: 5-10% 10-year CVD risk |

**PROBLEMS ASSOCIATED WITH MANAGEMENT OF CVD [29]**

Cardiovasvular events are the leading causes of death in diabetic subjects, and aspirin is the most frequently used medication for secondary prevention of ischemic events in patients with diabetes. However, many patients taking this drug eventually have cardiovascular events. Antiplatelet drug resistance has emerged as a new concept and is responsible for some of these treatment failures. However, not all treatment failures can be attributed to antiplatelet drug resistance.

**ASPIRIN CLOPIDOGREL RESISTANCE [30]**

Platelets play a central role in the pathogenesis atherothrombosis .Thus, achieving platelet inhibition is an important part of managing those patients who suffer from an atherothrombotic event. Low-dose aspirin is effective for preventing adverse vascular events in patients suffering with acute coronary syndrome stroke and/or peripheral vascular disease. Aspirin alone in many instances is not sufficient to prevent ischemic events in the high risk patients because aspirin inhibits only the cyclooxygenase pathway and it has no effect on the adenosine diphosphate P2Y12 receptor. Dual antiplatelet therapy with clopidogrel plus aspirin has been shown to reduce ischemic events in patients with unstable angina and MI and especially when they are undergoing percutaneous coronary intervention (PCI) and stenting. Despite its proven benefit, the responses of individual patients show considerable heterogeneity to aspirin and to clopidogrel. The recent data shows that adequate antiplatelet effects are not achieved in 5% to 45% of the patients taking aspirin and in 4% to 30% of patients

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taking clopidogrel, and this suggests that many patients are resistant or partially responsive in the drugs' antiplatelet effect. Thus, measuring the patients' responsiveness to aspirin and clopidogrel may be an important factor in monitoring these drugs' therapeutic efficacy and so improve the cardiovascular outcomes. However, there are no clinical guidelines to deal with treatment failure for the stent thrombosis and recurrent atherothrombotic events that are due to aspirin and clopidogrel resistance. 50% of aspirin resistant population are also resistant to clopidogrel.

**ROLE OF PHARMACIST CARDIOVASCULAR DISEASE PREVENTION AND MANAGEMENT [31]**

Pharmacists have long undertaken roles in the prevention and management of CVD that extend beyond the traditional dispensing of medicines. Evidence can now confirm the significant clinical benefits of pharmacist interventions for a range of major disease states and preventive health activities related to

- Diabetes (significant HbA1c reductions)
- Blood pressure,
- Smoking cessation,
- Lifestyle modification, medicines management and medicines adherence.
- Lipid level monitoring
- Diet management
- Assess their 10-year absolute risk using a validated scoring tool derived from the Framingham Heart Study.
- Check problem associated with management of CVD
- .Check the problems associated with duration of therapy
- Laboratory tests that provide information on clopidogrel or aspirin response can aid in the identification of persons who are at risk of

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experiencing recurrent cardiovascular events.

- Dosage adjustments

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# LITERATURE REVIEW

1) **Julia. et al (2016)[32]** conducted a study on diabetes treatment and risk of heart failure. This study assessed the association between risk of cardiovascular disease heart failure and mortality and different diabetic drugs in people with type two diabetes. The study concluded that use of gliptins or glitazones was associated with decreased risks of heart failure, cardiovascular disease, and all cause mortality compared with non-use of these drugs.

**2)** **Eral et al (2005)[33]** studied on risks for all causes mortality, cardiovascular disease and diabetes associated with metabolic syndrome. The study concluded that estimate suggest that the population attributable fraction for the metabolic syndrome as it currently conceived is 6-7% for all cause mortality,12-17% for cardiovascular disease and 30-52% for diabetes. Further research is needed to establish the use of metabolic syndrome in predicting risk for death, cardiovascular disease and diabetes in various population subgroup.

3) **John B et al (2007)[34]** conducted a study on primary prevention of cardiovascular disease in people with DM. The study concluded that life style and medical interventions that will prevent the development of CVD in people with DM. The study reveled that People with either type 1 or type 2 diabetes are at increased risk for CVD and have worse outcomes after surviving a CVD event. The aggressive use of lifestyle modifications can reduce or delay the need for medical intervention. Appropriate lifestyle and medical interventions will reduce the occurrence of CVD and allow people with diabetes to live healthier and longer lives.

4) **Anthony et al (2003)[35]** conducted a study on secondary prevention of cardiovascular events with long term pravastatins in patients with DM. The study reveals that cholesterol lowering treatment with pravastatins therapy prevents cardiovascular events such as stroke in patients with DM established CHD.

5) **Janet K. et al (2012)[36]** studied on hypoglycemia, diabetes, and cardiovascular disease. The study reveals that hypoglycemia is a common effect of treatment for diabetes and is prevalent among both type one and type two patients. Hypoglycemia may acutely increase the risk of CV complications, because of reduced blood flow in the heart and electrical disturbances leading to arrhythmia and prolonged QT interval.

6) **Komola et al (2014)[37]** conducted study on cardiovascular safety profile of currently available diabetic drugs. The study concluded that careful selection of drug therapy paying particular attention to cardiovascular safety is important in optimizing diabetic therapy. Thus, treatment and management of diabetes should be adjusted on an individual basis based on age, duration of diabetes, risk for CVD, and presence of microvascular and macrovascular complications

7) **Mary et al (2014)[38]** carried out study on risk of cardiovascular disease among diabetic patients.The study reveled that Primary prevention through improved control of risk factors and therapeutic lifestyle modification (including dietary modification, aerobic exercise, and smoking cessation).

8) **Arvind et al (2017) [39]**conducted a study on prevalence of diabetes and cardiovascular risk factors in middleclass urban participants in India. The study concluded that in the urban Indian middle class, more than a quarter of patients with diabetes are undiagnosed and the status of control is low. Cardiovascular risk factors—hypertension, hypercholesterolemia, low HDL cholesterol, hypertriglyceridemia, and smoking/smokeless tobacco use are highly prevalent. There is low awareness, treatment, and control of hypertension and hypercholesterolemia in patients with diabetes.

9) **Iciar et al (2014 )[40]** conducted a study on type 2 diabetes and cardiovascular disease. The study concluded that there are consistent evidences that optimal glycaemic control, along with control of hypertension, dyslipidaemia, smoking cessation, and weight loss are necessary for reducing cardiovascular risk in type two diabetic patients. Cardiovascular benefits are obtained if the control of traditional cardiovascular risk factors begins early in subjects with short duration of DM and low cardiovascular risk.

10) **Haitham et al (2016)[41]** conducted a study on prevalence and risk factors of clopidogrel non-response among Saudi patients undergoing coronary angiography. The study concluded that high rate of clopidogrel in-vitro non-response among Saudi patients undergoing coronary angiography.

11) **Chris R et al (2014)**[42] conducted a study on cardiovascular impact of drugs used in the treatment of diabetes. The study concluded that cellular basis for the therapeutic action of these drugs, addresses the evidence for their cardiovascular benefits and risks. A particular focus is provided on metformin as it is the first choice drug for most patients with type two diabetes.

12) **Bharti et al (2015)[43]** performed a study on statin use and risk of diabetes mellitus. The authors concluded that that statins have been found to increase glycosylated haemoglobin and fasting serum glucose levels. statins can have diabetogenic risk, they have more long term benefits which can outweigh the risk. In elderly patients and those with metabolic syndrome, as the risk of diabetes increase, the statins should be used cautiously. Other than a subset of population with risk for diabetes; statins still have long term survival benefits in most of the patients.

13) **Nathan et al ( 2016)[44]** conducted a study on cardiovascular risk factor targets cardiovascular disease event risk in diabetes The study reported that optimal levels of BP,LDL -C,HbA1C occurring together in individuals with DM are uncommon but are associated with lower risk of CHD and CVD.

14) **Mansour M. et al (2016)[45]** conducted a study on coronary artery disease and diabetes mellitus. The study revealed that an important part of any preventive program for CAD should include clear prevention strategies for DM and other associated metabolic risk factors, such as obesity. Preventive measures, such as physical exercise in high-risk groups, at the population level should be encouraged.

15) **Hisao et al (2002)[46]** conducted a study on low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes. The study concluded that in this study of patients with type two diabetes, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.

16) **Derun et al (2010)[47]** conducted a study on aspirin resistance and its associate with glycemic control in type two diabetes mellitus. The study reported that diabetic patients had significantly higher aspirin resistance, compared with nondiabetic controls. A correlation analysis revealed that aspirin resistance was positively correlated with body mass index, fasting blood glucose, and HbA1c levels. Using low-dose aspirin (100 mg/d) was a risk factor for aspirin-resistant status in both diabetic patients and overall study group.

17) **Antoni et al (2007)[48]** conducted a study on use of aspirin for primary and secondary prevention of cardiovascular disease in diabetic patients in an ambulatory care. The study concluded that treatment with aspirinis underused for primary prevention in patients with diabetes mellitus in primary care.

18) **Jack et al (2017)**[49] conducted a study on primary prevention of cardiovascular disease. The study revealed that the burden of cardiovascular disease can be ameliorated by careful risk reduction and, as such, primary prevention is an important priority for all developers of health policy.

19) **S. Fateh et al (2005)** [50]conducted a study on prevalence of aspirin resistance in patients with type two diabetes. The study concluded that the major finding of the present study is that a substantial number of patients with type 2 diabetes are resistant (21.5%) or semi-resistant (16.9%) to chronic aspirin treatment. Aspirin resistance may be poorer clinical long term prognosis in a substantial subgroup of patients with type2 DM.

20) **Waanger et al (2001)**[51] performed a study on diabetes mellitus and cardiovascular disease. The study revealed that diabetes is associated with poor prognosis of cardiovascular disease and with high short term long term mortaliy.

21) **Christo et al (2001)**[52] conducted a study on differences in expression of cardiovascular risk factors among type two DM Patients of different age. The study revealed that hyperglycemia, dyslipidemia, and lowgrade inflammation are present in different age groups of T2DM patients studied and reconfirm previous observations on the role of these conditions in predisposing the development of CVD in these patients.

22) **Christina et al (2007)**[53] performed a study on type II diabetes mellitus and cardiovascular risk factors: The study reveals that that insulin resistance, the metabolic syndrome and type II DM are inextricably linked with CVD, as apparent from the increased levels of CVD morbidity and mortality and from the presence of a complex array of CVD risk markers. Targeting multiple markers of CVD risk hopefully offers the best chance of improving CVD outcomes.

# SCOPE OF STUDY

Worldwide, approximately 200 million people currently have type II diabetes mellitus (DM), a prevalence that has been predicted to increase to 366 million by 2030. Rates of cardiovascular disease (CVD) mortality and morbidity are particularly high in this population, representing a significant cost for health care systems. Type II DM patients generally carry a number of risk factors for CVD, including hyperglycemia, abnormal lipid profiles, alterations in inflammatory mediators and coagulation/thrombolytic parameters, as well as other 'nontraditional' risk factors, many of which may be closely associated with insulin resistance. Therefore, successful management of CVD associated with diabetes represents a major challenge to the clinicians.[55]

An effective way of tackling this problem is to detect the associated risk factors and to target treatment toward their improvement. Targeting hyperglycemia alone does not reduce the excess risk in diabetes, highlighting the need for aggressive treatment of other risk factors. Although the current use of statin therapy is effective at reducing low-density lipoprotein cholesterol, residual risk remains for other independent lipid and nonlipid factors. [56]

Diabetes is endemic in India. The International Diabetes Federation has estimated that India currently has more than 65 million people with type 2 diabetes and the numbers are poised to double in the next 20 years. It has been reported that the prevalence of diabetes among urban participants in India is among the highest in the world and comparable to the high prevalence countries of West Asia and the Pacific. In India it has been reported that 60–80% of patients with diabetes die of cardiovascular events.

According to the WHO, "non-communicable diseases, mainly cardiovascular diseases, cancers, chronic respiratory diseases and diabetes, are the main cause of death and disability in the world, representing 63% of deaths. 80%

of cases of premature cardiovascular diseases and stroke, 80% of type 2 diabetes and 40% of cancers could be avoided by eating healthily, doing regular physical exercise and not smoking." According to the International Diabetes Federation "it is estimated that around 285 million people throughout the world, i.e. 6.6% of people in the 20 – 79 year age group, will develop diabetes in 2010, of which 70% live in low or middle-income countries. These figures will probably increase by over 50% over the next 20 years unless prevention programmes are put into place.

.Antiplatelet therapy is a cornerstone of cardiovascular medicine. Aspirin and clopidogrel have emerged as critical therapies in the treatment of cardiovascular disease. Despite their efficacy, patients on these medications continue to suffer complications. Millions of patients are currently on low-dose antiplatelet therapy but it is unknown how many of these patients are under-treated or on the wrong medication. Aspirin and clopidogrel resistance are emerging clinical entities with potentially severe consequences such as recurrent myocardial infarction, stroke, or death. The mechanism of resistance remains incompletely defined, but there are specific clinical, cellular, and genetic factors that influence therapeutic failure. These factors range from physicians who fail to prescribe these medications despite appropriate indications to polymorphisms of platelet membrane glycoproteins. Rapid and accurate diagnosis of antiplatelet resistance also remains an issue as new bedside tests are developed. By understanding the mechanism of therapeutic failure and by improving the diagnosis of this clinical entity, a new era of individualized antiplatelet therapy may arise with routine measurements of platelet activity in the same way that cholesterol, blood pressure, and blood sugar are followed, thus improving the care for millions of people.

Inter individual variability of platelet aggregation in response to these antiplatelet agents may be an explanation for some of these recurrent events, and small trials have linked "aspirin and/or clopidogrel resistance", as measured by platelet function tests, to adverse events. Systematically reviewed all available evidence on the prevalence of aspirin/clopidogrel resistance, their possible risk factors and their association with clinical outcomes. After analyzing the data on different laboratory methods found that aspirin/clopidogrel resistance seems to be associated with poor clinical outcomes and there is currently no standardized or widely accepted definition of clopidogrel resistance. Therefore, conclude that specific treatment recommendations are not established for patients who exhibit high platelet reactivity during aspirin/clopidogrel therapy or who have poor platelet inhibition by clopidogrel.

The study will attempt to categorize each patients depending on the risk and non-risk case of CVD in type 2 DM. The AHD guidelines are followed in risk cases of CVD to understand drug utilization ,duration of treatment possibility of resistance with anticoagulant therapy.[57]

# OBJECTIVE OF THE STUDY

- To evaluate drug utilization pattern in diabetic patients
- Assess the risk factors associated with CVD in type 2 diabetic patients
- Evaluate the primary and secondary management of CVD in type 2 DM
- Assess the therapy of CVD prevention in type II DM patients.
- Evaluate the drug interaction in the prescription

# PLAN OF THE STUDY

The proposed study was planned and carried out as per the given plan and it was designed as given below.

**STUDY SITE :** Cardiology and General medicine department.
**STUDY DESIGN:** Prospective-Observational study.
**STUDY PERIOD:** 10 months (November2016- August2017)

**PHASE I**

- Selection of study site and department.
- Literature survey
- Preparation of Protocol
- Obtaining consent from the hospital authorities.

**PHASE II**

- Designing of structured data entry format.
- Data collection using data entry format
- Evaluation of collected data of the patients
- Categorization of patients
- Assessment of CVD risk by Framingham Risk Score
- Evaluation of drug utilization pattern
- Assessment of CVD therapy
- Evaluate drug interaction in the prescription.

**PHASE III**

- Interpretation and data analysis.
- Preparation of the project report and submission to the study department.

# METHODOLOGY

## STUDY SITE:

The proposed work entitled **"Study on cardiovascular risk factors and its management in type II DM patients"** was carried out in a 750 bedded multi-speaciality hospital located at Coimbatore. The hospital is unique and it is well known for its services to people who come from various parts of country. The institution excels in diverse specialities like General Medicine, General Surgery, Obestrics and Gynecology, Peadiatrics and Neonatalogy, Orthopeadics, Psychiatry, Neurology, Radiology, Cardiology, Cardiothoracic surgery, Pulmunology and Critical care, Gastroenterology, Urology, Nephrology, E.N.T, Opthomology, Oncology, Dentistry, Plastic surgery and department of physical rehabilitation. The hospital has well-staffed Pharmacy and Drug Information Centre.

The hospital is well equipped with modern diagnostic facilities like CT scan, MRI scan, US, digital subtraction angiography, ECG, treadmill, color Doppler etc. The hospital also have twelve well equipped Hi-tech operation thetres, Intensive Care Units, Intensive Cardiac Units, Intensive Pulmunory Care unit, Neonatal Intensive Care unit, Catheterization laboratory performing diagnostic cardiac catheterization, balloon valvuloplasty, coronary stening, kidney transplantation unit with hemodialysis machines, assisted reproductive technology centre, 24hours microbiological and pathological services, round the clock casuality and pharmacy services etc.

## DEPARTMENT SELECTED FOR THE STUDY IN THE HOSPITAL:

The department selected for the study is General Medicine and Cardiology. The reason for the selection of these departments were the prevalence of variety of cases. The Department of Pharmacy Practice provides services to these departments and a good co-operation from medical team added up to the reason for selecting these departments for conducting the study.

**CONSENT FROM HOSPITAL AUTHORITIES:**

Every project work carried out in the hospital by the Pharmacy Practice department students has to be approved by the Dean of the hospital and should be informed to all the physicians and other healthcare professionals of the hospital. A protocol of the study which includes the objectives, methodology etc was submitted to the Dean of the hospital. The authorization from the Dean was procured through his letter **[SRH/EC.9-7/2017-18 dated 25th FEBRUARY 2017]** and the same is attached for the reference in the **[Annexure I]**. The study was conducted with the expert guidance of junior and senior physicians of the study departments. The authority was permitted to utilize the hospital facilities to make a follow up of the cases, in the selected departments. All the health care professionals were well informed through Dean's official circular.

**LITERATURE SURVEY:**

Extensive literature survey was being performed regarding the rationality of fixed dose combinations. The necessary information are collected and well documented. The literatures supporting the study were gathered from various sources such as:

- American Journal of Cardiology
- International Journal of Research in Pharmacology and Pharmacotherapeutics
- New England Journal of Medicines
- European Journal of Clinical Pharmacology
- Indian Journal of Hospital Pharmacy and some of the websites including www.medscape.com, www.pubmed.com and databases such as Micromedex.

**DATA ENTRY FORM:**

A separate data entry form were designed and the format contains the details such as name, age, sex, height, weight, IP. No, date of admission, date of discharge, reason for admission, past medical history, past medication history and social history. Provision was given in the format for entry of details like blood sugar levels, liver function test, renal function test, electrolytes, urine examination, lipid profile, diagnosis, drug chart, risk factors, 10 year cardiovascular risk calculation, ADR monitoring chart, Drug interaction chart and any interventions**.(Annexure-2)**

**DATA COLLECTION:**

**Ward Round Participation**

A regular ward round was carried out. Each patient's demographics were recorded including date, age, weight, date of admission and discharge, past medical and medication histories were also obtained.

**PATIENT SELECTION:**

**Inclusion criteria:**

- Patients above age of 18 years either the sex ,who have been diagnosed to have diabetes with or without CVD.
- Patients who are willing to participate in the study.

**Exclusion criteria:**

- Patients below age of 18 years, pregnant women, critically ill and patients not willing to participate excluded from the study

**PATIENT INFORMATION FORM**

A patient information form was prepared to inform the patient or the care givers about the purpose and necessity of the study.The patients were assured that the confidentiality will strictly maintained. The model of information form is given in( **Annexure 3)** for reference.

**PATIENT CONSENT FORM**

A patient consent form has been prepared and written consent was obtained from the patient or from the care givers. The format contains details like address, date, place, provision for signature of the patient or caregivers, investigator and supervisor. The same is given in the **[Annexure 4]** for reference.

**DATA ANALYSIS**

The data from the cases were evaluated. The study population were categorized into CVD and non CVD category. Assessment of cardiovascular risk was calculated for non CVD patients using Framingham risk score. Evaluvation of CVD preventive therapy has been carried out.

**REPORT SUBMISSION**

The report on the study results were prepared and the same was submitted to the study department for necessary action on future therapy for a safe and effective treatment.

# RESULTS AND DISCUSSION

The proposed work entitled "**Study on Cardiovascular Risk Factors and its Management in Type II DM patients**" was a carried out in a 750 bedded multispecialty hospital, in the department of General medicine and Cardiology. The study was carried out during November 2016 to October2017.

A total of 103 patients were included in the study based on the inclusion and exclusion criteria, among them 64 (62%) were males and 39 (37.86%) were females. **[Table No- 1].**The age categorization was done in which, it was found that 7 (3.8%) belonged to the age group of 30-40 followed by 9 (8.73) in the age group of 40-50 , 28 (27.1%) in the age group of 50-60, and 59 (57.2%) of them were >60 years. **[Table No-2 ]**

## ASSESSMENT OF PREVALENCE OF CARDIOVASCULAR DISEASES

Among the study population 73(70.87%) patients were found to be suffering from CVD and 30 (29.1%) were non CVD patients. **[Table No- 3].**The various types of CVD suffered by patients were analyzed , it was found that majority of them were diagnosed with IHD 30 (42%), followed by CAD 24 (32.8%), Stroke 6 (8.21%) and CCF 7 (9.58%), and ACS 6(5.82%), **. [Table No-4].**This result reveals that IHD and CAD are the most common CVDs among study population in Type II DM patients. A similar study conducted Anurag S Lekar et al (2013) revealed that IHD is the major disease suffered by their study population.

## CATEGORIZATION OF DRUG PRESCRIBED FOR DM

The study population was prescribed with various classes of anti-diabetic medications. The drug utilization pattern reveals that majority of the study population has received insulin therapy for 56 (54.36%)patients followed by

thiazolidinediones 15.5 (14.56%), sulfonyl ureas 14 (13.59%) and biguanides 7 (6.79%). **(Table No- 5)**

**DRUGS PRESCRIBED FOR CVD PATIENTS**

The CVD agents utilized by the study population was analyzed which has been classified into 11 categories. A total of 315 drugs were prescribed. Among which, the most frequently prescribed drug class was anticoagulants 132 (41.90%), followed by dyslipidemic agents 56 (17.77%), antianginals 31 (9.84%), diuretics 30 (9.52%), beta adrenergic blockers 16 (5.07%), cardiotonic agents 14 (4.44%), calcium channel blockers 10 (3.17%), angiotensin antagonists 8 (2.53%), antiarrhythmics 7 (2.22%) and alpha + beta adrenergic blockers 6 (1.90%)**. (Table No -6 )**.A similar study conducted by Ittaman SV et al (2014) reported that anticoagulant therapy is well-accepted as an agent for the prevention of cardiovascular events.

**RISK FACTORS ASSOCIATED WITH NON CVD PATIENTS**

Risk factors were categorized for non CVD patients and the results revealed that DM and gender were the major risk factors. This was followed by age, hypertension & cholesterol for 27(90%) patients, 21(70%) & 21(70%) respectively. Other risk factors found in the study population were family history, obesity for 18 (60%) and 9 (30%) patients respectively. **(Table No -7).** A study conducted by Maguy Chiha (2012) revealed that Diabetes mellitus is associated with an increased risk of cardiovascular death and a higher incidence of CVD.

**FRAMINGHAM RISK SCORE:**

The Framingham risk score is a scale used to assess the 10 year future CVD risk percentage for the non-CVD patients. The patients belonging to non-CVD group were assessed using Framingham risk scale to determine the cardiovascular risk percentage. The results revealed that 19 (63.33%) patients have >20% future CVD risk followed by ,8 (26.66%) patients with 10-20% of future CVD risk and about 3 (10%) patients with <10% of future CVD risk**. [Table No: 8].**

**PATIENTS ON PRIMARY AND SECONDARY PREVENTION OF CVD**

Among the study population, 30 (29.1%) patients were provided with primary CVD prevention and 73 (70.87%) patients received secondary CVD prevention therapy. **(Table No-9).** Aspirin and clopidogrel were the drugs prescribed for primary prevention for about 20 patients (66%) and 10 patients (33%) respectively.(**Table No- 10)** Drugs given for secondary prevention includes atorvastatin for 57 (78.08%) patients , followed by clopidogrel for 54 (73.97%), aspirin for 40 (54.79%), atenolol for 16 (21.97%), isosorbide mononitrate for 15 (20.54%) and enalapril for 5 (6.84**%**) patients**. (Table No- 11).**

**EVALUATION OF DRUGS INCREASING CVD RISK**

Certain non CVD drugs on prolonged use can increase risk of cardiovascular disease. The non CVD drugs prescribed for the study population which possess cardiovascular risk was identified .The result revealed that 11 (10.61%)patients were prescribed with diclofenac 5(4.85%) patients were prescribed with glimepride and1(0.970%) patient on terbutaline are at increased risk of CVD.**(Table No-12)** A similar study conducted by Schellack N, B (2014) reported that NSAIDS, sulfonylureas and terbutaline carry the risk of serious cardiovascular adverse effects **.**

**DRUG INTERACTION**

In the present study around 168 drug –drug interaction were identified among which 4 (2.38%) prescription were major interaction 36(26.4%) were moderate interaction 128 (76.19%) were on minor interactions**.(Table No-13)** The moderate drug interaction involving clopidogrel and pantoprazole was found to be maximal in current study.(**Table No- 14)**

Diabetes mellitus is associated with an increased risk of cardiovascular death and a higher incidence of CVD. Though aspirin and clopidogrel had proven benefits in cardiovascular events, their prolonged use can develop resistance in patients. Significant number of type 2 diabetic patients are resistant to aspirin therapy. Therefore aspirin resistance should be evaluated by point of care testing and should be recognized in diabetic patients who are treated for primary and secondary prevention. Efficient and affordable laboratory tests (bleeding time, optical aggregometry, platelet aggregation ratio) with standard techniques should be used to correlate the results with clinical outcomes.

**TABLE NO:1 GENDER CATEGORIZATION**

| Sex | No of patients( n=103) | Percentage (%) |
|---|---|---|
| Male | 64 | 62.2 |
| Female | 39 | 37.8 |

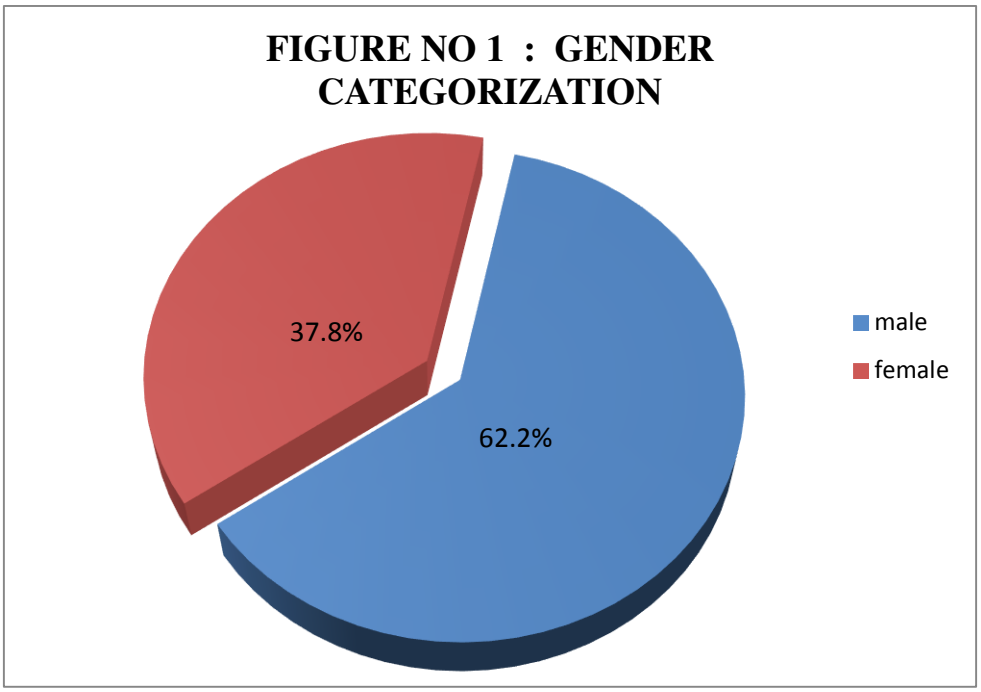

**TABLE-2 AGE DISTRIBUTION**

| Age in years | No of patients (n=103 ) | Percentage(%) |
|---|---|---|
| 30-40 | 7 | 3.8 |
| 40-50 | 9 | 8.7 |
| 50-60 | 28 | 27.1 |
| Above60 | 59 | 57.4 |

**FIGURE NO:2 AGE DISTRIBUTION**

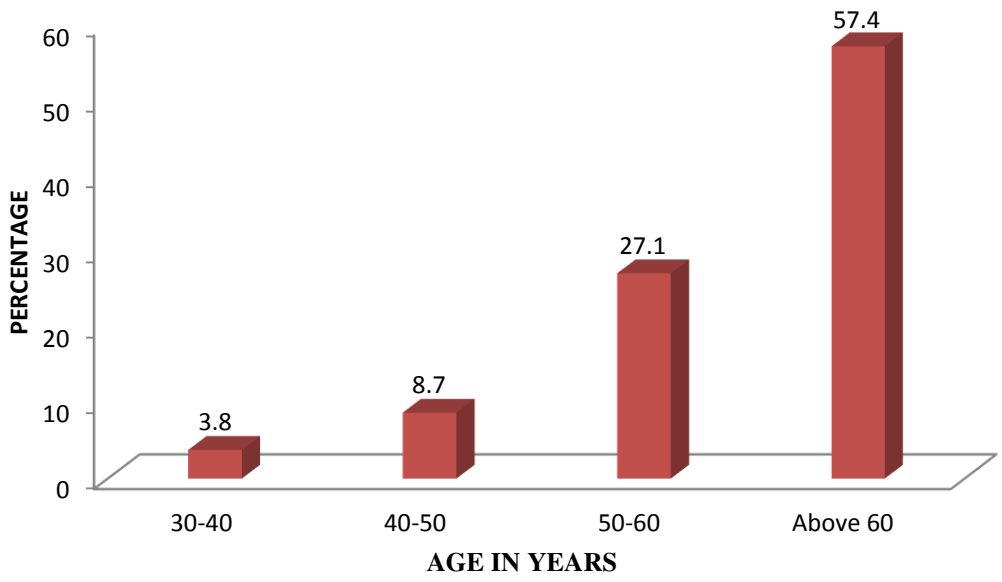

**TABLE- 3 ASSESSMENT OF PREVALAENCE OF CVD**

| Prevalence | No of patients (n=103) | Percentage (%) |
|---|---|---|
| CVD patients | 73 | 70.8 |
| Non CVD patients | 30 | 29.2 |

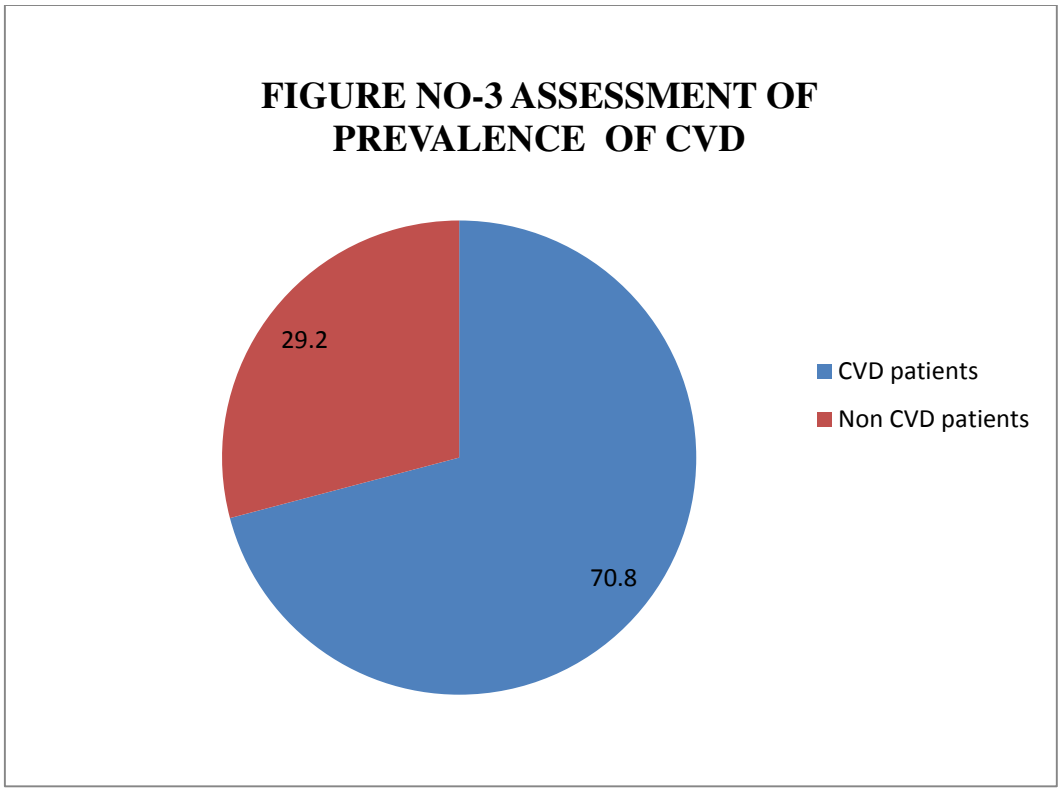

**TABLE 4 CATEGORIZATION OF CVD PATIENTS**

| Types of CVD | No of patients (n=73) | Percentage( %) |
|---|---|---|
| CCF | 7 | 9.5 |
| STROKE | 6 | 8.5 |
| CAD | 24 | 32.8 |
| ACS | 6 | 8.2 |
| IHD | 30 | 42.0 |

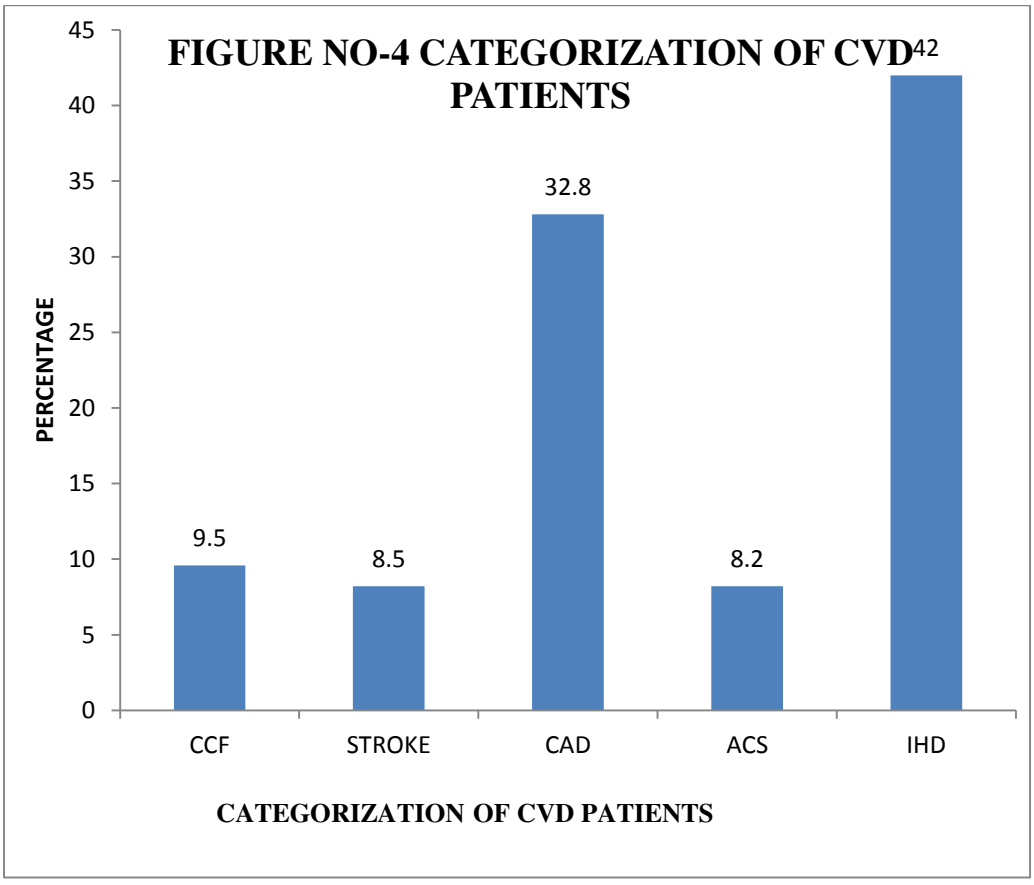


**FIGURE NO-4 CATEGORIZATION OF CVD[42] PATIENTS**

**TABLE-5 CATEGORIZATION OF DRUG PRESCRIBED FOR DM**

| Antidiabetic Drugs | No of patients (n=103) | Percentage(%) |
|---|---|---|
| Insulin Therapy | 56 | 54.3 |
| Bigunides | 7 | 6.8 |
| Thiazolidinediones | 15 | 14.5 |
| Sulfonyl Urea | 14 | 13.5 |
| Combination drugs | 11 | 10.6 |

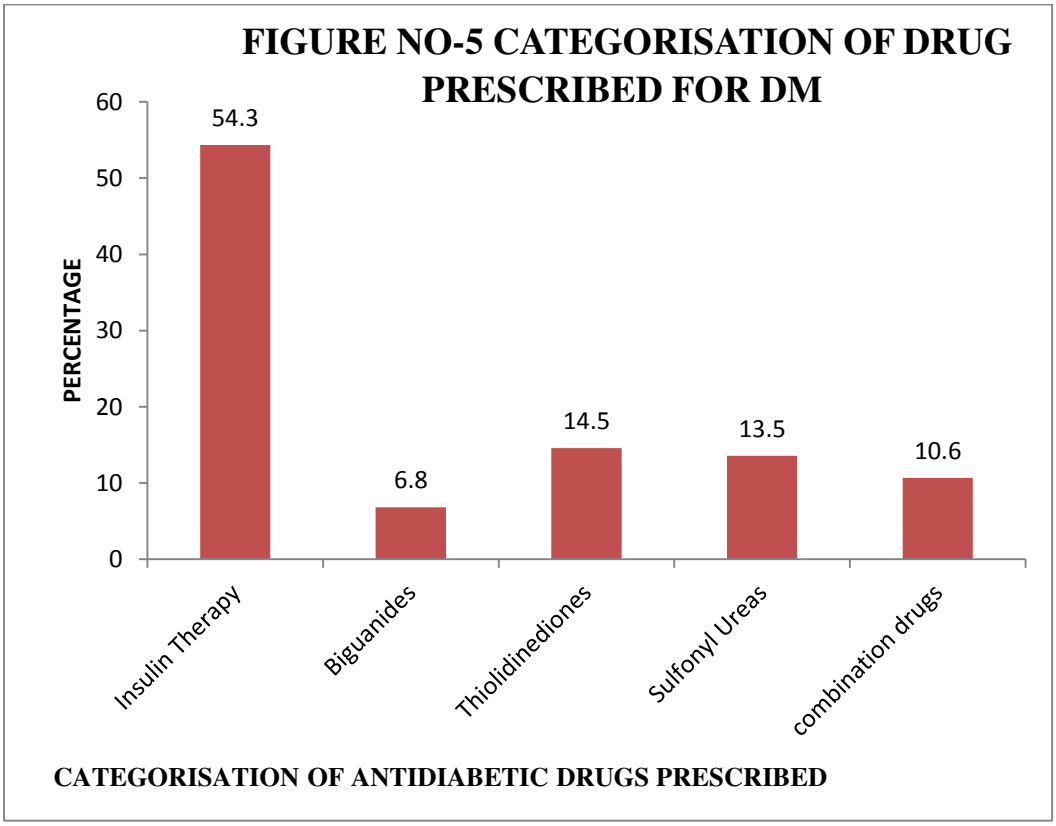


**TABLE-6 DRUGS PRESCRIBED FOR CVD PATIENTS**

| Drugs for CVD | No prescriptions | Percentage( %) |
|---|---|---|

| | (n=315) | |
|---|---|---|
| Anticoagulants | 132 | 41.9 |
| Dyslipidemic agents | 56 | 17.7 |
| Calcium channel blockers | 10 | 3.1 |
| Beta adrenergic blockers | 16 | 5.0 |
| Alpha+ beta adrenergic blockers | 6 | 1.9 |
| ACE inhibitors | 5 | 1.5 |
| Angiotensinogen antagonist | 8 | 2.5 |
| Antianginal drugs | 31 | 9.8 |
| Antiarrthmic drugs | 7 | 2.2 |
| Cardiotonic agents | 14 | 4.4 |
| Diuretics | 30 | 9.5 |

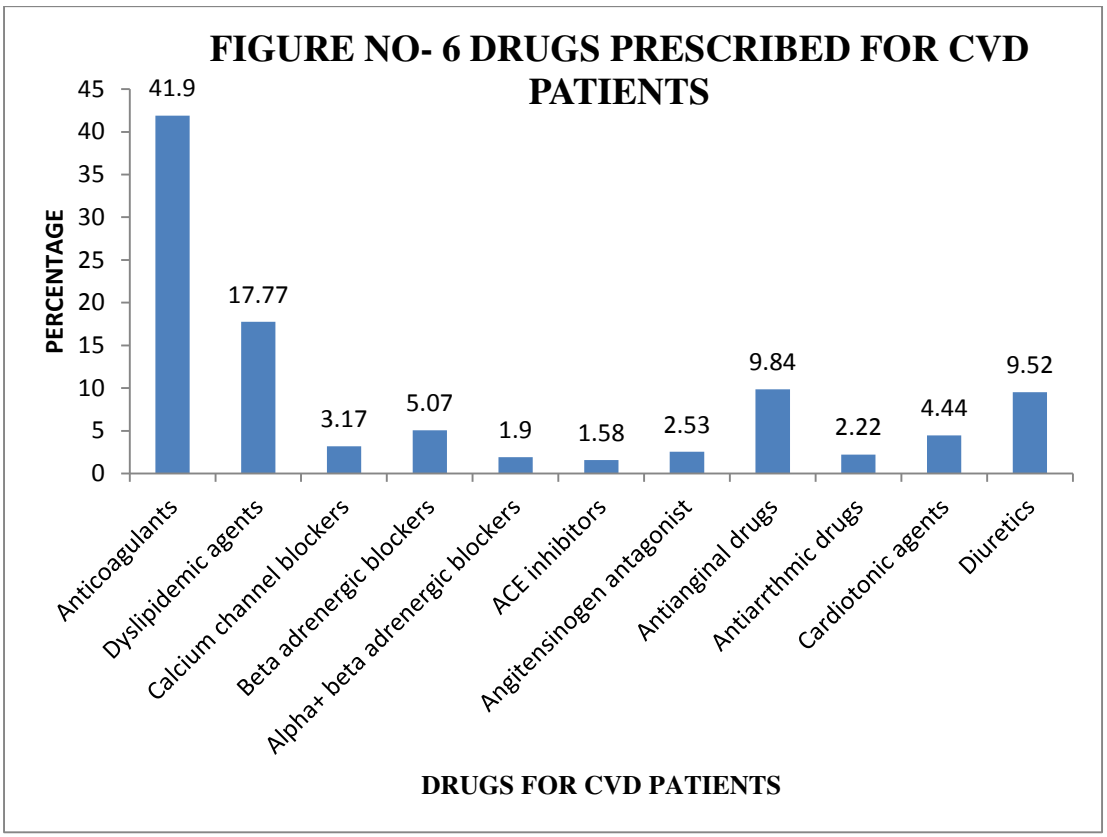


**TABLE- 7 RISK FACTORS ASSOCIATED WITH NON CVD PATIENTS**

| Risk factors | No of patients (n=30) | Percentage (%) |
|---|---|---|
| Age | 27 | 90 |
| Sex | 30 | 100 |
| DM | 30 | 100 |
| Obesity | 9 | 30 |
| Hypertension | 21 | 70 |
| Physical inactivity | 17 | 56.6 |
| Family history | 18 | 60 |
| Smoker | 9 | 30 |
| High blood cholesterol levels | 21 | 70 |

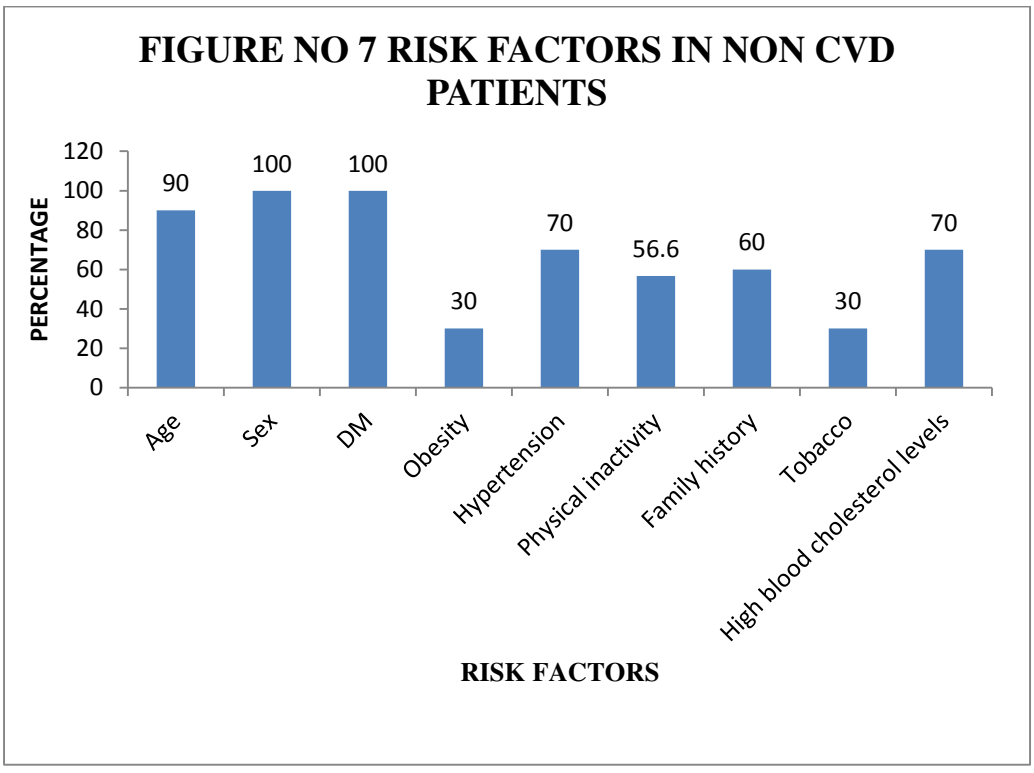


**TABLE-8 FRAMINGHAM RISK SCORE**

| Risk percentage (For Future 10 Year) | No of patients( n=30) | Percentage(%) |
|---|---|---|
| >20 | 19 | 63.3 |
| 10-20 | 8 | 26.6 |
| <10 | 3 | 10.1 |

**FIGURE NO 8 FRAMINGHAM RISK SCORE**

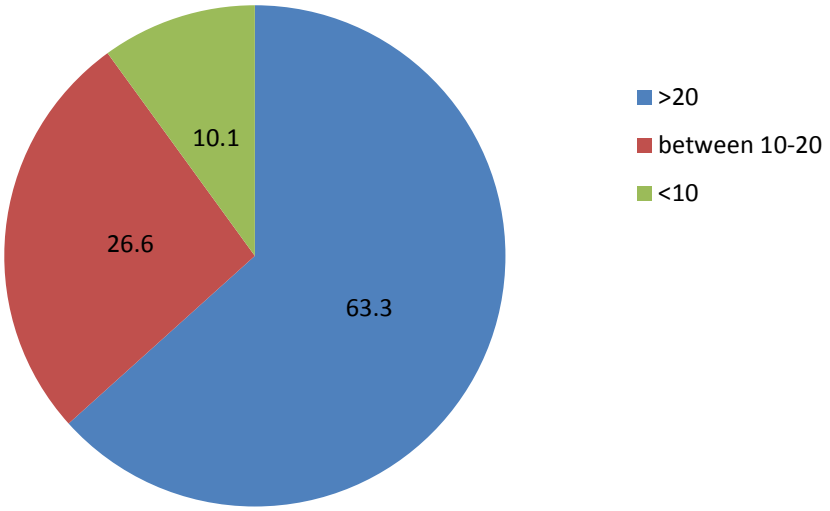


**TABLE-9 PATIENTS ON PRIMARY AND SECONDARY PREVENTION OF CVD**

| | No of patients (103) | Percentage(%) |
|---|---|---|

| | | |
|---|---|---|
| Primary prevention | 30 | 29.2 |
| Secondary prevention | 73 | 70.8 |

**FIGURE NO -9 PATIENTS ON PRIMARY AND SECONDORY PREVENTION**

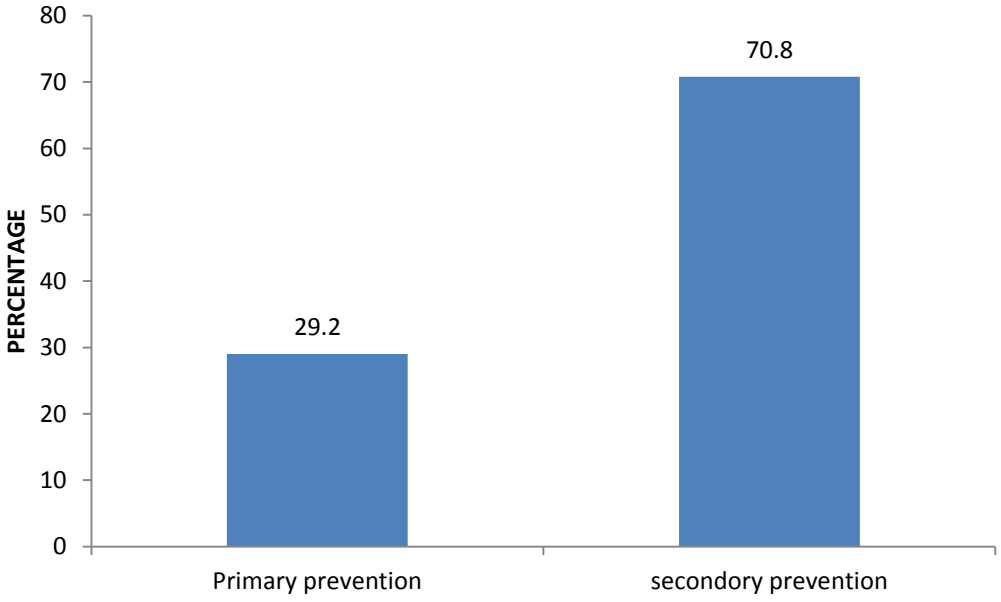


**TABLE 10 DRUGS PRESCRIBED FOR PRIMARY PREVENTION**

| Drugs for primary prevention (n=30) | No of patients | Percentage (%) |
|---|---|---|

| | | |
|---|---|---|
| Aspirin | 20 | 66.6 |
| Clopidogrel | 10 | 33.4 |

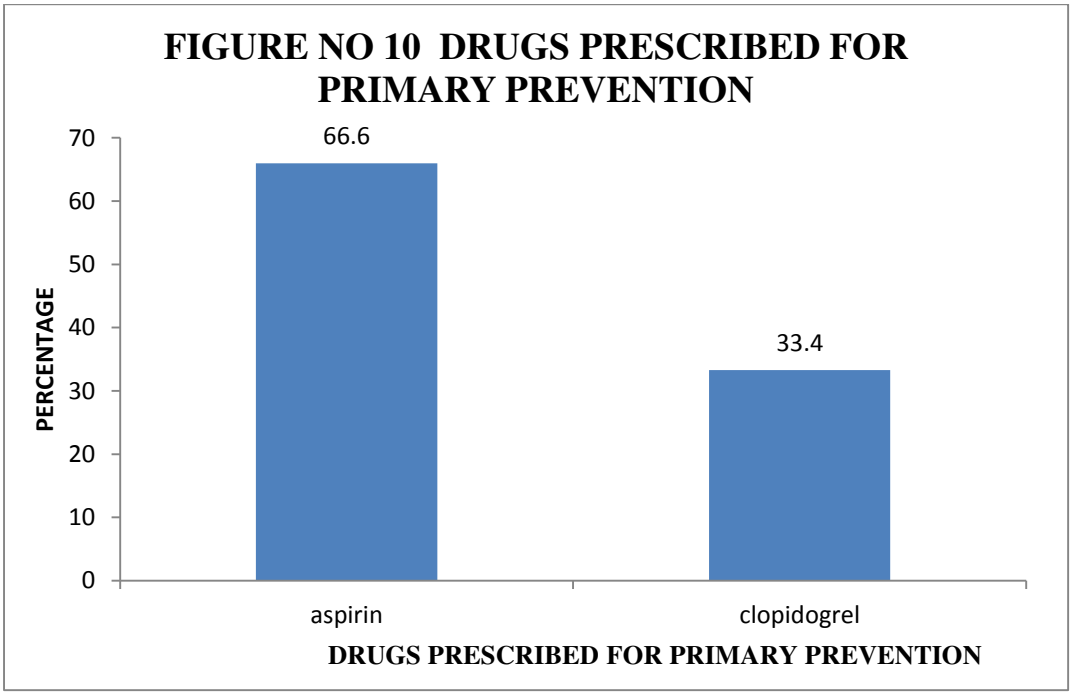


**TABLE NO 11 DRUGS PRESCRIBED FOR SECONDARY PREVENTION**

| Drugs for secondary prevention ( n=73) | No patients | Percentage(%) |
|---|---|---|
| Aspirin | 40 | 54.7 |

| | | |
|---|---|---|
| Atenolol | 16 | 21.9 |
| Atorvastatins | 57 | 78 |
| Enapril | 5 | 6.8 |
| Clopidogrel | 54 | 73.9 |
| Isosorbidate mononitrate | 15 | 20.5 |

**FIGURE NO 11 DRUGS PRESCRIBED FOR SECONDORY PREVENTION**

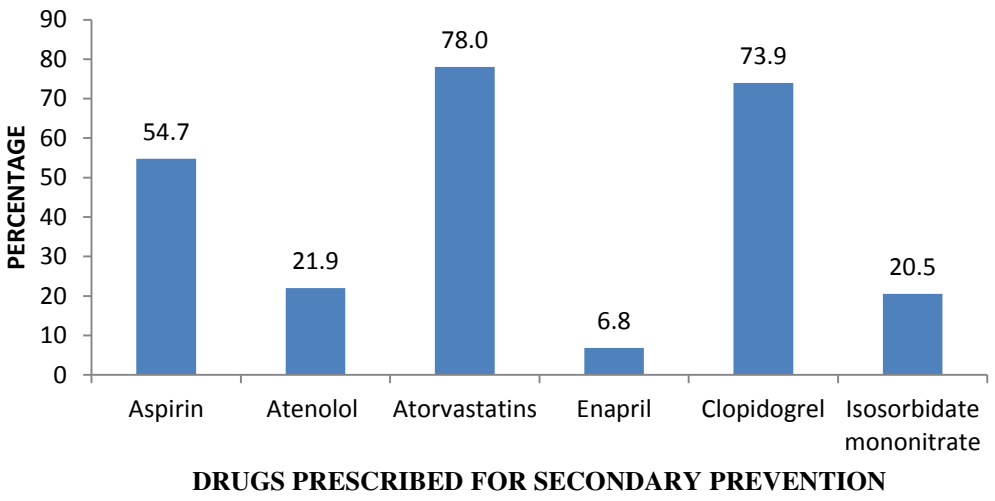


**TABLE 12 - EVALUATION OF DRUGS INCREASING CVD RISK**

| Drugs | No of prescription (n=103) | Percentage (%) |
|---|---|---|
| Diclofenac | 11 | 10.6 |

| | | |
|---|---|---|
| Glimepride | 5 | 4.8 |
| Terbutaline | 1 | 0.97 |

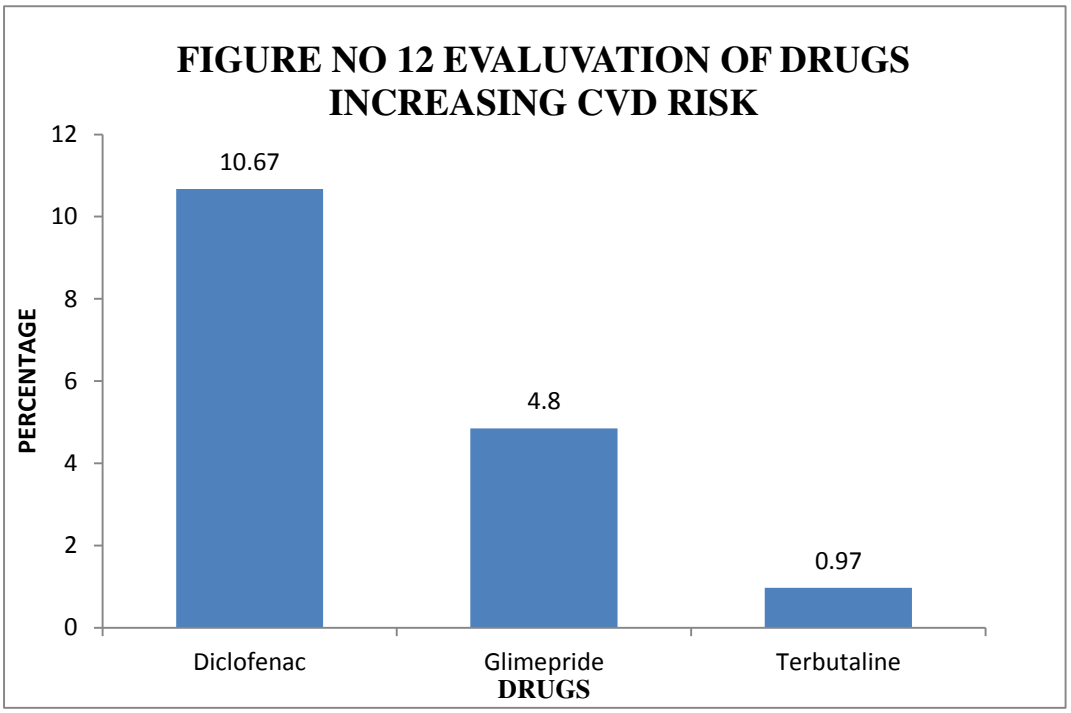


**TABLE-13 DRUG INTERACTIONS**

| Drug interaction | No of prescription (n=168) | Percentage (%) |
|---|---|---|
| Major | 4 | 2.3 |
| Moderate | 36 | 21.4 |

| | | |
|---|---|---|
| minor | 128 | 76.3 |

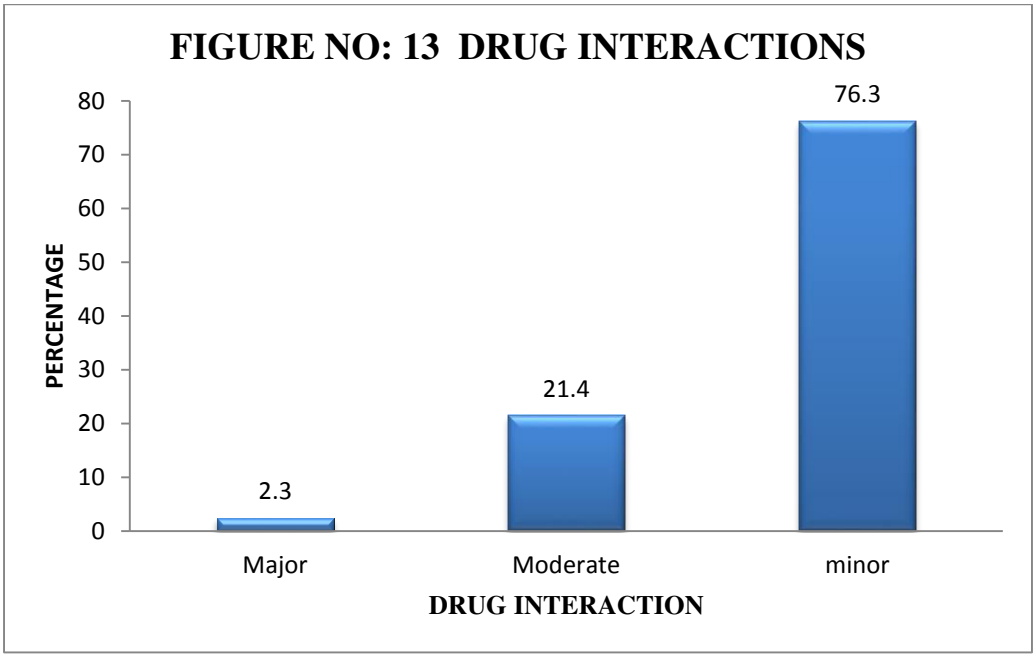


**TABLE 14 DRUG INTERACTIONS**

| Drugs | Effects | No prescriptions (n=168) | Severity |
|---|---|---|---|

| Drugs | Effects | No prescriptions (n=168) | Severity |
|---|---|---|---|
| Clopidogrel+Pantoprazole | Pantoprazole reducing effect of clopidogrel in preventing heart attack and stroke. | 39 | Moderate |
| Clopidogrel+heparin | Both increase anticoagulations | 21 | Minor |
| Aspirin +clopidogrel | Increase toxicity | 21 | Moderate |
| Clopidogrel+torsemide | Clopidogrel increase effect of torsemide | 4 | Minor |
| Heparin+acetaminophen | May increase effect of heparin | 6 | Minor |
| Heparin+aspirin | May increase anticoagulation | 29 | Moderate |
| Heparin+ramipril | May increase levels of potassium in the body | 1 | Moderate |
| Aspirin +metoprolol | May increase levals of potassium in the body | 4 | Minor |
| Aspirin+telmisartan | May increase serum potassium levels. | 3 | Moderate |
| Aspirin+ketorlac | Either increase toxicity of other | 1 | Major |
| Aspirin +glimipride | Aspirin increase effect of glimepride | 1 | Moderate |
| Aspirin +nebivilol | Both increase serum potassium levels | 3 | Moderate |
| Aspirin+carvedilol | Aspirin decrease effect of carvedilol | 4 | Moderate |
| Aspirin+sotalol | Both increase serum potassium levels | 2 | Moderate |

| Drugs | Effects | No prescriptions (n=168) | Severity |
|---|---|---|---|
| Aspirin+torsemide | Aspirin increase and torsemide decrease serum potassium levels | 2 | Moderate |
| Aspirin+spirolactone | Both increase serum potassium levels | 5 | Moderate |
| Aspirin+torsemide | Aspirin increase and torsemide decrease serum potassium levels | 2 | Moderate |
| Telmisartan +metoprolol | Both increase serum potassium levels | 5 | Moderate |
| Telmisartan+atorvastatins | Telmisartan increase toxicity of atorvastatins | 1 | Moderate |
| Telmisartan+torsemide | Telmisartan increase torsemide decrease serum potassium level | 2 | Moderate |
| Atorvastains+azithromycin | Atorvastatins will increase level or effect of azithromycine | 1 | Moderate |
| Clonidine+metoprolol | Increase toxicity of one another | 1 | Moderate |
| Clonidine+insulin | Clonidine decrease effect of insulin | 1 | Minor |
| Azithromycin+sotalol | Both may increase QT intervel | 1 | Moderate |
| Azithromycin+ondansetrol | Both increase QT intervels | 3 | Major |
| Calcium accete+amlodipine | Calcium acetate decrease effect of amlodipine | 1 | Moderate |
| Ramipril+spirolactone | May be risk of hyperkalemia | 4 | Moderate |

| Drugs | Effects | No prescriptions (n=168) | Severity |
|---|---|---|---|
| Ranolazine+metoprolol | Ranolazine increase levels of metoprolol | 2 | Moderate |
| Atorvastatins+spirolactone | Spirolactone will increase levels of atorvastains | 5 | Moderate |
| Atorvastatins+prednisolone | Prednislone will decrese levels of atorvastatins | 2 | Moderate |
| Metformin+insulin | May increase risk of hypoglycemia | 1 | Moderate |
| Budesonide+insulin | Budesonide decrease effect of insulin | 2 | Moderate |
| Budesonide+atorvastatins | Atorvastatins increase effect of budesonide | 2 | Moderate |
| Budesonide+pantoprazole | Pantoprazole decrease effect budesonide by increase gastric pH levels | 1 | Moderate |
| Budesonide+heparin | May chance of decrease anticoagulant effect | 2 | Moderate |
| Budesonide+clopidogrel | Budesonide will increase effect of clopidogrel | 3 | Moderate |

# CONCLUSION

Current study results reveals patient with Type II Diabetes are either having one of the CVD or they are at high risk of developing CVD in future. Therefore, CVD prevention in such patients is mandatory. The CVD prevention therapy is long term management that may even continue for life time depending on the patient condition. Aspirin and Clopidogrel are the most widely used drugs in CVD prevention. Aspirin and Clopidogrel are having high chance of forming resistance in Type 2 Diabetic patients. Hence the use of aspirin and clopidogrel necessitates monitoring the effectiveness of these drugs CVD prevention. Clinical pharmacist has a great responsibility in such monitoring and preventing such resistance that occurs with the use of aspirin and clopidogrel. The results also implicates there is a high prevalence rate of CVD in Type 2 diabetic patients. The incidence of CVD would have reduced if proper patient education and management are implemented. It is essential to follow guidelines such as ADA and AHA continuous monitoring by Clinical Pharmacist for reducing rate of CVD in Type 2 Diabetic patients. Hence the study concluded that implementation of pharmaceutical care activities in Type 2 diabetic patients will ensure safe and efficient CVD prevention therapy.

# FUTURE OUTLOOK

The diabetic patients are increasing globally and the management of diabetes has significantly improved. Being chronic disorder diabetes has many complications which makes prevention and management of these complications highly challenging. The most typical complication of diabetes is occurrence of CVD. The numbers of CVD patients among type2-diabetics are drastically increasing, due to complicated task of CVD prevention. The guidelines for CVD prevention in Diabetics must be regularly updated. Currently there are no Indian guidelines on CVD prevention and management of type 2 diabetic patients, hence there is a need for developing guidelines for Indian population for an effective CVD prevention and management in Type 2 Diabetes. Resistance formation by the long term use of aspirin and clopidogrel warrants the need for continuous monitoring these drugs for their safety and efficacy. Hence future studies can focus on identifying the causes and prevention of resistance for aspirin and clopidogrel. The monitoring parameters and guidelines for aspirin and clopidogrel use in diabetics can be developed, which will be beneficial for an effective CVD prevention in patients with diabetics.

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# Sri Ramakrishna Hospital

Medical Service : M/s. S.N.R. SONS CHARITABLE TRUST

## SRI RAMAKRISHNA HOSPITAL ETHICAL COMMITTEE

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Ethics Committee Registration No. ECR/690/Inst/TN/2014


SRH/EC.9 – 7/2017-18

25th February 2017

## ETHICAL CLEARANCE CERTIFICATE

**Project title:** "Study on Cardiovascular risk factors and its appropriate management in Type 2 Diabetes Mellitus patients".

**Researcher: MS.ANJU LIZA THOMAS**
M.Pharmacy II year,
Department of Pharmacy Practice,
College of Pharmacy,
Sri Ramakrishna Institute of Paramedical Sciences,
Coimbatore – 641 044

The following members of the ethics committee were present at the meeting held on 18.02.2017 at 11am at New Auditorium, Sri Ramakrishna Hospital Campus, Coimbatore.

| Sl NO | Members Name | Qualification | Designation | Address | Affiliation To the Institution Yes/NO |
|---|---|---|---|---|---|
| 1. | Dr.P.Murali | M.Sc.,Ph.D., D.Sc | Scientist Mg. Director & CEO | Mg.Director & CEO Evolve Biotech Pvt.Ltd., 401 – 405, 4th floor Ticel Bio park Ltd, Taramani, Chennai - 13 | No |
| 2. | Dr.P.Sukumaran | MS., M.Ch., FIACS | Scientific / EC Member Secretary Dean | Dean Sri Ramakrishna Hospital, 395, Sarojini Naidu Road, Sidhapudur, Coimbatore | Yes |
| 3. | Dr.T.Mohan Kumar | MD.,D.Sc., AB.,DPPR., FCCP., | Clinician | Sr.Consultant Pulmonologist Sri Ramakrishna Hospital, 395, Sarojini naidu Road, Sidhapudur, Coimbatore. | Yes |
| 4. | Dr.R.Lalitha | DGO.,(OG) | Clinician | Sr.Consultant Gynecologist & HOD Sri Ramakrishna Hospital, 395, Sarojini naidu Road, Sidhapudur, Coimbatore. | Yes |

# Sri Ramakrishna Hospital

Medical Service : M/s. S.N.R. SONS CHARITABLE TRUST

## SRI RAMAKRISHNA HOSPITAL ETHICAL COMMITTEE

395, SAROJINI NAIDU ROAD, SIDHAPUDUR, COIMBATORE - 641 044.
Phone : 0422 - 4500000, 4500201, Grams :"RAMHOSP" Fax : 0422-2240521
E-mail : dean@snrsonstrust.org, website : sriramakrishnahospital.com


Ethics Committee Registration No. ECR/690/Inst/TN/2014



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| 5. | Dr.T.K.Ravi | M.Pharm Ph.D | Scientific Member | Principal Sri Ramakrishna College of pharmacy 395, Sarojini naidu Road, Sidhapudur, Coimbatore. | Yes |
| 6. | Dr.N.Paramasivan | MBBS.,MD | Basic Medical Scientist | Prof.of pharmacology and HOD Sri Ramakrishna Dental College and Hospital, Coimbatore. | Yes |
| 7. | Dr.M.Rangasamy | B.E., M.Sc., Ph.D., | Lay Person | Former Professor Government College of Technology, Coimbatore. | No |
| 8. | Mrs.Mythili Padmanabhan | M.Sc., (Physiology) | Social Scientist | Corresponded Vriksha 5/14, 2nd street, G.G.Avenue Coimbatore | No |

This is to certify that the research work entitled "Study on Cardiovascular risk factors and its appropriate management in Type 2 Diabetes Mellitus patients", placed before the Institutional Ethical Committee has been approved as there is no objection to do this research work.

This ethics committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report.

The Ethics Committee wishes her well in her research.

Yours Truly,

Member Secretary,

Institutional Human Ethics Committee,

Dr. P. SUKUMARAN, M.S.,M.Ch.,FIACS.
Dean
SRI RAMAKRISHNA HOSPITAL.
395, Sarojini Naidu Road,
Sidhapudur, Coimbatore-641 044