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A PROSPECTIVE COMPARISON STUDY ON BEMPEDOIC ACID, EZETIMIBE, AND STATINS AS SECONDARY PREVENTION TO CORONARY ARTERY DISEASE

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ABSTRACT

Background: This study is to comprehend the association between LDL cholesterol levels and the drug-of-choice prescribing trends for bempedoic acid, ezetimibe, and statins in CAD patients. The other objectives include categorizing the patients with CAD based on demographics, comorbidities, and BMI, to analyze other parameters - total cholesterol, triglycerides, HDL, and VLDL cholesterol levels in lipid profile test. **Methods:** A prospective and comparative study was held with a total sample size of 200 cases. These two hundred cases were collected from KIMS Sunshine Hospital, Secunderabad in 6 months. The patients who were diagnosed with CAD and prescribed any of the following drugs: statins, ezetimibe, and bempedoic acid were eligible for the study. **Results:** Males are more affected than females, and the maximum number of individuals belong to the age group of 51 – 60 years. A lion's portion of the study sample (69.5%) had abnormal HDL values. In LDL cholesterol levels, the percentage of statins alone and other drugs/combinations (which include Ezetimibe (alone), Bempedoic acid (alone), Statin + Ezetimibe combination, Statin + Bempedoic acid combination, Bempedoic acid + Ezetimibe combination, and Statin + Ezetimibe + Bempedoic acid combination) is 80.5% and 19.5% respectively in optimal levels (<100 mg/dl). The percentage of statins alone and other

drugs/combinations is 82.6% and 17.4% respectively in above optimal levels (100-129 mg/dl). The percentage of statins alone and other drugs/combinations is 60% and 40% respectively at borderline high levels(130-159 mg/dl). The percentage of statins alone and other drugs/combinations is 37.5% and 62.5% respectively in high levels (160-189 mg/dl), The percentage of statins alone and other drugs/combinations is 33.33% and 66.67% respectively in very high levels (>190 mg/dl). **Conclusion:** Coronary artery disease (CAD) patients are prescribed Statins, Ezetimibe, and Bempedoic acid, and their combinations as secondary prevention. This study attests that with the increase in LDL-C levels, the count of prescriptions with statins alone is decreasing, and the count of prescriptions of other drugs/combinations (which include Ezetimibe (alone), Bempedoic acid (alone), Statin + Ezetimibe combination, Statin + Bempedoic acid combination, Bempedoic acid + Ezetimibe combination, and Statin + Ezetimibe + Bempedoic acid combination) is increasing.

KEYWORDS: Coronary Artery Disease, Bempedoic acid, Ezetimibe, Statins.

INTRODUCTION

CORONARY ARTERY DISEASE (CAD)

Coronary Artery Disease (CAD) commonly called CHD, is a condition involving insufficient blood supply to the myocardium occurring because of occlusion of the lumen of coronary arteries with atherosclerotic plaque. It is a lead reason of death in the US and globally.[1] Asian Indians have a 20-50% greater mortality from CAD than any other population.[2]

CAD is caused by atherosclerosis which is exacerbated by risk variables like HTN, DM, hyperlipidemia, smoking, etc. It may present as ACS, which includes unstable angina and non-ST-segment elevation (NSTE) or ST-segment elevation (STE) myocardial infarction (MI), ischemia without symptoms, chronic stable exertional angina, microvascular angina, ischemia due to coronary artery spasm (Prinzmetal or variant angina).[3]

Etiology

CAD is predominantly caused by diseases that affect the coronary arteries. In particular, atherosclerosis accounts for over 90% of cases.

Atherosclerotic lesions, commonly known as plaques, are typically found in 1 or more of three major coronary arterial trunks, with the top incidence being in the LAD. This is followed by the RCA and CXA, with a decreasing frequency of occurrence. In approximately

one-third of cases, only one vessel is affected (Single Vessel Disease - SVD), with the LAD being the most commonly involved artery. Another one-third of cases have two-vessel disease (Double vessel disease - DVD), while the remaining one-third have three major vessel disease (Triple vessel disease - TVD).[4]

Pathophysiology

The establishment of atherosclerotic plaque is an integral component of the pathophysiology of CAD – the buildup of fatty material leads to the genesis of plaque causing the vessel lumen to narrow and impede blood flow.[1]

The formation of a "fatty streak" accrues from the sub-endothelial deposition of lipid-laden macrophages, also called foam cells is 1st step in the process.[1] The endothelial dysfunction due to disturbed laminar flow, promotes the accumulation of LDL particles within the tunica intima by allowing them to cross the endothelial layer of blood vessels.[5] The circulating monocytes permeate into artery wall because of elevated permeability as a consequence of impairment of endothelial integrity. Then the monocytes undergo differentiation to form mature macrophages through the inflammatory processes.[6] These macrophages incorporate modified lipoproteins like βVLDL (beta very low-density lipoprotein), OxLDL (oxidized low-density lipoprotein), and AcLDL (acetylated low-density lipoprotein) by binding to the Scavenger receptors (SRs).[7] Macrophages emerges as Foam cells by continuous LDL phagocytosis. Foam cells can either be liable to degradation or further promote the expansion of foam cells leads to the origination of plaque in the sub-endothelial layer.[5,8]

This plaque may eventually grow in size or become stable as long as the endothelium is not damaged further. If it stabilizes, the lesion will eventually calcify and develop a fibrous cap. Fibrous cap comprising bundles of smooth muscle cells (SMC), collagen fibers, and a few macrophages and lymphocytes- covers the lipid core.[9] Over time, the lesion may become significant enough to cause angina symptoms due to inadequate blood flow to the myocardial tissue during times of peak demand or exertion. Nevertheless, the symptoms are minimized during rest as the need for oxygen decreases. A lesion needs to be at least 90% stenosed to elicit angina while at rest.[1]

In some plaques, the ulceration of the fibrous cap occurs, which may cause thrombosis by exposing blood to the lipid-rich necrotic debris of the core is the major severe complication.[10] Depending on the measure of damage, thrombosis may partially or

completely block the artery, leading to acute coronary syndrome (ACS), including unstable angina, non-ST elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI).[1]

Typically, CAD is classified as

1. Stable ischemic heart disease (Stable IHD)
2. Acute coronary syndrome (ACS)

i) ST-elevation-myocardial infarction (STEMI)

ii) Non-ST elevation ACS (NSTE-ACS)

- Non-ST elevation-myocardial infarction (NSTEMI)
- Unstable angina

Diagnosis

Diagnostic procedures like Electrocardiogram (ECG), Echocardiography (2D ECHO), Chest X-ray, Stress test, Blood tests, and Cardiac Catheterization are performed to diagnose CAD.[1]

Treatment

Treatment includes both non-pharmacological and pharmacological interventions. Non-pharmacological include lifestyle modifications such as smoking cessation, managing diabetes and hypertension, exercising regularly, weight loss, and a healthy diet. In addition to optimizing lifestyle choices, pharmacotherapy is generally required for secondary prevention. A low-dose aspirin, beta-blocker, as-needed nitroglycerin, and a moderate-to-high-intensity statin are all part of guideline-directed medical therapy (GDMT), which is recommended for every patient. At times, calcium channel blockers and long-acting nitrates should be considered, if symptoms are not in control.[1]

Revascularization surgeries like Percutaneous Coronary Interventions (PCI) also called Percutaneous Transluminal Coronary Angioplasty (PTCA), and Coronary Artery Bypass Grafting (CABG) are performed in severe cases of Coronary Artery Disease.[11]

As we discussed about CAD, we shall also focus on Lipids and lipoproteins, its pathway and related drugs like β-Hydroxy β-Methylglutaryl-CoA (HMG-CoA) reductase inhibitors or statins, Ezetimibe, Bempedoic acid and their combinations used in reduction of LDL-C levels in CAD patients.

LIPIDS AND LIPOPROTEINS

Cholesterol and triglycerides are hydrophobic and non-polar molecules that are insoluble in aqueous solutions. Due to their chemical properties, they require specialized carriers to transport them within the bloodstream. These lipids are transported in association with proteins, forming lipoprotein particles that vary in size, density, and composition. Lipoproteins are intricate particles comprising of a core that holds cholesterol esters and triglycerides, enveloped by free cholesterol, phospholipids, and apolipoproteins. These apolipoproteins play a pivotal role in the formation and functioning of lipoproteins. Plasma lipoproteins can be classified - seven distinct categories based on their size, lipid composition, and the apolipoproteins present in them. These categories include chy., chy. rem., VLDL, IDL, LDL, HDL, and Lipoprotein a (Lp (a)). While chy. rem., VLDL, IDL, LDL, and Lp (a) are deemed to be pro-atherogenic in nature, HDL is deemed to be anti-atherogenic.[12]

Table 1: Characteristics and function of plasma lipoproteins.[13]

S. no	Lipoprotein class	Diameter (nm)	Lipid contained	Source of lipid	Function
1	Chy	100-500	TG>>CHF	Diet	Dietary TG transport
2	Chy. rem.	30-50	CHF>>TG	Diet, Chy.	Dietary CH transport
3	VLDL	40-80	TG>>CHF	Liver	Endogenous TG transport
4	IDL	30-35	CHF≥*TG*	VLDL	Transport CHF and TG to liver, LDL source
5	LDL	20-25	CHF	IDL	Transport CH to tissues and liver
6	HDL	5-10	Phospholipid, CHF	Tissues, cell member	Removal of CH from tissues

Chy - Chylomicrons; Chy. Rem. - Chylomicron remnant; VLDL - Very low density lipoprotein; IDL - Intermediate density lipoprotein; LDL - Low density lipoprotein; HDL- High density lipoprotein; CHE- Cholesteryl esters; TG - Triglyceride; CH - Cholesterol, FA – fatty acids, LPL - lipoprotein lipase

Lipoprotein pathway

The exogenous lipoprotein pathway is initiated by the incorporation of dietary fats into chylomicrons in the small intestine. In the bloodstream, the triglycerides carried in chylomicrons undergo metabolism in the adipose tissue and muscles via lipoprotein lipase. This process results in the release of free fatty acids(FA), which are further biotransformed by the fat tissue and muscle. The remaining chylomicron remnants are engrossed by the liver,

completing the exogenous lipoprotein pathway.

The endogenous lipoprotein pathway is initiated in the liver where VLDL is formed. The triglycerides carried in VLDL are broken down by lipoprotein lipase in the muscle and adipose tissue, releasing free FA, and IDL is generated. The IDL is subsequently metabolized to LDL, which is taken up by the LDL receptor present in various tissues, including the liver, which is the primary site of uptake.

When the liver and intestines produce newly formed HDL, the process of reversing CH movement begins. Through the ABCA1 transporter, these tiny HDL particles can efficiently absorb phospholipids and cholesterol that are produced by cells. Maturity in HDL is the outcome of this. Mature-HDL can take up more cholesterol from cells by passive diffusion, SR-B1 receptor, and ABCG1 transporter.

When it comes to delivering cholesterol to the liver, HDL is essential. It can be accomplished directly through interaction with hepatic SR-B1 or indirectly through the use of CHE transfer protein to transfer cholesterol to VLDL or LDL lipoproteins. The process by which excess cholesterol leaves macrophages is known as cholesterol efflux. And this excess cholesterol is transferred to HDL, which is a pivotal mechanism in preventing the onset and progression of atherosclerosis.[12] Lipid abnormalities elevate the peril of coronary, cerebrovascular, and periphery arterial disease, collectively called ASCVD.[3]

Lipid profile test

A lipid profile, also known as a lipid panel, is a comprehensive set of blood tests that aims to detect any abnormalities in the level of various types of lipids, including cholesterol and triglycerides. The test results can be accustomed to identify certain inherited disorders and provide an estimate of the risk of emerging various diseases, such as cardiovascular disease.

Table 2: Lipid screening (mg/dl) and the Risk of stable IHD.[14,15]

Lipid	Desirable Level (Less Risk)	Borderline Level (Moderate Risk)	Abnormal (High Risk)
TC	<200	200-240	>240
LDL cholesterol	<130	130-160	>160
DL cholesterol	>60	40-60	<40
Triglycerides	<200	200-400	>400
VLDL	<30	31-40	>40

The risk increases further with other RFs such as diabetes, and HTN.

SECONDARY PREVENTION (SP)

After a CAD diagnosis has been obtained, secondary prevention aims to prevent further disease progression and damage. Its main objective is to reduce the impact of disease by diagnosing it early before critical and irreversible damage has been caused.[16]

The topic that needs to be addressed is who qualifies for secondary prevention. Individuals who had a heart attack previously, are currently exhibiting symptoms of CAD, and have undergone CABG or percutaneous coronary intervention (PCI),[16] acute coronary syndrome (ACS), history of myocardial infarction (MI), stable or unstable angina, are all considered to be clinical cases of atherosclerotic coronary artery disease (CAD) which are qualified for secondary prevention.[17] The goal is to decrease the chance of recurrence incidents or mortality, slow down the advancement of CAD, and regress CAD.[16]

Management of hyperlipidemia is a crucial step in regressing the advancement of atherosclerosis in CAD. Lipid-lowering drugs like 3-hydroxy-3-methyl–glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (also called statins), Cholesterol absorption inhibitors like ezetimibe, Bile acid sequestrants, n-3 fatty acids, Proprotein convertase subtilisin/kexin type-9 (PCSK-9) inhibitors, Fibrates, Adenosine triphosphate Citrate Lyase (ACLY) inhibitor named bempedoic acid are employed in treating hypercholesterolemia.[18]

Statins are recommended for both Primary and secondary prevention of cardiovascular disease. Patients with ACS ought to take high-dose statins. Old therapies, such as niacin, bile acid sequestrants, and fibrates, are no longer used to treat hypercholesterolemia due to limited effectiveness, side effects, and lack of evidence for reducing cardiovascular events.[19]

If the LDL-C levels are still high in defiance of taking statins, the guidelines suggest adding ezetimibe and PCSK-9 inhibitors to the therapy. Bempedoic Acid (BMA) and Inclisiran are cures that can reduce hypercholesterolemia. BMA works upstream of the enzyme HMG CoA reductase and up-regulates LDL receptors by inhibiting ACLY. Its liver-specific mechanism of action results in no muscle-related adverse effects. BMA also possesses strong systemic anti- inflammatory effects that lead to significant Atherosclerotic Cardiovascular Disease (ASCVD) risk reduction. Before attempting PCSK9 inhibitors, which have various drawbacks such as injectable preparation and higher costs, the recently approved BMA-

ezetimibe combination could be tried with an emphasis on the patient.[19] However, Statins, ezetimibe, and bempedoic acid are discussed below.

Statins (St.)

HMG-CoA reductase inhibitors, or statins, are lipid-lowering drugs that reduce illness and mortality in individuals at high risk of cardiovascular disease. These are the drugs that are most commonly suggested to lower cholesterol.[20]

Through the mechanisms outlined by the lipid hypothesis, LDL, which are carriers of cholesterol, play a crucial role in the development of atherosclerosis and coronary artery disease. Since statins effectively lower low-density lipoprotein LDL cholesterol, they are mostly susceptible for both primary prevention in those at high threat of developing cardiovascular disease and SP in individuals with pre-existing cardiovascular disease.[21]

Mechanism of action: Hepatocytes normally eliminate 70% - 75% of plasma LDL through a process known as receptor-mediated endocytosis. To liberate free cholesterol, the liver hydrolyzes cholesterol esters from LDL molecules. A coenzyme known as Hydroxy methyl glutaryl (HMG) coenzyme A reductase forms mevalonic acid in the liver's de novo synthesis pathway, which is another method by which the liver generates cholesterol. This rate-limiting enzyme is inhibited by statins. The process of hepatic cholesterol synthesis is reduced, resulting in the upregulation of high-affinity LDL receptors on the surface of liver cells. This leads to an elevated uptake or clearance of low-density lipoprotein (LDL) cholesterol from plasma, resulting in a subsequent decrease in plasma LDL cholesterol levels. The efficacy of this action is proportional to the dosage administered, and the maximum effect is usually observed within six weeks.[14]

Table 3: List of Statins and recommended dose[14]

Statins	High-intensity statin Therapy (mg/day)	Moderate-intensity statin Therapy (mg/day)
Atorvastatin	40-80	10-20
Rosuvastatin	20-40	5-10
Simvastatin	-	20-40
Pravastatin	-	40-80
Lovastatin	-	40
Fluvastatin	-	Extended-release:80 40 twice a day
Pitavastatin	-	2-4

Ezetimibe (EZ)

Ezetimibe is a lipid-lowering agent belonging to the class of Cholesterol absorption inhibitors.[22] In 2002, the FDA gave its approval. In individuals with primary hyperlipidemia, mixed hyperlipidemia, familial hypercholesterolemia (HoFH), and homozygous sitosterolemia (phytosterolemia), EZ is recommended to lower total cholesterol, low-density lipoprotein (LDL), apolipoprotein B (apo B), and increase high-density lipoprotein (HDL).

Mechanism of action: Cholesterol is engrossed from the GI tract or synthesized in the liver. Ezetimibe is a synthetic 2-azetidinone agent. Either the liver produces cholesterol or the gastrointestinal system absorbs it. A synthetic 2-azetidinone agent is called ezetimibe. Since it does neither boost bile acid excretion nor hinder the liver's ability to synthesize cholesterol, ezetimibe differs from other cholesterol-lowering medications. Through inhibition of the sterol transporter Niemann-Pick C1-Like-1 (NPC1L1), ezetimibe reduces the absorption of cholesterol at the brush border of the small intestine.

The reduction in absorption of cholesterol results in minimized delivery of cholesterol to the liver, thereby causing an increase in the clearance of cholesterol from the circulation and decrement in hepatic cholesterol stores. There is a curtail in total cholesterol, triglycerides, and LDL cholesterol and an increase in HDL cholesterol due to this sequential reduction in cholesterol absorption. Vitamins A, D, and E are fat- soluble vitamins that are not considerably impacted by ezetimibe. There is a 13–20% decrease in LDL values after using ezetimibe.

Dosage administration: Since ezetimibe has a lengthy half-life of roughly 22 hours, it can be taken orally once a day with a diet that lowers cholesterol, either with or without meals. 10 mg should be taken every day. It may be used at the same time as fenofibrate or HMG-CoA reductase inhibitors, although the guideline is to dose it at least 2 hours before or 4 hours after administration of bile acid sequestrants. As there are minimal undesirable effects and a once-daily dosage, compliance shouldn't be an issue.[23] It is available under brand names Etimibe, Ezedoc, etc.

Bempedoic Acid (BMA)

Bempedoic acid is a drug used to treat hypercholesterolemia or elevated blood cholesterol levels. It is marketed in the US and EU under the trade names nexletol, and nilemdo, respectively. In Feb 2020, BMA received approval for use in the US, and in April 2020, it

received approval for use in the EU.[24,25,26] The FDA identified Nexletol as a First-in-class novel drug for the year 2020.[27] Bempedoic acid is marketed in India under the brand name Bemdac by the pharmaceutical company Zydus Life Sciences.[28]

Mechanism of action: BMA is an ACL inhibitor that works by hindering the liver from synthesizing cholesterol, therefore lowering LDL-C. In the cholesterol-making pathway, ACL is an enzyme that comes before 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. Coenzyme A (CoA) must be activated by very long-chain acyl-CoA synthetase 1 (ACSVL1) for bempedoic acid and its active metabolite, ESP15228, to form ETC-1002-CoA and ESP15228-CoA, respectively. The liver is where ACSVL1 is mainly expressed. When ACL is inhibited by ETC-1002-CoA, the liver produces less cholesterol, and the blood's level of LDL-C is reduced because low- density lipoprotein receptors are upregulated.[29]

Dosage administration: The approved dose of Bempedoic acid is 180 mg, orally, once daily.[29]

Combination therapy

Combining statins with ezetimibe, monoclonal antibody PCSK9 inhibitors, bempedoic acid, or inclisiran shows additive effects on LDL-C reduction but doubling the statin dose offers only roughly 5–6% extra LDL-C reduction. Thanks to advances in medical care, the early introduction of a combination regimen can help minimize the possibility of ASCVD as a consequence of LDL-C reduction. Let’s discuss a few such combinations used for additional reduction of LDL-C levels in CAD patients with dyslipidemia.

Statin + Ezetimibe: Ezetimibe is a medication that can be used alone, in auxiliary with fenofibrate, or in auxiliary with inhibitors of the hydroxy methyl glutaryl coenzyme A (HMG-CoA) reductase. Since 2002, ezetimibe and simvastatin have been available in a fixed-dose combination. In 2012, a new combination agent consisting of ezetimibe and atorvastatin was authorized. It isn't being sold commercially in the USA right now. Nonetheless, the FDA authorized the Fixed-Dose Combination (FDC) of ezetimibe with rosuvstatin.[23]

Statin + Bempedoic acid: When statin is taken concomitantly with bempedoic acid, it efficiently decreases LDL- C and may improve cardiovascular outcomes.[30]

In the US, adults with established ASCVD who require further lowering of LDL cholesterol may be prescribed BMA in addition to diet and the highest tolerated St. therapy to treat their

hypercholesterolemia.[29]

Whereas in the EU, if a patient cannot reach LDL-C goals with the maximum tolerated dose of a statin, BMA is recommended as an auxiliary to diet in combo with a statin or statin with other lipid-lowering therapies.[31]

BMA + Ezetimibe: In both the US and the EU, the FDC received approval for therapeutic use in February and March of 2020, respectively. This combination is available under the brand names Nexlizet in the US and Nustendi in the EU.[32,33] BMA is marketed in India under the brand name Bemdac EZ 180mg/10mg by the pharmaceutical company Zydus Life Sciences.[34]

A research study showed LDL C values reduction by 23% in participants taking BMA in addition to ezetimibe compared with an increase of around 5% in participants taking placebo and ezetimibe, after three months of respective therapy with very low levels of St. or no statin.[32]

BMA + Ezitimibe + Statins: In the US, individuals with established ASCVD or HeFH who need further lowering of LDL-C can be treated with BMA/ezetimibe as an adjuvant to diet and high-dose St. medication.[35]

A research study showed LDL-cholesterol levels declined by 36% in participants taking BMA and EZ compared with a declination of 23% with ezetimibe alone, and 17% with BMA alone, after three months of respective therapy with high-dose of statin.[32]

In summary, bempedoic acid, ezetimibe, and statins are compared as the secondary prevention to atherosclerotic Coronary Artery Disease (CAD). The principal goal of the research is to comprehend the association between LDL, HDL, and triglycerides and the drug-of-choice prescribing trends for bempedoic acid, ezetimibe, and statins in CAD patients.

OBJECTIVES

The principal goal of this work is to comprehend the relation between LDL-cholesterol levels and the drug-of-choice prescribing trends for bempedoic acid, ezetimibe, and statins in CAD patients.

The other objectives include categorizing the patients with CAD based on demographics, comorbidities, and BMI, to analyze other parameters - total cholesterol, triglycerides, HDL, and VLDL cholesterol levels in lipid profile test.

METHODOLOGY

STUDY SITE

The study site was KIMS-SUNSHINE HOSPITAL, Secunderabad.

STUDY PERIOD

Six months were dedicated to the conduct of this investigation.

SAMPLE SIZE

A total of 200 prescriptions were incorporated into the research and were followed for the project.

STUDY DESIGN

The study design was a comparative prospective study.

STUDY CRITERIA

Inclusion Criteria

- Every individual who is prescribed Statins, Ezetimibe, and Bempedoic acid for CAD is enclosed in this study.
- All patients aged 18 years and above are included.
- Male and female patients are included.
- Patients having comorbidities like Diabetes, Hypertension, and Dyslipidemia.
- In-patients.

Exclusion Criteria

- Pediatrics
- Pregnant and lactating women.
- Psychiatric patients.
- Individuals who refuse to provide consent.
- Outpatients.
- Patients with CAD, but not treated with Statins, Ezetimibe, and Bempedoic acid.

DATA COLLECTION - SOURCE

REFERENCE SUPPLIES

- Patient consent forms.
- Forms for collecting patient data.
- Patient profile forms.

PATIENT CONSENT FORMS

It includes the patient's demographic information, the study's title, its specifics, and the participant's and researcher's signatures. Participants must sign the no-cost patient consent form to express their willingness to take part in a clinical research investigation.

PATIENT PROFILE FORM

The name, hospital number, age, gender, date of admission and discharge, complaints at the time of admission, objective and subjective evidence, plan of care, preliminary and final diagnoses, medication schedule, specifics of any surgeries, progress notes, and discharge medications are all included.

DATA COLLECTION FORM

Age, gender, weight, date of admission and discharge, complaints at admission, medical history, medication history, social habits, familial history, physical examination/vitals, cardiac history, laboratory results, and other cardiac tests are among the demographic information included. Other details include the provisional diagnosis, final diagnosis, details of any cardiac revascularization procedures, progress chart, and, in the end, the medications prescribed for discharge.

PROCEDURE OF THE STUDY

This is a comparison and prospective study in which patients willingly participate after getting consent. The work required no patient inquiry or intervention. KIMS-Sunshine Hospital's ethics committee has authorized the study's conduct. We enrolled 200 individuals of both genders in our trial. All of the data needed for our investigation was gathered through a data collection form. In the course of the 6-month trial period, the first four months were invested in data collecting. During the data collection process, we addressed patients who met the study's inclusion criteria, detailed the particulars of our research to them thoroughly, and got consent after they fully understood the study. A department of cardiology is under consideration.

Additionally, we asked about their prior medical history. Following data collection, we used the next month for data analysis. Microsoft Office Excel was used for all statistical analysis, and it produced the graphs, tables, and other visual aids. The research took place in KIMS Sunshine Hospital. The thesis preparation took up the last month of the study period.

RESULTS

1. GENDER-WISE DISTRIBUTION IN CAD PATIENTS

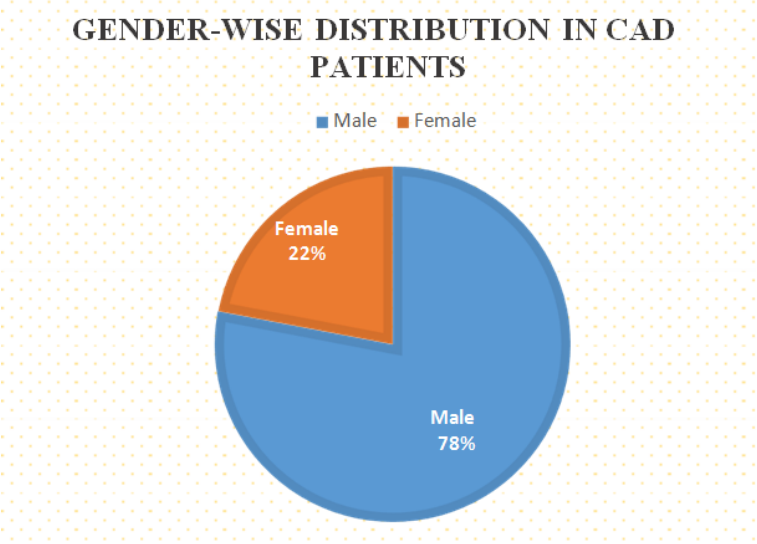

Figure 1: Gender-wise distribution.

2. AGE-WISE DISTRIBUTION IN CAD PATIENTS

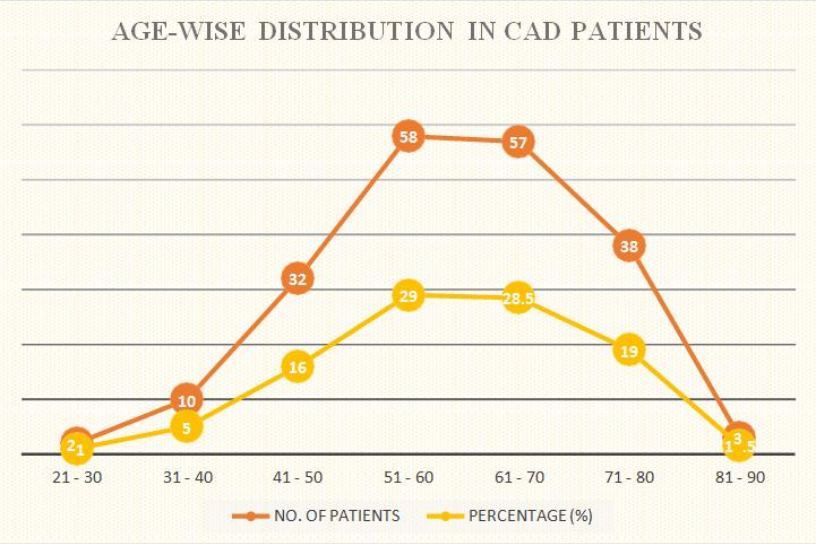

Figure 2: Age-wise distribution.

3. COMORBIDITIES-WISE DISTRIBUTION IN CAD PATIENTS

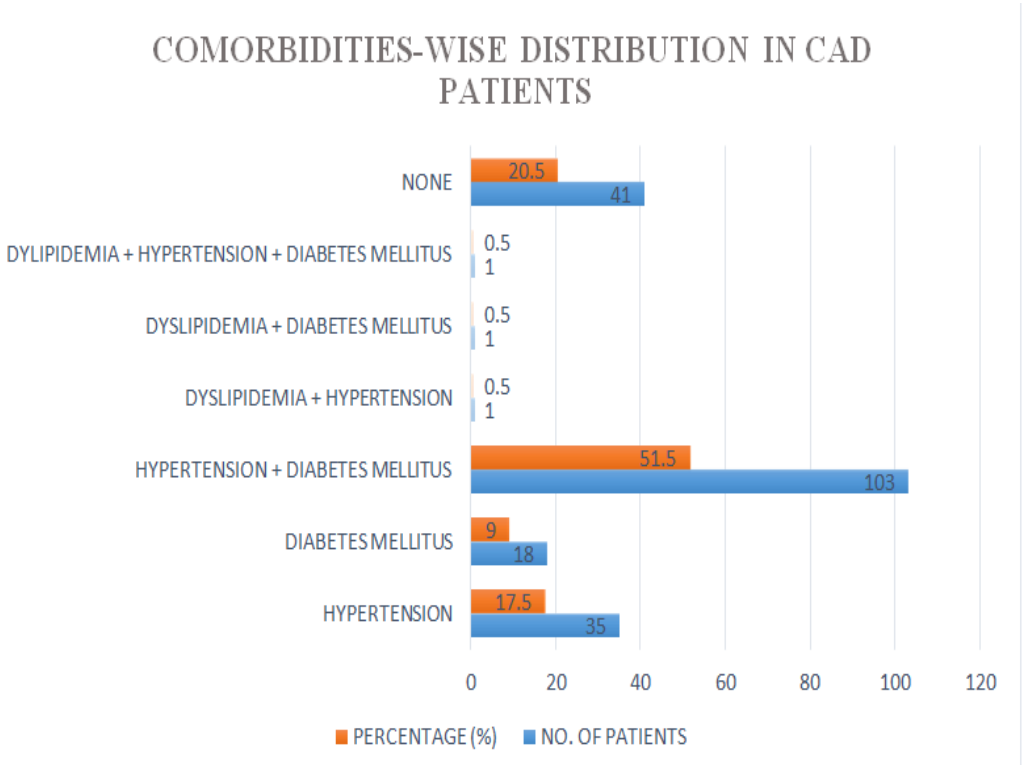

Figure 3: Comorbidities-wise distribution.

4. BODY MASS INDEX (BMI) WISE DISTRIBUTION IN CAD PATIENTS

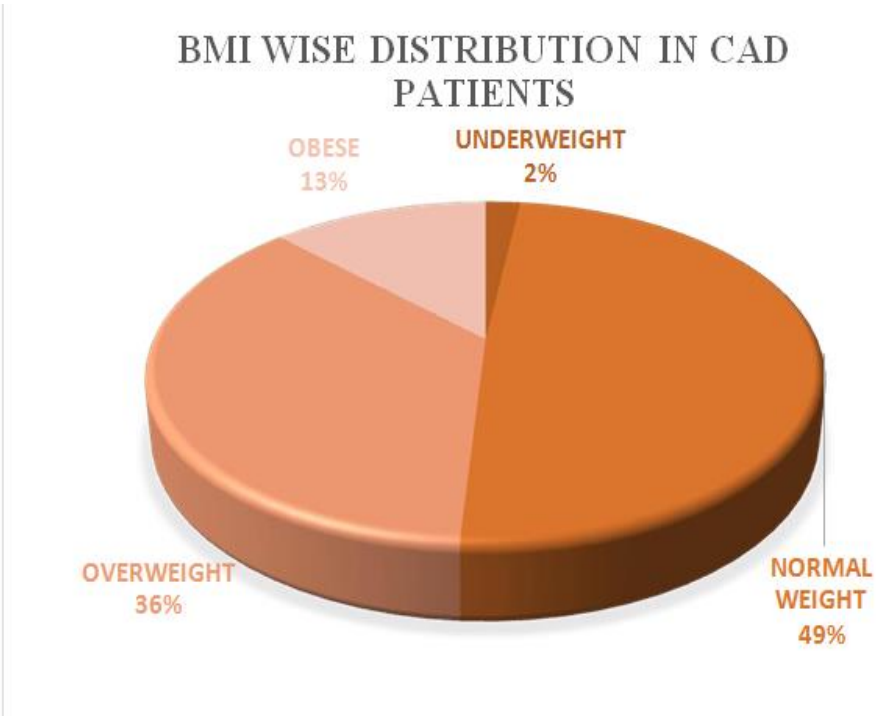

Figure 4: BMI-wise distribution.

5. DRUGS-WISE DISTRIBUTION IN CAD PATIENTS

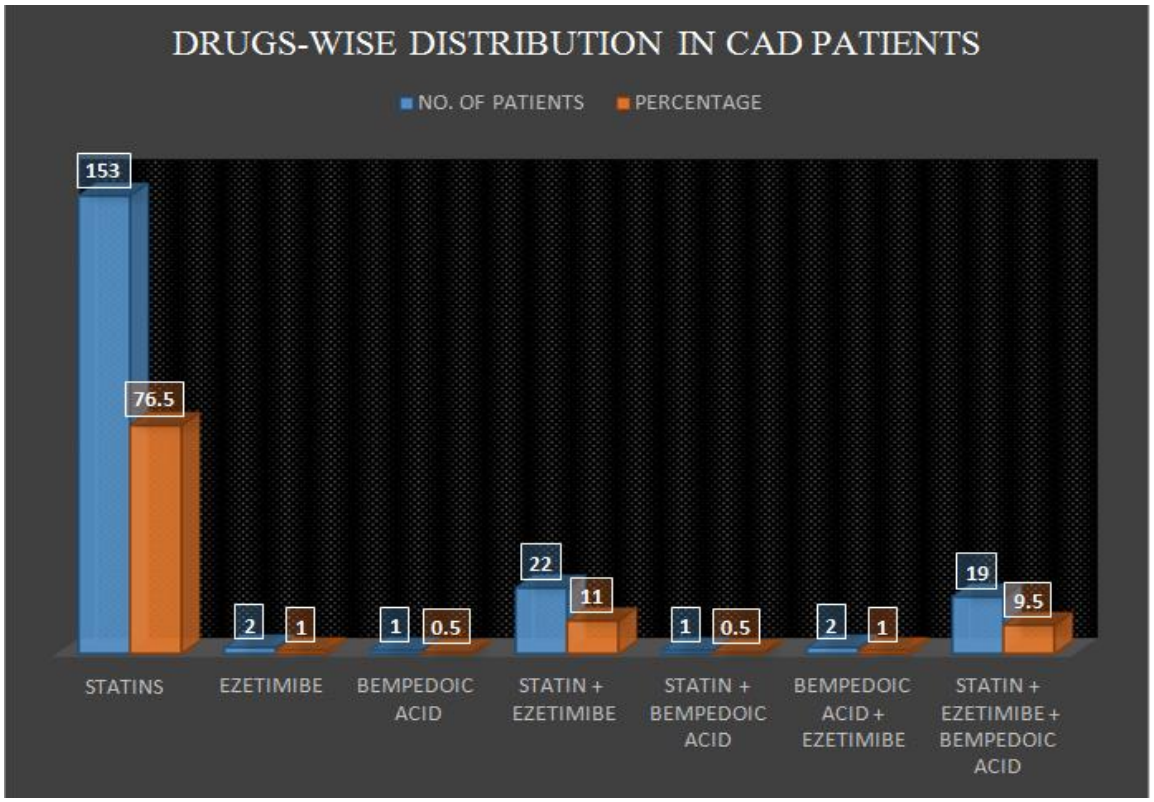

Figure 5: Drugs-wise distribution.

6. TOTAL CHOLESTEROL LEVELS-WISE DISTRIBUTION IN CAD PATIENTS

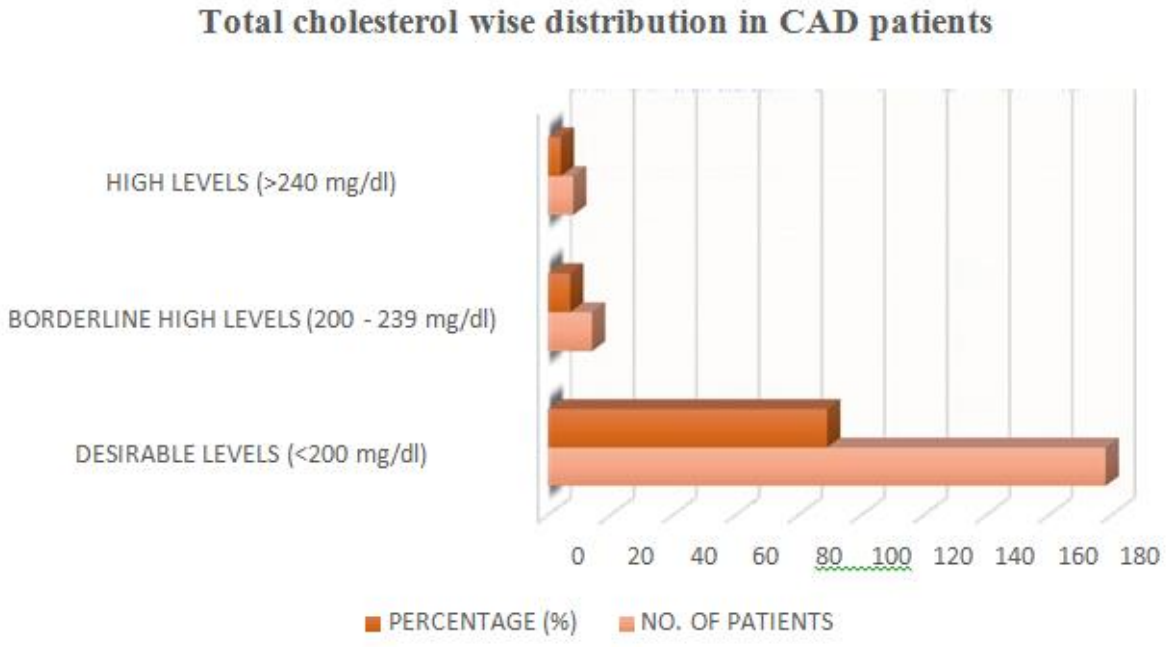

Figure 6: Total cholesterol-wise distribution.

7. VERY LOW-DENSITY LIPOPROTEIN (VLDL) CHOLESTEROL LEVELS-WISE DISTRIBUTION IN CAD PATIENTS

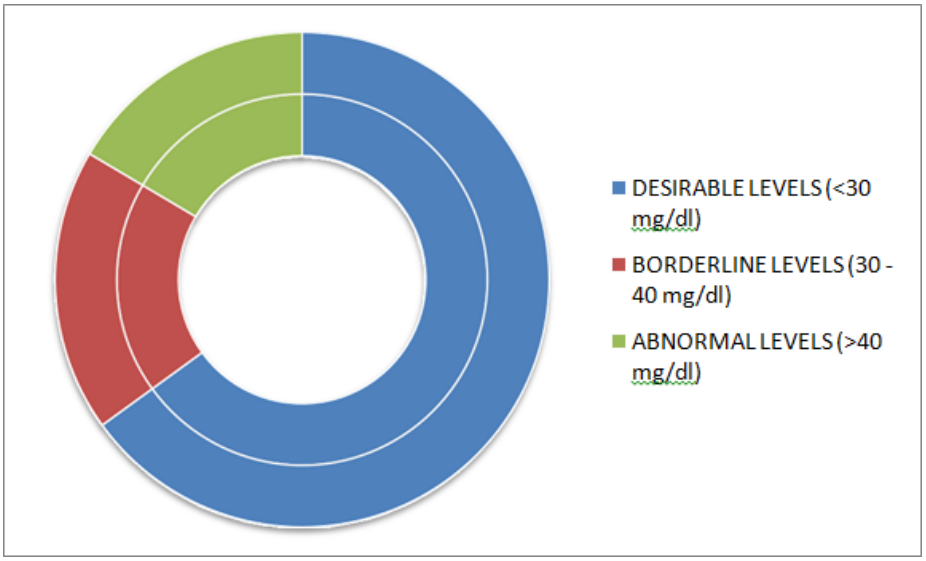

Figure 7: VLDL levels-wise distribution.

8. HIGH-DENSITY LIPOPROTEIN (HDL) CHOLESTEROL LEVELS-WISE DISTRIBUTION IN CAD PATIENTS

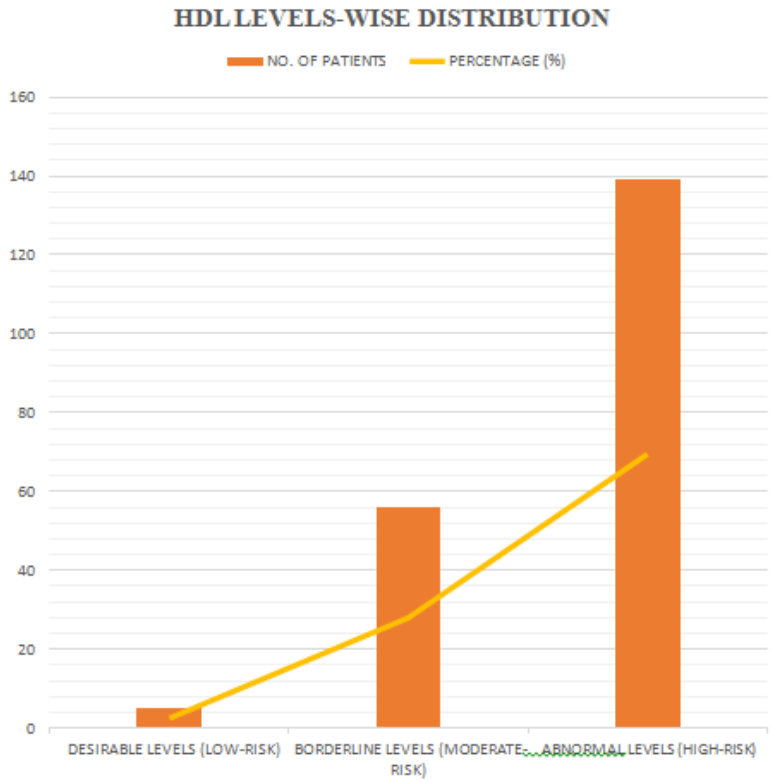

Figure 8: HDL levels-wise distribution.

9. DRUGS-WISE DISTRIBUTION OF TRIGLYCERIDE LEVELS

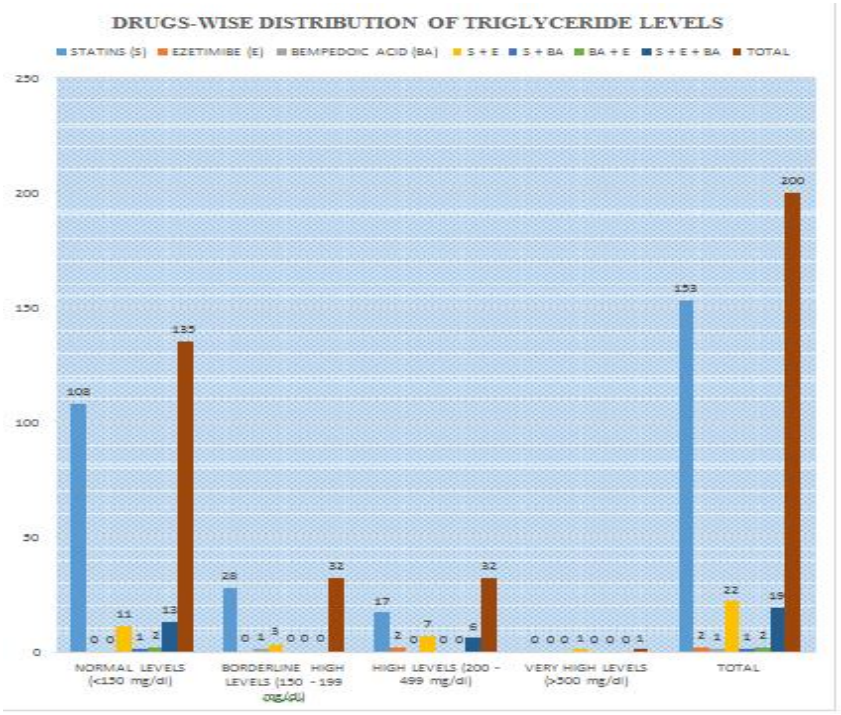

Figure 9: Drugs-wise distribution of triglyceride levels.

10. DRUGS-WISE DISTRIBUTION OF HIGH-DENSITY LIPOPROTEIN (HDL) CHOLSTEROL LEVELS

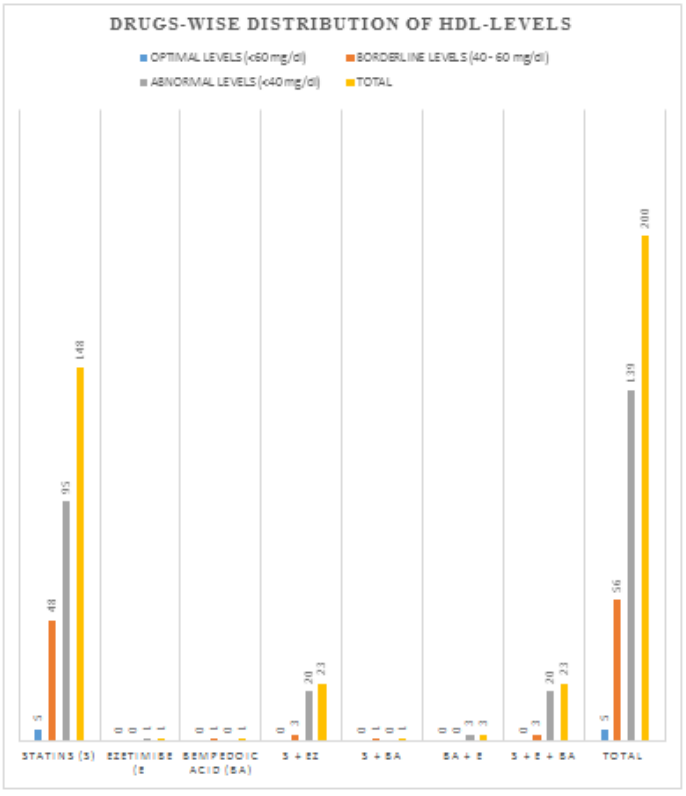

Figure 10: Drugs-wise distribution of HDL levels.

11. DRUGS-WISE DISTRIBUTION OF LOW-DENSITY LIPOPROTEIN (LDL) CHOLESTEROL LEVELS

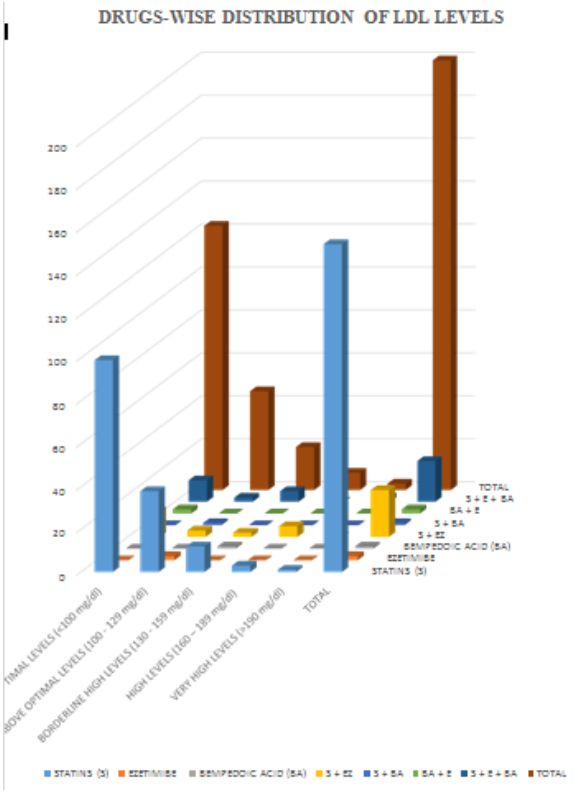

Figure 11: Drugs-wise distribution of LDL levels.

12. DRUGS-WISE DISTRIBUTION OF CARDIAC REVASCULARIZATION SURGERIES.

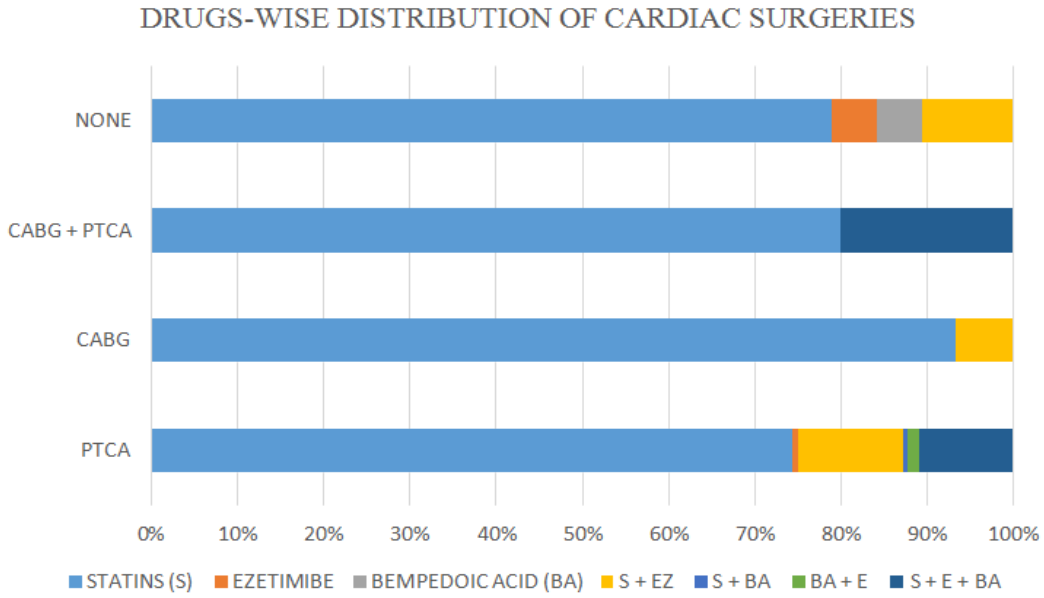

Figure 12: Drugs-wise distribution of Cardiac surgeries.

13. DRUGS-WISE DISTRIBUTION OF VESSEL DISEASES

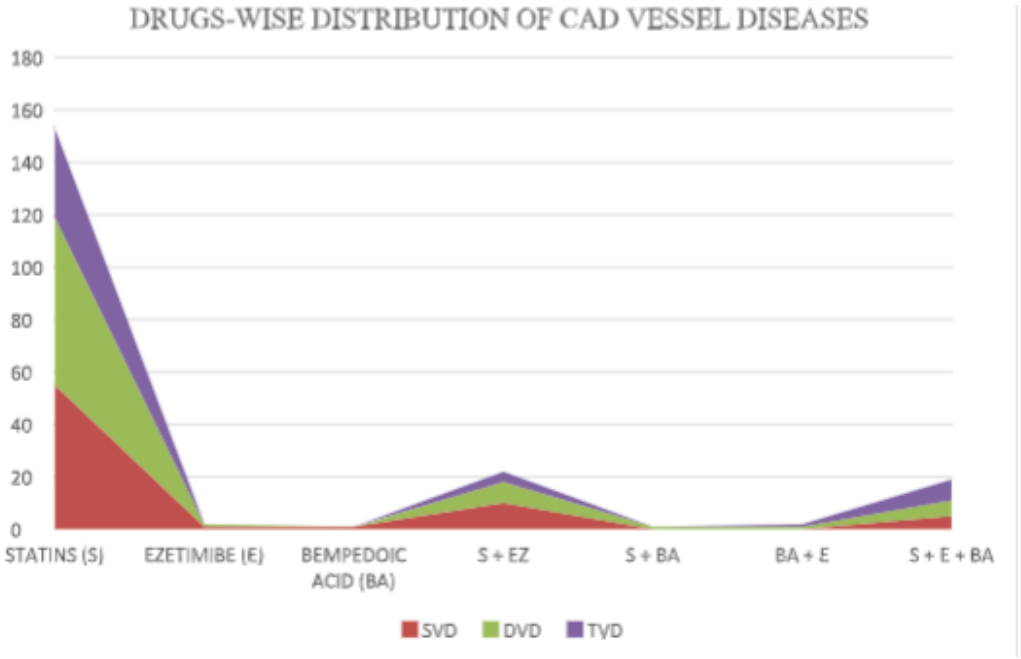

Figure 13: Drugs-wise distribution of vessel diseases.

14. COMPARISON OF PERCENTAGE OF STATINS ALONE AND OTHER DRUGS/COMBINATIONS (WITH OR WITHOUT STATINS)

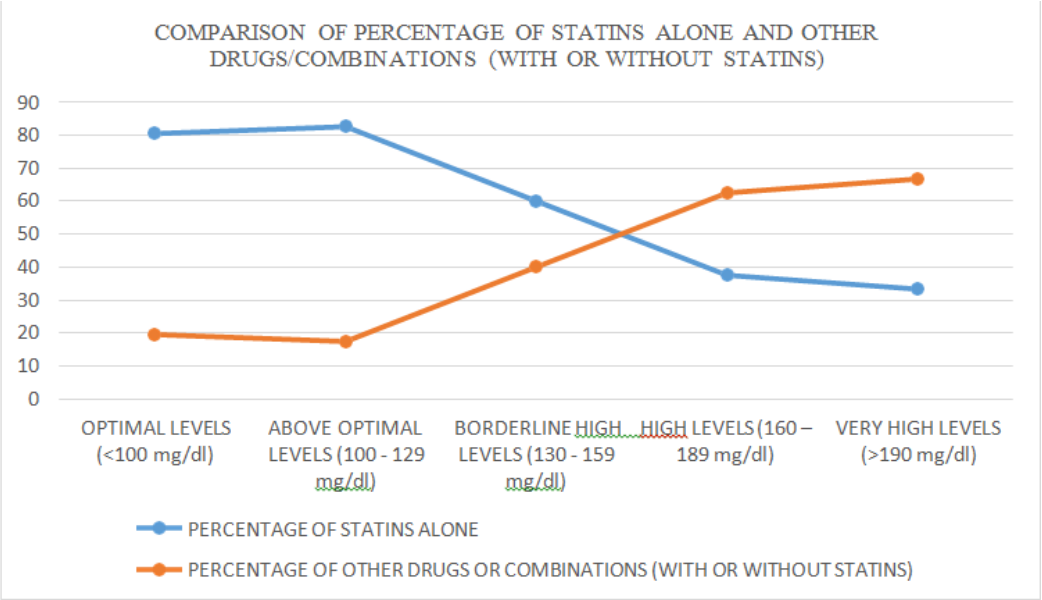

Figure 14: Comparison (Statins alone vs other drugs/combinations).

DISCUSSION

The prospective and comparative study was performed in a tertiary care multi-specialty hospital which included a sample size of 200 CAD patients.

For CAD, Males are more impacted than females *(Fig.1)*, and the maximum number of individuals belong to the age group of 51 – 60 years *(Fig.2)*.

The majority of the study sample had both Hypertension and Diabetes Mellitus as comorbidities (51.5%). Dyslipidemia with other comorbidities was observed in 1.5% in total *(Fig.3)*.

BMI results showed that most of the sample size has normal weight (49%), followed by overweight (36.5%) and obesity (12.5%). Underweight patients were very low (2%) *(Fig.4)*.

Previous research studies have shown that there is a connection between high levels of plasma lipids (which includes cholesterol, TG) and atherosclerosis (which ultimately leads to CAD). In individuals with atherosclerosis, it has been observed that they have an increased level of plasma LDL cholesterol and TG. The risk of IHD is about three times higher in these individuals compared to those with normal plasma cholesterol levels. However, a reduction in plasma lipids through dietary restrictions or medication can help in preventing the progression of atherosclerosis. Studies have also confirmed that a decrease in elevated plasma LDL-cholesterol levels can reduce the risk of MI.[14]

The bulk of the study sample has abnormal HDL levels (high-risk - <40%) contributing 69.5% *(Fig.8)*. 22% of the 69.5 % abnormal HDL level patient population was prescribed other drugs/combinations [including Ezetimibe (alone), Bempedoic acid (alone), Statin + Ezetimibe combination, Statin + Bempedoic acid combination, Bempedoic acid + Ezetimibe combination, and Statin + Ezetimibe + Bempedoic acid combination], while others are prescribed with statins alone (47.5%). Other drugs/combinations were considered for 4% of 28% of the sample population with borderline HDL levels *(Fig.10)*.

The other parameters of lipid profile test like TC, TG, VLDL-cholesterol, and LDL-cholesterol were found to be in desirable levels in the larger portion of the study population *(Fig.6,7,9,11)*.

According to LAI, ESC and EAS, for very High-Risk patients, including those with previous ACS (MI or unstable angina), SA, stroke, TIA, PAD, MVD with 2 epicardial arteries possessing more than 50% stenosis, long-standing diabetes with microvascular complications, severe chronic kidney disease (eGFR less than 30 mL/min/1.73 m2), and familial hypercholesterolemia (FH), it is endorsed to achieve low- density lipoprotein

cholesterol (LDL-C) goal of less than 55 mg/dl. This goal is also advised for patients who have undergone coronary revascularization procedures such as percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and other arterial revascularization procedures. For Extreme-Risk patients, including those with Diabetes poly-vascular disease (CAD/PAD/CVD), recurrent ACS within 12 months despite LDL-C goals, and homozygous familial hypercholesterolemia (FH), it is recommended to maintain the LDL-C level at or below 30 mg/Dl.[36,37]

To achieve the recommended lipid profile levels, 23.5% of the patient population was prescribed other drugs/combinations [including Ezetimibe (alone) (1%), Bempedoic acid (alone) (0.5%), Statin + Ezetimibe combination (11%), Statin + Bempedoic acid combination (0.5%), Bempedoic acid + Ezetimibe (1%) combination, and Statin + Ezetimibe + Bempedoic acid combination (9.5%)], while the lion's share is of statins alone (76.5%) *(Fig.5)*.

Above 20% of patient population in PTCA and PTCA + CABG were prescribed with other drugs/combinations [Ezetimibe (alone), Bempedoic acid (alone), Statin + Ezetimibe combination, Statin + Bempedoic acid combination, Bempedoic acid + Ezetimibe combination, and Statin + Ezetimibe + Bempedoic acid combination], while <80% of patient population are prescribed with statins alone. Whereas in CABG >90% of the patient population is prescribed Statins *(Fig.12)*.

In SVD, DVD, and TVD, the patient population was prescribed other drugs/combinations [including Ezetimibe (alone), Bempedoic acid (alone), Statin + Ezetimibe combination, Statin + Bempedoic acid combination, Bempedoic acid + Ezetimibe combination, and Statin + Ezetimibe + Bempedoic acid combination], was shown to be 23.6%, 20.9%, and 27%, respectively, while the larger portion of them are prescribed statins *(Fig.13)*.

Agency EM says that their research study showed LDL-cholesterol levels declined by 36% in participants taking BMA and EZ compared with a declination of 23% with ezetimibe alone, and 17% with BMA alone, after three months of respective therapy with high-dose of statin in patients diagnosed with hypercholesterolemia & heart disease (HD) or those with greater risk of HD.[32]

This study attests that with the increase in LDL-C levels, the count of prescriptions with statins alone is decreasing, and the count of prescriptions of other drugs/combinations [which

include Ezetimibe (alone), Bempedoic acid (alone), Statin + Ezetimibe combination, Statin + Bempedoic acid combination, Bempedoic acid + Ezetimibe combination, and Statin + Ezetimibe + Bempedoic acid combination] is increasing (as shown in *Fig.14*). We observe this prescription trend aimed at lowering LDL-C levels, as elevated LDL-C levels can raise the risk of CAD.

CONCLUSION

- The present prospective observational comparative study concludes that CAD patients are prescribed with Statins, Ezetimibe, and Bempedoic acid, and their combinations as secondary prevention.
- Statins were the most prescribed medication for secondary prevention to CAD.
- Although statins were mostly prescribed medication, Statin + Ezetimibe combination and Statin + Ezetimibe + Bempedoic acid combination were prescribed in a good number. While Ezetimibe and Bempedoic acid alone were prescribed the least.

- **This study attests that with the increase in LDL-C levels, the count of prescriptions with statins alone is decreasing, and the count of prescriptions of other drugs/combinations [which include Ezetimibe (alone), Bempedoic acid (alone), Statin + Ezetimibe combination, Statin + Bempedoic acid combination, Bempedoic acid + Ezetimibe combination, and Statin + Ezetimibe + Bempedoic acid combination] is increasing. We observe this prescription trend aimed at lowering LDL-C levels, as elevated LDL-C levels can raise the risk of CAD.**

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