STATINS CURRENT STATUS AND FUTURE OUTLOOK

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at
Claris Life Science,
Ahmedabad

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Under the Guidance of
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□aipur
2015

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(WHO Collaborating Centre for District Health System Based on Primary Health Care)

IIHMR UNIVERSITY

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This is to certify that **Anshul Tyagi** student of MBA Pharmaceutical Management from The IIHMR University, Jaipur has undergone internship training at **Claris Life Science, Ahmedabad** from 6th March, 2015 to 6th May, 2015.

The Candidate has successfully carried out the study designated to him during internship training and his approach to the study has been sincere, scientific and analytical.

The Internship is in fulfillment of the course requirements.

I wish him success in all his future endeavors.

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This is to certify that **Mr. Anshul Tyagi** has completed his dissertation successfully at Claris lifescience, Ahmedabad. From **March 6th 2015 to may 6th 2015**. He has successfully completed the project on "Statins: current ststus and future outlook".

He was found to beco-operative,punctual during his tenure with us.

Yours truly,

For **Claris lifescience pvt. Ltd.**

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CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled Statins: current status and future outlook submitted by Anshul Tyagi Enrollment No 196 under the supervision of Dr. Sandeep Narula (Associate Professor The IIHMR University) for award of MBA Pharmaceutical Management of the university carried out during the period from 6th March, 2015 to 6th May, 2015 embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other Institute or other similar institution of higher learning.

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1. Executive Summary

Hyperlipidemia is recognized as one of the major risk factors for the development of coronary artery disease and progression of atherosclerotic lesions. Dietary therapy together with hypolipidemic drugs are central to the management of hyperlipidemia, which aims to prevent atherosclerotic plaque progression, induce regression, and so decrease the risk of acute coronary events in patients with pre-existing coronary or peripheral vascular disease. In patients at high risk of coronary artery disease but without evidence of atherosclerosis, treatment is designed to prevent the premature development of coronary artery disease, whereas in those with hypertriglyceridemia, treatment aims to prevent the development of hepatomegaly, splenomegaly, and pancreatitis. **The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins,** are the most potent lipid-lowering agents currently available.

Currently in the statin market **Atorvastatin** and **Rosuvastatin** are the two most prescribed statins. Atorvastatin is the leading molecule in the statin therapy with the highest market share. Rosuvastatin is a new molecule compared to Atorvastatin however it is gaining the acceptance in the market. Most of the Doctors prefer Atorvastatin as a first line therapy due to its lower cost. Atorvastatin+ Fenofibrate combination is preferred by the doctors for the treatment of Diabetic dyslipidemia. For high risk patients doctors prefer to prescribe atorvastatin 40mg or rosuvastatin 20mg, less no of doctors prefer Atorvastatin 80mg. Major factors affecting the Rosuvastatin therapy is cost, whereas for Atorvastatin therapy is titration to achieve LDL-C goals.

2. COMPANY PROFILE – Claris lifescience pvt. Ltd.

2.1 Claris overview

Claris lifescience Ltd., a flagship company of Claris Group which is a US $ 1.73 billion (Rs. 8200cr) group . Company was ventured by Shri. Arjun handa way back in 1998 . Claris has shown turnover of Rs. 2226 cr in 2013-14 year and achieved CAGR of 26.33% (between 2010-2014).

Claris engages in the manufacture and sale of branded and unbranded generic pharmaceutical products in India and internationally. The company focuses on the cardiovascular, gastrointestinal, central nervous system, diabetology, anti-infective, and pain management areas. Further, it offers contract manufacturing services comprising sourcing, manufacturing, and supplying insulin formulations under the third-party brand name. Claris is the 5th largest player in India in CVS segment and 7th largest player in CNS segment.

Manufacturing and R&D facilities

3 Major manufacturing facilities are at:

(1) Village Indrad, Gujarat

(2) Village Bhud,Baddi, Himachal Pradesh

(3) Gangtok, Sikkim

Its manufacturing facility at Indrad, Gujarat has received ISO 9001, ISO 14001 and OHSAS 18001 and ISO/IEC-17025 certifications and complies with WHO norms and has received approvals from German health authorities, MHRA (UK), TGA (Australia), Anvisa (Brazil) and MCC (South Africa). It has set up a world-class R&D facility at an investment of EUR 35.53 mn that employs >630 scientists dedicated to drug discovery and development, NDDS and Generic Drug Development. It has 8 discovery projects in pipeline with 4 in advance stages. Its bio-equivalence facility has been approved by ANVISA and has also received the OELD GLP Certification from the Dutch Health Ministry.

The Company is currently working on several in-house New Chemical Entities (NCE) projects within the areas of diabetes and its related complications, metabolic and cardiovascular disorders, ischemic diseases and neuropathic pain. The Company has cumulatively filled 426 patents for NCEs from these and earlier projects in all major markets of which, 199 patents have been granted/accepted so far. Claris spends almost 6-8% of its sales on research activities. Approx. 50% of this amount is spent on NDDS and NCE research.

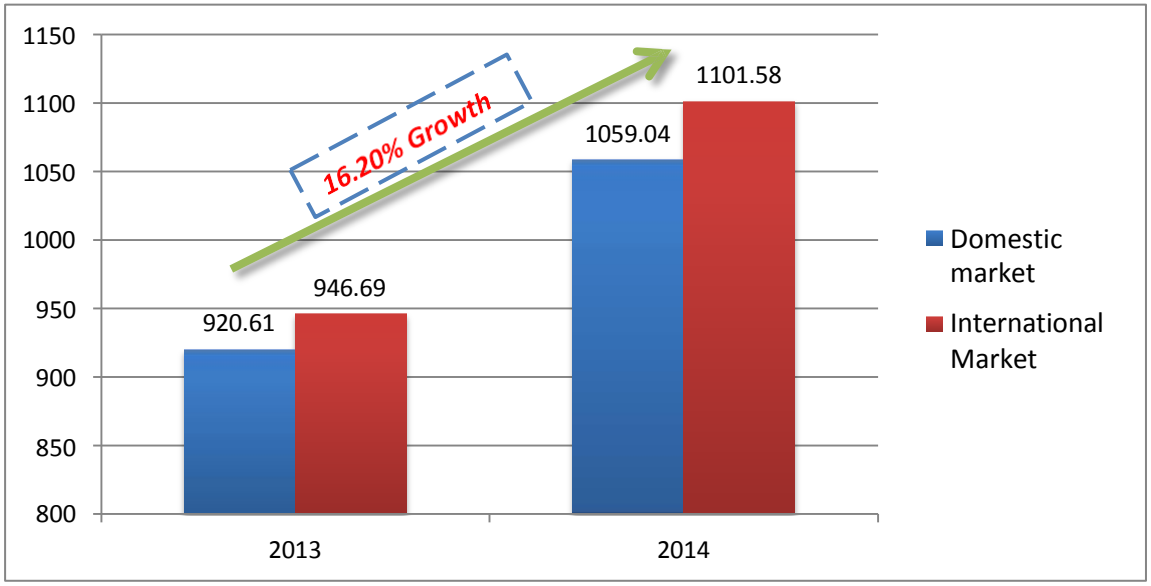
International operation

Claris Pharma today has a strong international presence spanning over 90 countries with over 1000 product registration and over 200 products in the pipeline. Its international business has been broadly divided into five zones – USA, Latin America, Russia and Commonwealth of Independent States, Europe, and Rest of the World.

2.2 claris – Performance overview

Claris has registered sales of Rs. 2226 cr in 2013-14 year. It has seen a growth of 16.20% over the last year with sales of Rs. 1916 cr in 2012-13 year. International market registered higher growth rate as compared to domestic one.

Graph 2.1: Break-up of Domestic and International market sales of claris



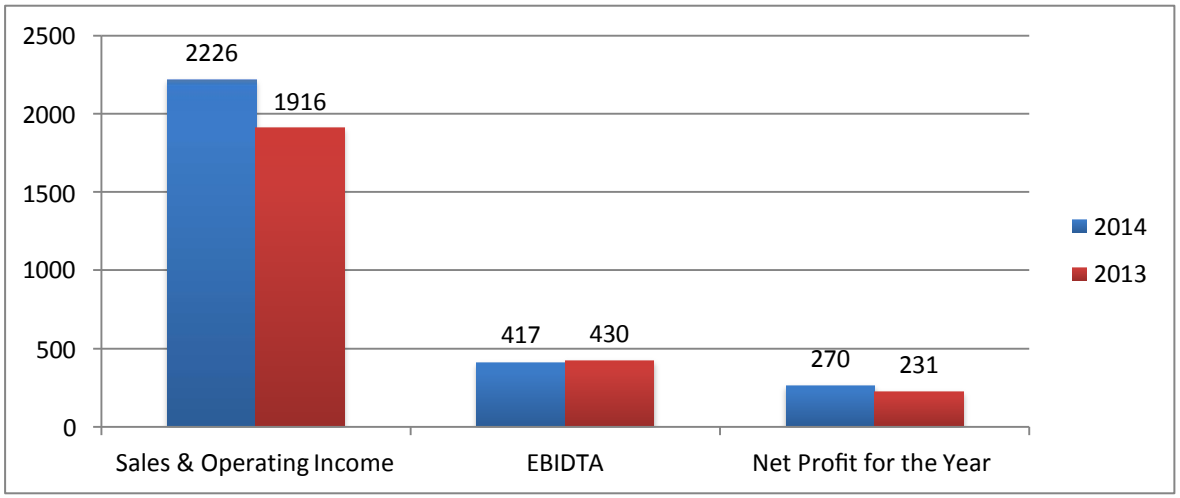
** values are in Rs. Cr*

*source: claris annual report 2014.

Claris revenue for the 2013-14 year has crossed figure of Rs. 2000 cr. As per BMI India Pharmaceuticals and Healthcare report Q1, 2014, claris has market contribution of 1.54% to total Indian pharmaceutical market which is considerable number in highly fragmented Indian pharmaceutical market. Financial year 2013-14 was a good growing year for the claris when company record sales of Rs. 2226 cr domestically and internationally. Net profit elevates from Rs. 231 cr in 2012-13 to Rs. 270 cr in 2013-14, growth of 16.88% in this

year. The share holding pattern of claris Pharmaceuticals Ltd provides the insight of strong holding condition of the promoters. This creates credibility in the ever-changing scenario of the competitive pharmaceutical industry.

Graph 2.2: claris financial performance for the year 2013-14

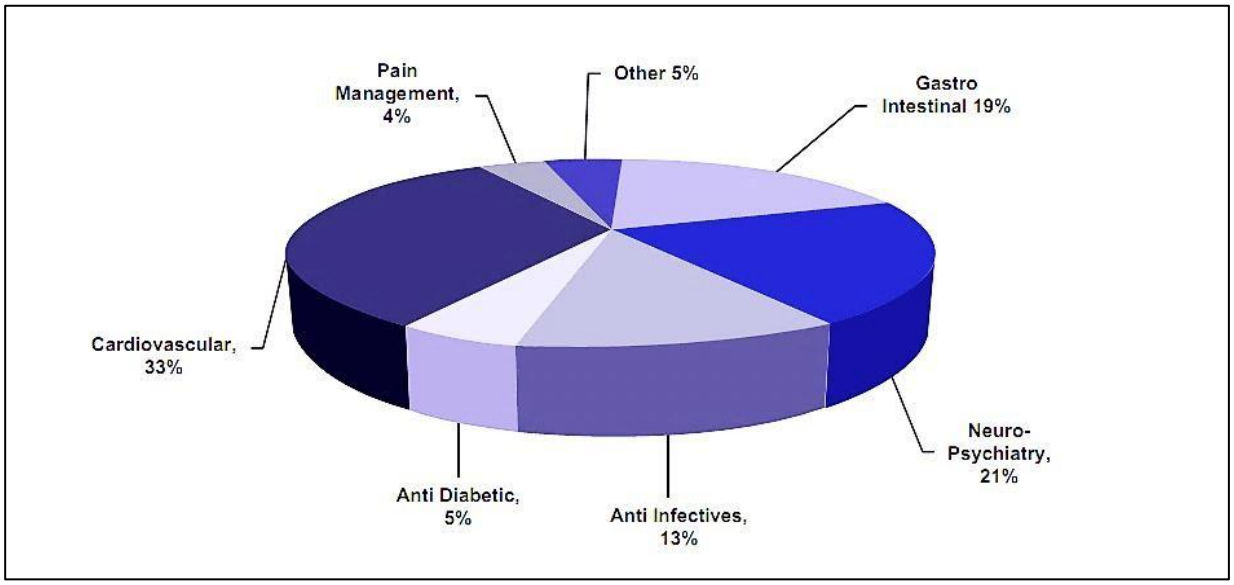


**values are in Rs. Cr*

*source: claris annual report 2014

Cardiovascular segment is the major contributor (33%) to the total revenue generation. Neuro-Psychiatry is the 2nd largest contributing segment (21%) for torrent. Gastro-intestinal segment with 19% contribution to total torrent revenue constitutes 3rd largest segment for company. Anti-infective segment contributes 13% to total revenue. Anti-diabetics segment is 5% contributing to the company.

Graph 2.3: Claris revenue generation from various therapeutic segments

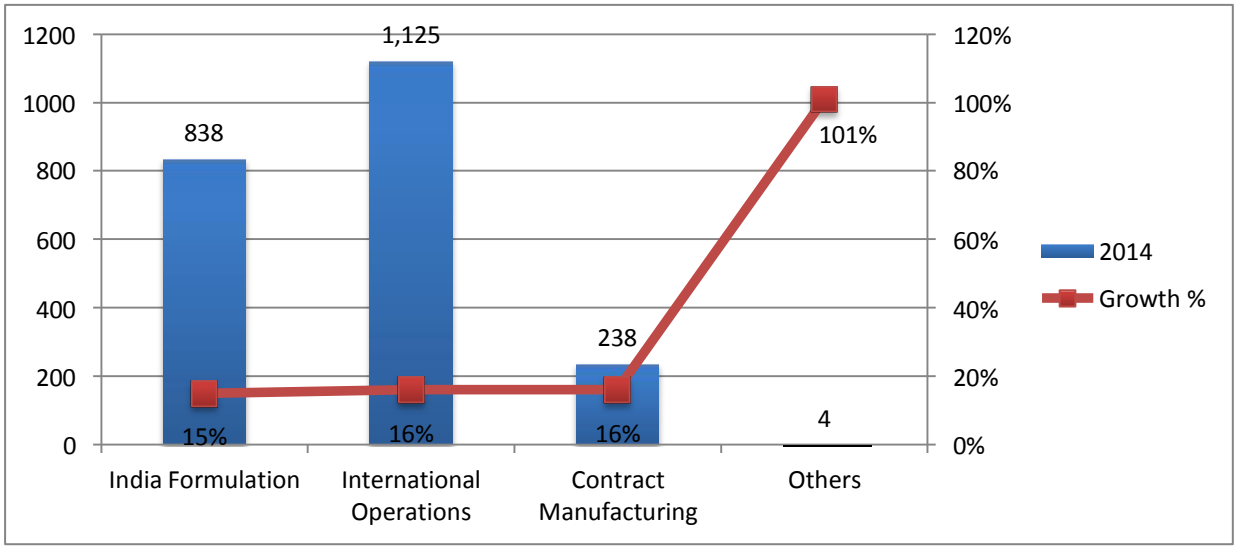


*source: claris annual report 2014

Claris major revenue (>60% of total revenue) come from chronic therapies like CVS, CNS, Anti-diabetics etc. >36% of total torrent revenue come from acute therapy segment. Top 3 therapeutic segments contribute to over 73% of company's revenue. claris has recently entered in the gynecology segment which is having a market size of Rs. 2740 crore growing at 14% (Source: ORG - IMS MAT Mar 14).

International operations is the major revenue generating pie for the Claris Pharmaceutical Limited whose contribution is 51% of total sales. Indian Formulation business contributes 38% revenue generation while Contract manufacturing business constitutes 11% of the total sales. Others business activities have contributed Rs. 4 cr in 2013-14. International operations and contract manufacturing both have noted growth of 16% in last fiscal year. Indian formulation business grows at rate of 15% in 2013-14.

Graph 2.4: Segment wise break-up of claris revenue:



*values are in Rs. Cr

*source: claris annual report 2014

Table 2.1: Human resource at claris

	No. in 2013-14	No.in 2012-13	Growth rate %
Field-force	4059	3364	20.7
R & D center (Scientists)	907 (773)	804 (683)	12.8 (13.2)
Workforce	1354	796	70.1
Others	2683	2000	34.2
Total employees	9003	6964	29.3

*source: claris annual report 2014

2.3 Claris product portfolio

The Company introduced 38 new products during financial year 2013-14 as compared to 55 in financial year 2012-13.The growth in India Formulations revenues based on age of the portfolio is given below:

Table 2.2: Growth of Torrent's product portfolio

Portfolio	**2013-14 Growth**	**2012-13 Growth**
Existing Product	9%	11%
New product introduced in the previous year	3%	1%
New product introduced in the current year	3%	4%
Total	**15%**	**14%**

Claris new product launched in the 2013-14 year shows 3% growth rate by both current and previous year introduction leading to combined 6% growth compare to 5% growth rate in the 2012-2013 year.

3. HYPERLIPIDEMIA

3.1 Introduction

Hyperlipidemia is an excess of fatty substances called lipids, largely cholesterol and triglycerides, in the blood. It is also called hyperlipoproteinemia because these fatty substances travel in the blood attached to proteins. This is the only way that these fatty substances can remain dissolved while in circulation. Hyperlipidemia, in general, can be divided into two subcategories:

- Hypercholesterolemia-: In which there is a high level of cholesterol
- Hypertriglyceridemia-: In which there is a high level of triglycerides, the most common form of fat.

The fat-protein complexes in the blood are called lipoproteins. There are mainly five types of lipoproteins.

1. Chylomicron
2. VLDL (Very low density lipoprotein)
3. LDL (Low density lipoprotein)
4. IDL (Intermediate density lipoprotein)
5. HDL (High density lipoprotein)

The best-known lipoproteins are LDL (low density lipoprotein) and HDL (high density lipoprotein). Excess LDL cholesterol contributes to the blockage of arteries, which eventually leads to heart attack. Population studies have clearly shown that the higher the level of LDL cholesterol, the greater the risk of heart disease. This is true in men and women, in different racial and ethnic groups, and in all adult age groups. Hence, LDL cholesterol has been labeled the bad cholesterol. In contrast, the lower the level of HDL cholesterol, the greater the risk of coronary heart disease. As a result, HDL cholesterol is commonly referred to as the good cholesterol. Low HDL cholesterol levels are typically accompanied by an increase in blood triglyceride levels. Studies have shown that high triglyceride levels are associated with an increased risk of coronary heart disease.

High lipid level causes serious health complications including

- Coronary artery diseases
- Acute MI
- Stroke
- Diabetes

Desirable lipid levels are as follows.

- LDL less than 130 mg/dL or < 70 if you have established diagnosis of diabetes
- HDL greater than 40 mg/dL (men) or 50 mg/dL (women);
- Total cholesterol less than 200 mg/dL; and
- Triglycerides less than 200 mg/dL or 150 if you have established heart disease or diabetes

*Source- NCEP ATP III guidelines

3.2 Causes and Risk Factors

Common secondary causes of hypercholesterolemia (specifically, high LDL cholesterol) includes

- Hypothyroidism (that is, low thyroid hormone levels)
- Pregnancy and kidney failure.

Common secondary causes of hypertriglyceridemia include

- diabetes
- excess alcohol intake
- obesity
- Certain prescription medications (such as glucocorticoids and estrogen).

Hyperlipidemia, along with diabetes, hypertension, positive family history of CHD,obesity, sedentary lifestyle and smoking are all major risk factors for coronary heart disease.

3.3 Pathophysiology of hyperlipidemia

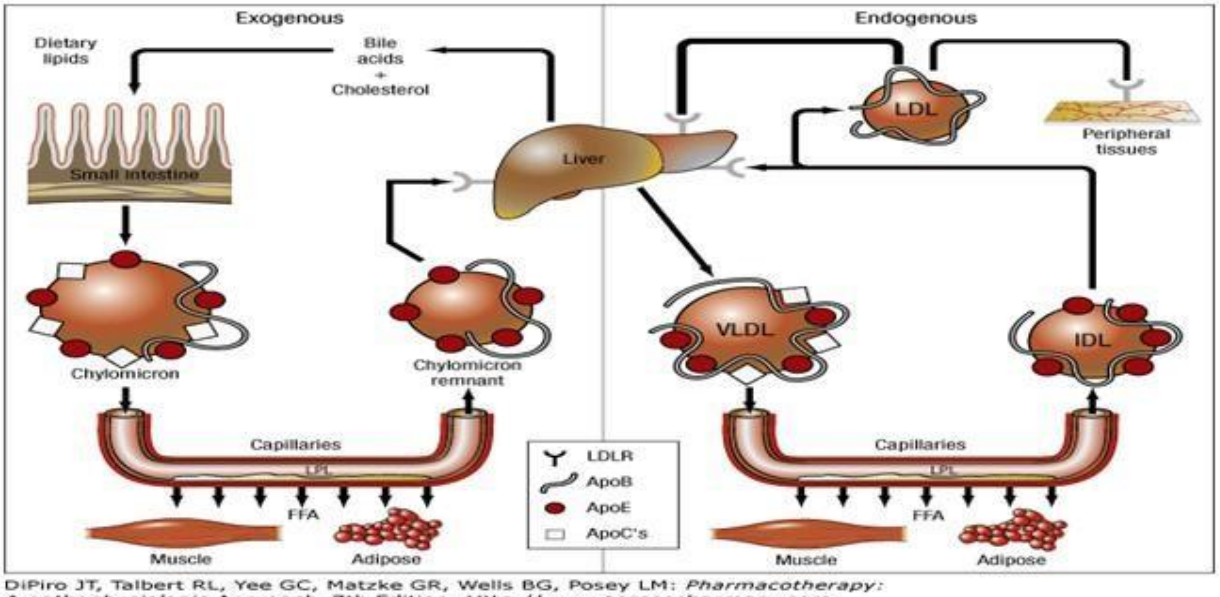
Cholesterol is essential for cell membrane formation & hormone synthesis. Lipids are not present in free form in plasma but circulate as lipoproteins. There are mainly three major plasma lipoproteins

- **VLDL** carries ~10 to 15 % of total serum cholesterol; carried in circulation as TG
- **LDL** carries 60 to 70% of total serum cholesterol; IDL is also included in this group
- **HDL** carries 20 to 30% of total serum cholesterol; reverse transportation of cholesterol

VLDL secreted from the liver is converted to IDL then LDL. Plasma LDL taken up by receptors on liver, adrenal, & peripheral cells. LDL internalized & degraded by these cells. An increased intracellular cholesterol level inhibits HMG-CoA reductase & decreases LDL receptor synthesis .Because of the decreases in LDL receptors the plasma LDL is not readily taken up & broken down by cells.

LDL also excreted in bile joins enterohepatic pool eliminated in stool. It can be oxidized in subendothelial space of arteries these Oxidized LDL in artery walls provokes inflammatory response. Monocytes recruited & transformed into macrophages results in cholesterol laden foam cell accumulation Foam cells begins the formation of arterial fatty streak If processes continues there is a risk of angina, stroke, MI, peripheral artery disease, arrhythmias, and death.

Fig3.1: Pathophysiology of Hyperlipidemia



DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A pathophysiologic Approach*, 7th Edition: Http://www.accesspharmacy.com

3.4 TYPES OF HYPERLIPOPROTEINEMIA

Hyperlipidemia (elevation of cholesterol levels and/or triglyceride levels) has been defined by the Fredrickson classification, which is based on a beta-quantification, a process involving ultracentrifugation followed by electrophoresis. In this system, all categories except type IIa are forms of hTG.

Table-3.1: Types of Hyperlipoproteinemia

Hyperlipoproteinemia	Increased lipoprotei	Defect	Treatments
Type I	Chylomicrons	Decresed lipoprotein lipase or altered Apo-C2	Diet control
Type IIa	LDL	LDL receptor deficiency	Statins, Bile acid sequestrants,niacin
Type IIb	LDL & VLDL	Decreased LDl receptor & increased apo-B	Statins,Niacin , Fibrates
Type III	IDL	Defect in Apo-E2 synthesis	Statins, Fibrates
Type IV	VLDL	Increased VLDL production.	Statins,Niacin , Fibrates
Type V	VLDL & Chylomicrons	Increased VLDL production.	Niacin, Fibrate.

Type I is a rare disorder characterized by severe elevations in chylomicrons and extremely elevated triglycerides, always reaching well above 1000 mg/dL and not infrequently rising as high as 10,000 mg/dL or more. It is caused by mutations of either the lipoprotein lipase gene (*LPL*), which is critical for the metabolism of chylomicrons or very low-density lipoprotein (VLDL), or of the gene's cofactor, apolipoprotein (apo) C-II.

Type IIb is the classic mixed hyperlipidemia (high cholesterol and triglyceride levels), caused by elevations in LDL and VLDL.

Type III is known as dysbetalipoproteinemia, remnant removal disease, or broad-beta disease typically; patients with this condition have elevated total cholesterol and triglyceride levels and are easily confused with patients with type IIb hyperlipidemia. Patients with type III hyperlipidemia have elevations in intermediate-density lipoprotein (IDL), a VLDL remnant, and a significant risk for developing coronary artery disease.

Type IV is characterized by abnormal elevations of VLDL, and triglyceride levels are almost always less than 1000 mg/dL. Serum cholesterol levels are normal.

Type V is characterized by elevations of chylomicrons and VLDL. Triglyceride levels are invariably greater than 1000 mg/dL, and total cholesterol levels are always elevated. The LDL cholesterol level is usually low.

3.5 Symptoms and Diagnosis of Hyperlipidemia

Hyperlipidemia usually has no noticeable symptoms and tends to be discovered during routine examination or evaluation for atherosclerotic cardiovascular disease. However, deposits of cholesterol may form under the skin (especially around the eyes or along the Achilles tendon) in individuals with familial forms of the disorder or in those with very high levels of cholesterol in the blood. Individuals with hypertriglyceridemia may develop numerous pimple-like lesions across their body. Extremely high levels of triglycerides may also result in pancreatitis, a severe inflammation of the pancreas that may be life-threatening. Diagnosis is typically based on medical history, physical examination, and blood tests (done after overnight fasting) in order to determine the specific levels of LDL cholesterol, HDL cholesterol, and triglycerides.

4. TREATMENTS OF HYPERLIPIDEMIA

4.1 Available Treatments

Initial treatment of hyperlipidemia includes dietary changes, weight reduction and exercise. If lifestyle modification is not sufficient for achieving optimal lipid levels then drug treatment should be considered. Life style changes should includes

- Restricted total fats, saturated fats, cholesterol intake
- Modest increase in polyunsaturated fat
- Increased soluble fiber intake
- Exercise: moderate intensity 30 min/day most days
- Weight reduction (initial goal of 10%) if needed
- Smoking cessation

There are mainly five drug classes which are used in the treatment of hyperlipidemia.

1) Statins
2) Fibrates
3) Niacin
4) Bile acid sequestering resins
5) Cholesterol absorption inhibitors

Table-4.1: Treatments of Hyperlipidemia

Drug	Mechanism of Action	Effects on Lipids	Effects on Lipoprotein
Cholestyramine resin	↑ LDL catabolism ↓ Cholesterol absorption	↓Cholesterol	↓ LDL ↓ VLDL
Niacin	↓ LDL and VLDL synthesis	↓ Triglyceride ↓Cholesterol	↓ LDL ↑ HDL
Fibrates	↑ VLDL clearance ↓ VLDL synthesis	↓ Triglyceride ↓Cholesterol	↓ VLDL ↓ LDL ↑ HDL
Statins	**↑ LDL catabolism; inhibit cholesterol synthesis**	**↓Cholesterol**	**↓ LDL**
Ezetimibe	Blocks cholesterol absorption	↓Cholesterol	↓ LDL

4.2 Statins: Best treatment of Hyperlipidemia

3-Hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase catalyzes the conversion of HMG-CoA to mevalonate during cholesterol synthesis. Statins competitively inhibit HMG-CoA reductase, thereby lowering serum cholesterol levels. HMG-CoA reductase is the rate-limiting enzyme in de novo cholesterol synthesis. HMG-CoA reductase inhibitors reduce the production of mevalonic acid from HMG-CoA, resulting in a reduction in hepatic cholesterol synthesis. This in turn results in a compensatory increase in the expression of high affinity low-density lipoprotein (LDL) receptors on hepatocyte membranes and stimulation of LDL catabolism.

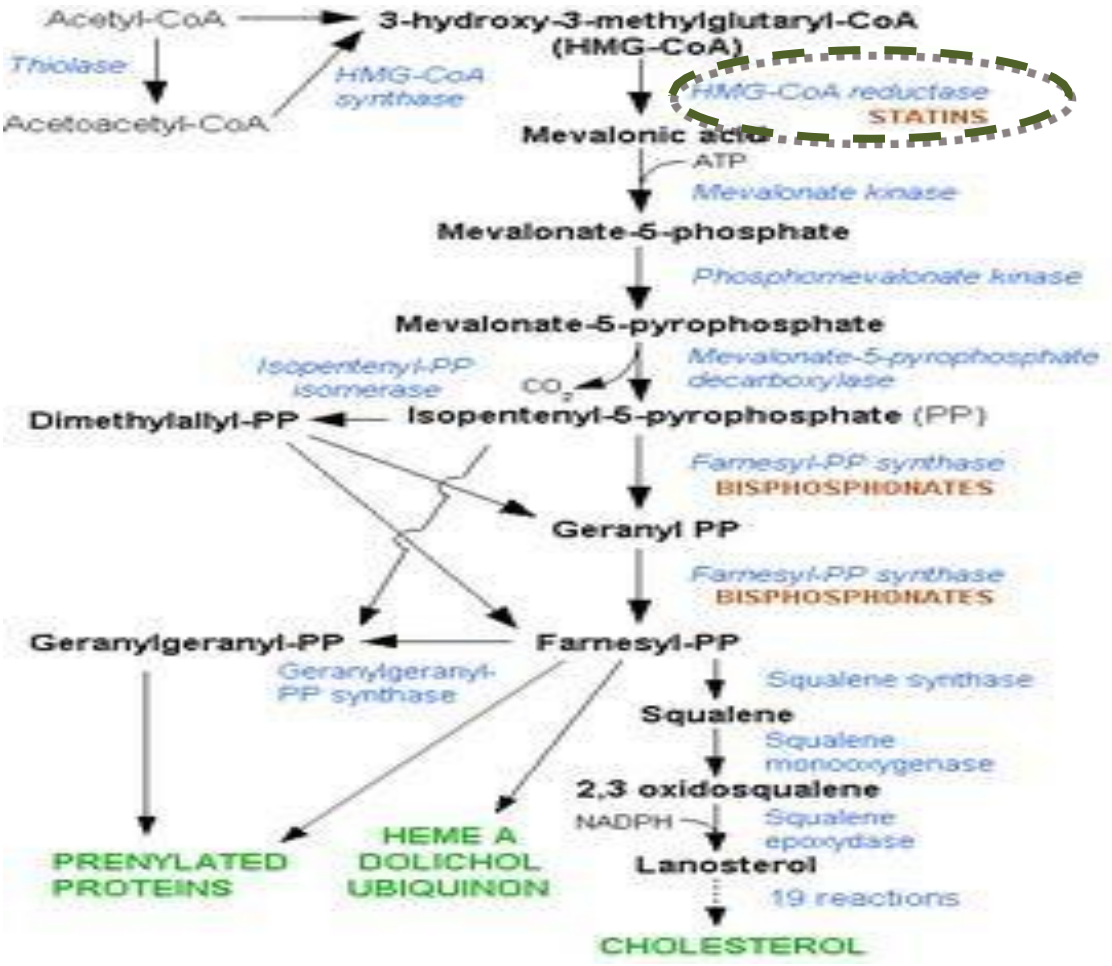
Cholesterol is critical to the normal function of every cell in the body. However, it also contributes to the development of atherosclerosis, a condition in which cholesterol-containing plaques form within arteries. These plaques block the arteries and reduce the flow of blood to the tissues that arteries supply. When plaques rupture, a blood clot forms on the plaque, thereby further blocking the artery and reducing the flow of blood. When blood flow is reduced sufficiently in the arteries that supply blood to the heart, the result is angina (chest pain) or a heart attack. By reducing the production of cholesterol, statins are able to slow the formation of new plaques and occasionally can reduce the size of plaques that already exist. In addition, through mechanisms that are not well understood, statins may also stabilize plaques and make them less prone to rupturing and promoting the development of clots. Statins differ in several ways. The most obvious difference is in their ability to reduce cholesterol. Currently, atorvastatin and rosuvastatin are the most potent.

Statins also has non-cholesterol related role as follows.

- Improving endothelial function
- Modulate inflammatory responses
- Maintain plaque stability
- Prevent thrombus formation

Currently Atorvastatin and Rosuvastatin are the two most prescribed statins in the statin therapy.

Fig-4.1: Mechanism of Action of Statins



4.3 Comparison of Atorvastatin and Rosuvastatin

ATORVASTATIN

- Atorvastatin is a synthetic, selective reversible competitive inhibitor of HMG-CoA reductase, the enzyme that catalyzes the irreversible, rate-limiting reaction in which 3-hydroxy-3-methyl glutaryl-coenzyme A (HMG-CoA) is converted to mevalonate, a precursor of sterols.

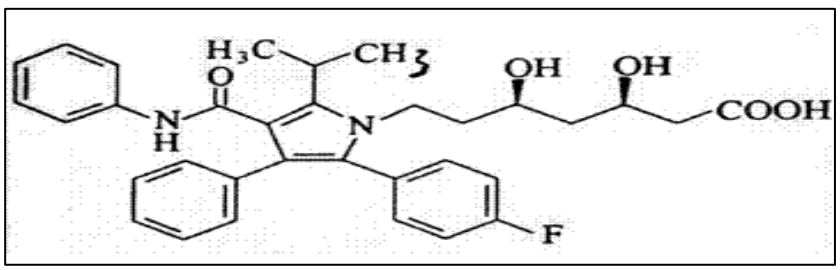


Fig-4.2: Structure of Atorvastatin molecule

Pharmacokinetics of Atorvastatin

- It is rapidly absorbed and peak plasma level occurs at ~2.5 hrs
- Due to extensive first-pass metabolism, the bioavailability of the parent drug is ~12% and it is not significantly affected by food. However, the bioavailability of HMG-CoA reductase inhibitory activity is ~ 30%
- Atorvastatin is >98% bound to plasma proteins and is extensively metabolized by cytochrome P450 3A4 to active metabolites, which account for about 70% of the circulating HMG-CoA reductase inhibitory activity.
- Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however the drug does not appear to undergo enterohepatic re-circulation.
- Mean plasma elimination half-life is ~ 14 hrs, but because the contribution of active metabolites, the half-life of HMG-CoA reductase inhibitory activity is ~24 hrs. Since the kidney plays no role in the disposition of atorvastatin, dosage adjustment in patients with renal impairment is not necessary

Side effects

- Gastrointestinal side effects like

  - Flatulence
  - Abdominal pain
  - Constipation

- Hepatic side effects like

  - Altered liver function
  - Cholestatic jaundice

- Musculoskeletal side effects like

  - Rhabdomyolysis, Myalgia

Drug interactions

- Concurrent use of atorvastatin and drugs that may interfere with its metabolism (Cytochrome P450 3A4) or its protein binding like erythromycin, azole antifungals (e.g. ketoconazole or fluconazole), cyclosporine, gemfibrozil,HIV protease inhibitors,

macrolides, Streptogramins, verapamil or niacin may increase serum concentrations of atorvastatin and the risk of myopathy.

- Concurrent use of atorvastatin may increase digoxin serum concentrations
- Bosentan, carbamazepin, efavirenz or rifampin may decrease atorvastatin effectiveness.

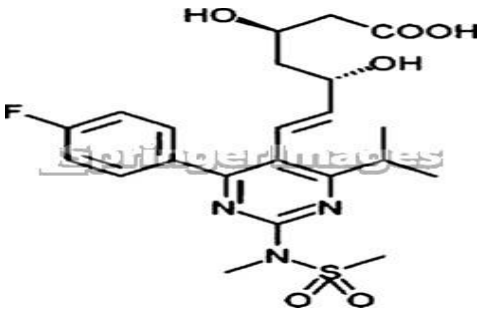
Dosage

- Initial dose: 10 mg once daily;
- Range: 10 to 80 mg once daily, and can be given as a single dose.
- Dose can be given at any time of the day with or without food.
- Dose should be changed based on the observed response and the goal of therapy.

ROSUVASTATIN

- Rosuvastatin is a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is used for the treatment of hypercholesterolemia. HMG-CoA reductase is the rate-limiting enzyme in de novo cholesterol synthesis. HMG-CoA reductase inhibitors reduce the production of mevalonic acid from HMG-CoA, resulting in a reduction in hepatic cholesterol synthesis. This in turn results in a compensatory increase in the expression of high affinity low-density lipoprotein (LDL) receptors on hepatocyte membranes and stimulation of LDL catabolism. It is in this manner that rosuvastatin produces the lowering of plasma total and LDL cholesterol levels observed in patients with hypercholesterolemia.

Fig-4.3: Structure of Rosuvastatin molecule



Pharmacokinetic

Rosuvastatin is metabolized by liver enzyme CYP4502C9. However hepatic metabolism is very less. Most of the rosuvastatin is excreted unchanged in the feces. Major metabolite is N-desmethyl rosuvastatin and it is an active metabolite. Its bioavailability is more compared to atorvastatin.

Adverse effects and contraindications

- Contraindicated in Active liver disease or unexplained persistent elevations of serum transaminases & in Pregnancy and lactation.
- Rhabdomyolysis
- Unexplained muscle pain
- Kidney failure
- Dyspepsia

Drug interactions

- Cyclosporin
- Warfarin
- Gemfibrozil

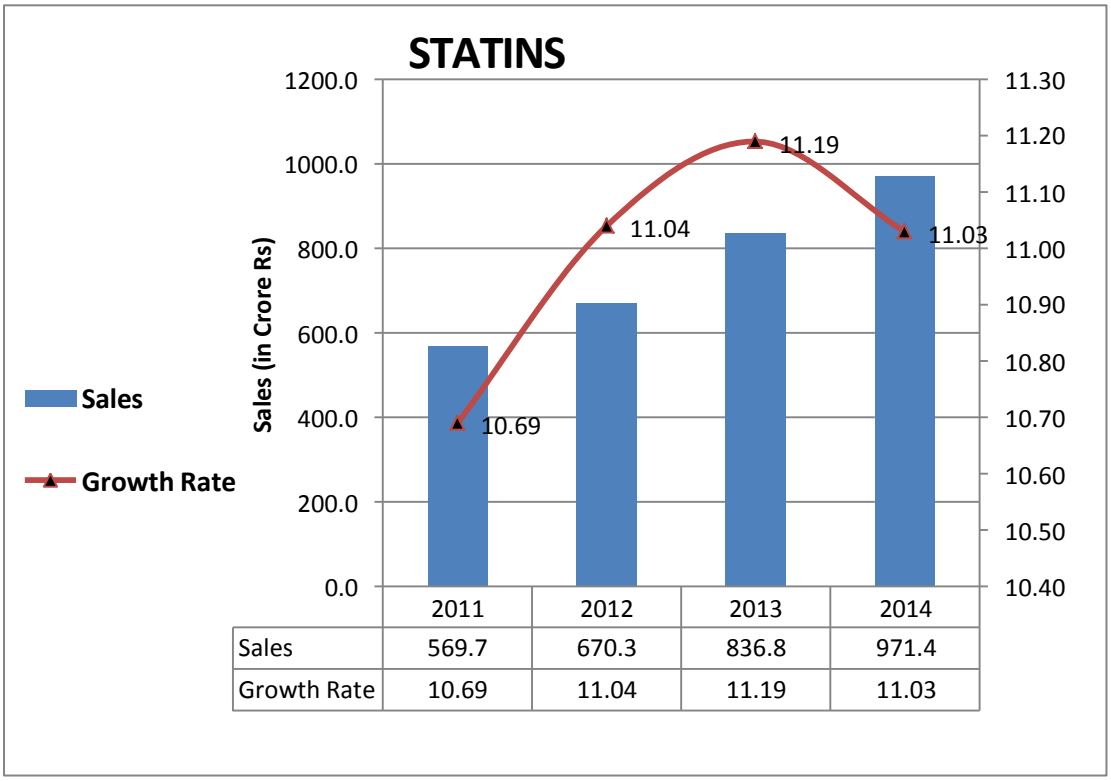
Table-4.2: Comparison of Atorvastatin and Rosuvastatin

Attributes	Rosuvastatin	Atorvastatin
potency	High	low
Absolute bioavailability	20%	12%
Protein binding	88%	98%
Volume of distribution	134 L	565 L
Metabolism	Minimal hepatic metabolism. Metabolized by CYP450 2C9.	Hydrolyzed by liver (CYP450 3A4)
Excretion	Feces(90%) Urine(10%)	Feces (98%) Urine (2%)
Half-life	19 hours	14 hours
Effect on kidney	Damaging	Protecting
Cost of Therapy	High	Low

4.4 Current statin market scenario

- Statin constitute one of the most important sectors of the pharmaceutical industry, with total revenues exceeding $25 billion in 20.statin market in India is also growing.
- Total statin market is growing year by year with a CAGR (2011-2014) of 14.27%.
- Total statin market is around 971 crore Rs.

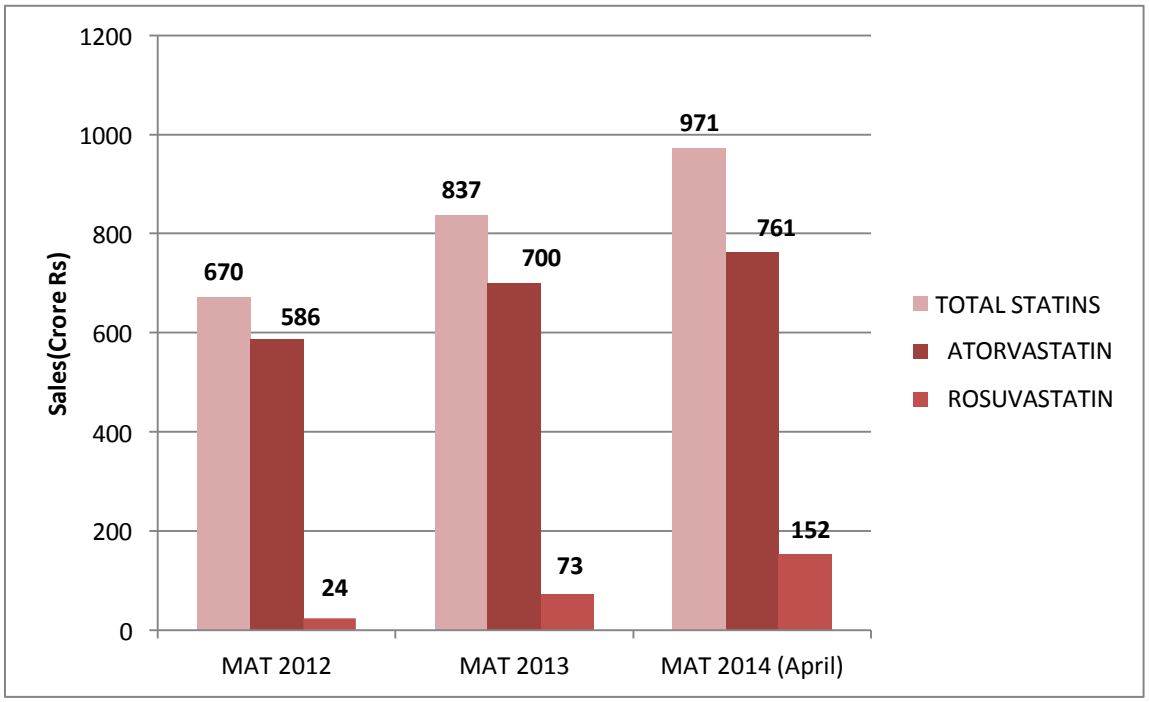
Graph-4.1: Statin market overview



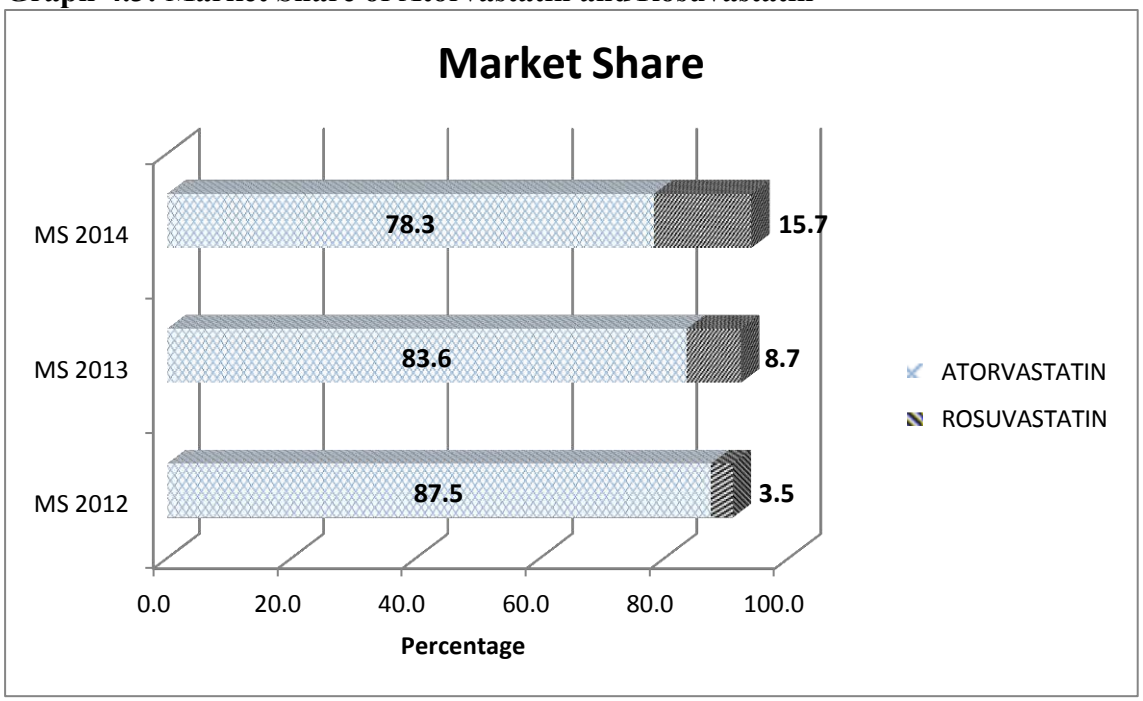
	2011	2012	2013	2014
Sales	569.7	670.3	836.8	971.4
Growth Rate	10.69	11.04	11.19	11.03

- In current statin market atorvastatin is the leading molecule with the highest market share.
- On the second position Rosuvastatin molecule is there with market share of 15.7% but growing at very high rate
- Rosuvastatin is new molecule however it is growing at a rate of more than 100%.
- Since the last three years Atorvastatin market share and growth rate is declining, whereas Rosuvastatin market share and growth rate is increasing at a higher rate.

Graph-4.2: Atorvastatin and Rosuvastatin sales



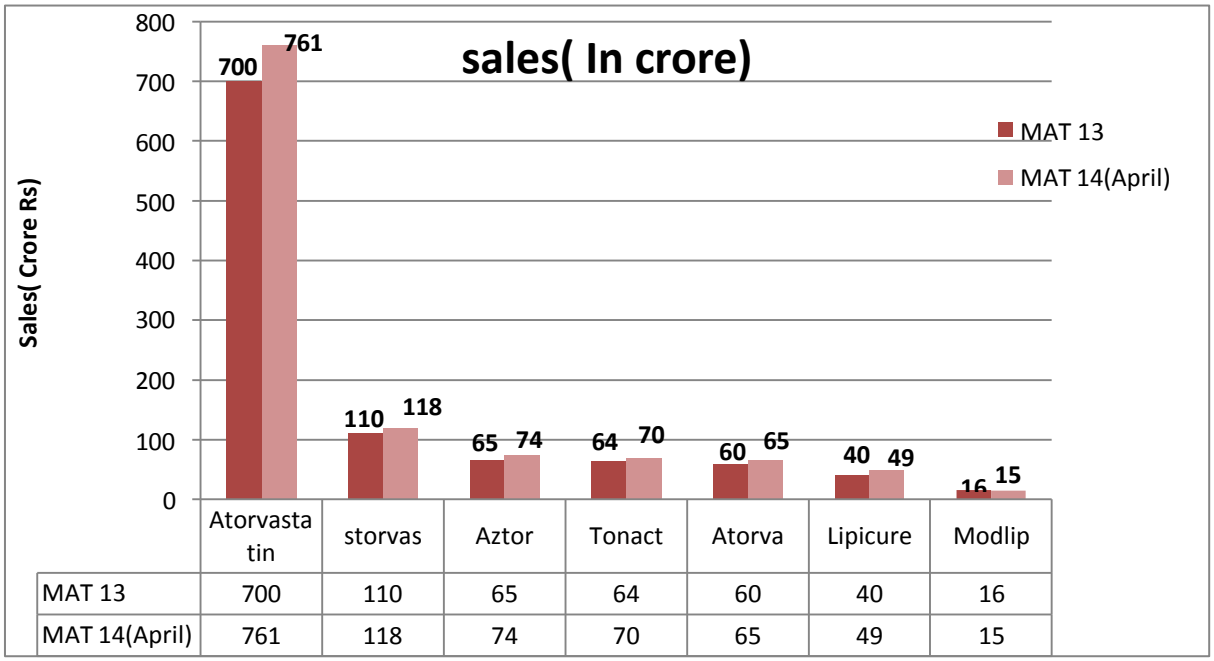
Graph-4.3: Market Share of Atorvastatin and Rosuvastatin



Comparison of various Atorvastatin brands

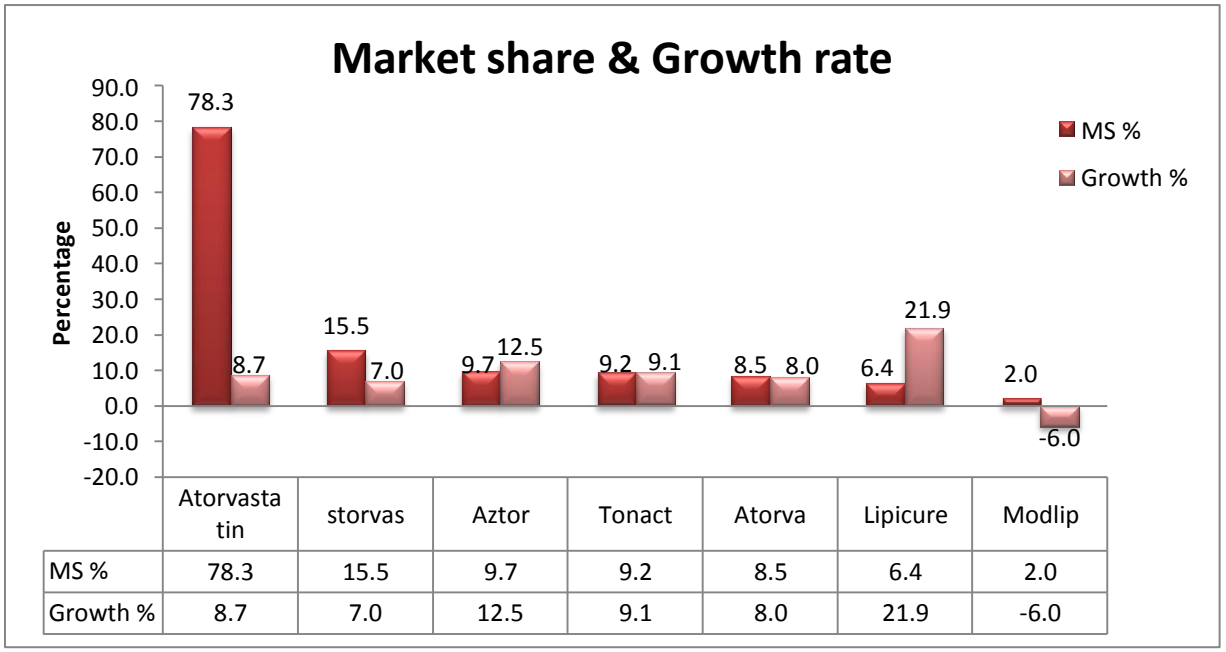
- Atorvastatin is the leading molecule in statin therapy. There are large no of atorvastatin brands in the market.
- Storvas is the leading brand in atorvastatin therapy with a market share of 15.5%.
- Modlip has a sales of 15 crore in 2014 with a Market share of 2%

Graph-4.4: Atorvastatin brands sales



	Atorvastatin	storvas	Aztor	Tonact	Atorva	Lipicure	Modlip
MAT 13	700	110	65	64	60	40	16
MAT 14(April)	761	118	74	70	65	49	15

Graph-4.5: Atorvastatin brands market share

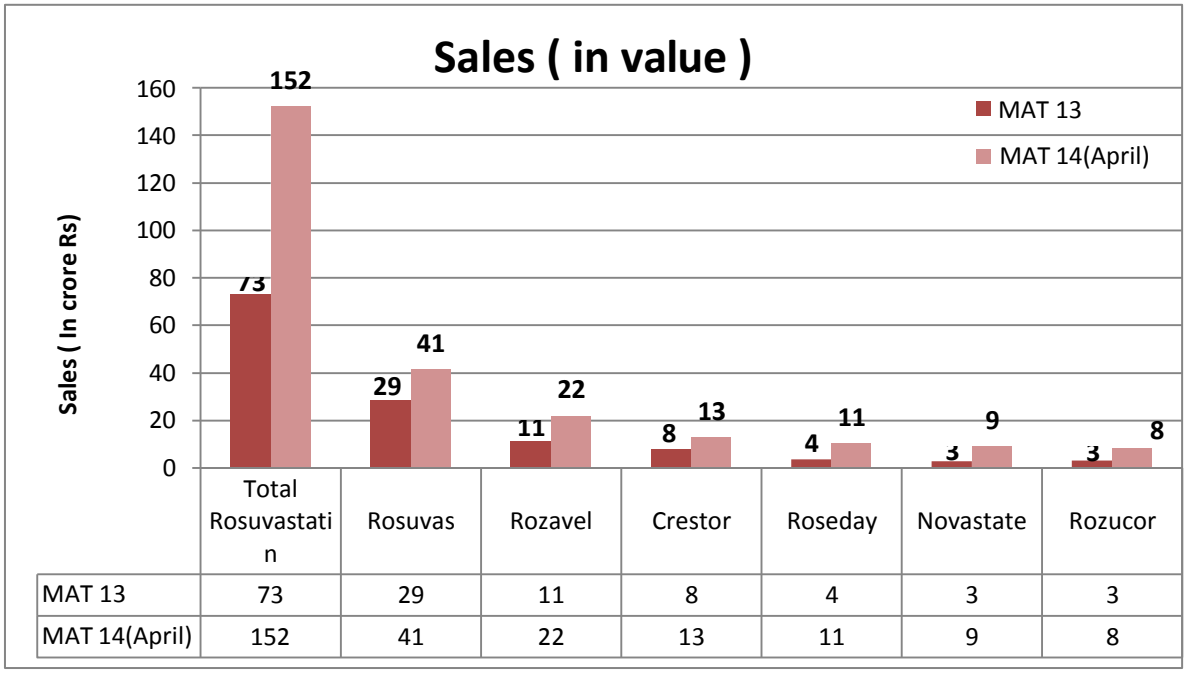


	Atorvastatin	storvas	Aztor	Tonact	Atorva	Lipicure	Modlip
MS %	78.3	15.5	9.7	9.2	8.5	6.4	2.0
Growth %	8.7	7.0	12.5	9.1	8.0	21.9	-6.0

Comparison of various Rosuvastatin brands

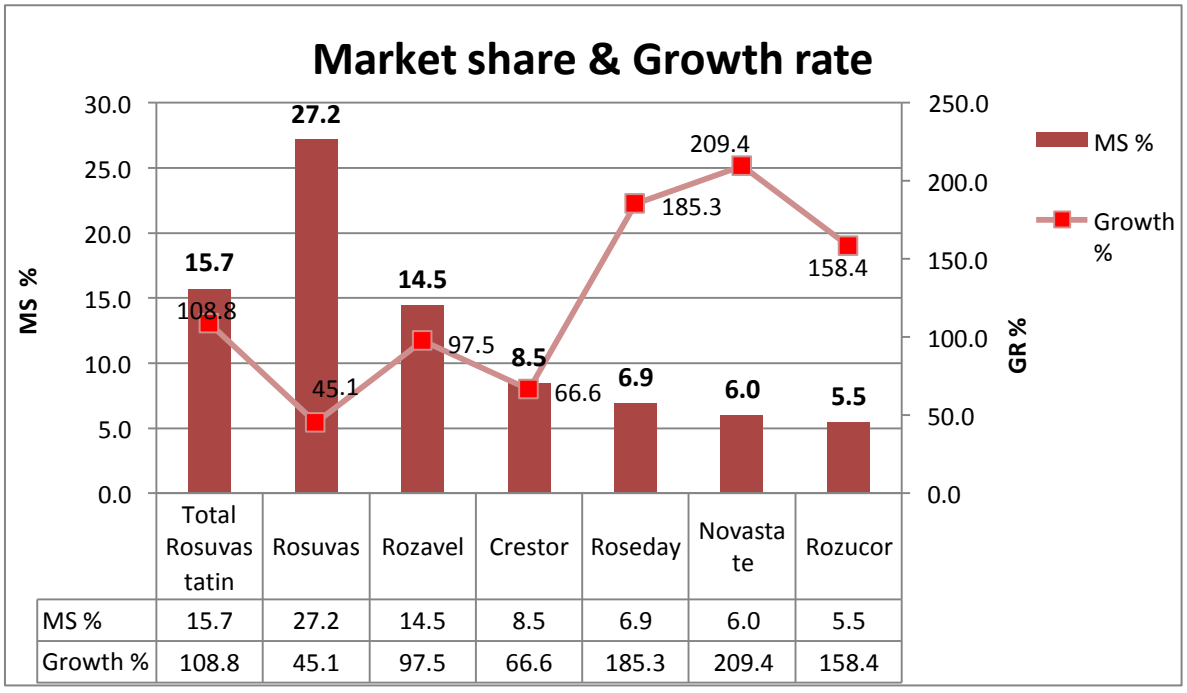
- Rosuvastatin is a new molecule however it is growing at a faster rate. There are less no of rosuvastatin brands available in the market.
- Rosuvas is the brand leader with the 27.2% market share, whereas Rozucor is having the market share of 5.5%.

Graph-4.6: Rosuvastatin brands sales



	Total Rosuvastatin	Rosuvas	Rozavel	Crestor	Roseday	Novastate	Rozucor
MAT 13	73	29	11	8	4	3	3
MAT 14(April)	152	41	22	13	11	9	8

Graph-4.7: Market share of Rosuvastatin brands



	Total Rosuvastatin	Rosuvas	Rozavel	Crestor	Roseday	Novastate	Rozucor
MS %	15.7	27.2	14.5	8.5	6.9	6.0	5.5
Growth %	108.8	45.1	97.5	66.6	185.3	209.4	158.4

5. PRIMARY MARKET RESEARCH & THEIR FINDING

5.1 Questionnaire preparation

Questionnaire for Statins is prepared to accomplish primary and secondary objective of the study. Primary and Secondary objective of the study is as followings:

Primary Objective:

- To assess market and find out the current status of Statin therapy.
- To determine the future trends in statin therapy.

Secondary Objective:

1. Comparative analysis of 2 most prescribed statins :
   a) Atorvastatin b) Rosuvastatin
2. Comparison of 2 statins based on
   a) Preference
   b) Choice for diabetic patients
   c) In primary prevention of CVD and strength preferred for achieving LDL-C
   d) Major advantages and drawbacks
3. Determine the preference of doctor for monotherapy and combination therapy of statins based on LDL-C goals.
4. Find out the unmet needs of statins and suggest options to satisfy those unmet needs.

- **TYPE OF QUESTIONS:**

Open ended question	**2**
Close ended (Multiple Choice)	**8**
Close ended (Dichotomous Choice)	**1**
Branching Question	**1**
Tabular Rating Questions	**1**

5.2 Market research particulars: research tools, sample size, limitations

Fieldwork for data collection regarding use of DPP-IV Inhibitors is conducted in Ahmedabad with keep in view to cover all aspect of market including government and private hospitals, private clinics with posh and general areas of city.

- **Research Type:** Exploratory and Conclusive Research
- **Research Class:** Problem Identification and Problem Solving research
- **Research Instrument:** Questionnaire
- **Technique of data collection:** In-Depth personal interview, probing is done whenever required
- **Sampling Technique:** Random, Convenient Technique & Snowball Technique
- **Sample Size:** 160
- **Target Respondent:** Specialty Covered: MD (Med),Cardiologist
- **Target Area**: Ahmedabad (Tier1 city)
- **Limitation:** Sample size is small and project is carried out in Ahmedabad. Results may vary when generalized to population level. Target sample were majorly MD(Med). Researcher, Respondent & Interviewer errors may occurred during field-work.

5.3 Data analysis and interpretations

For Data analysis and interpretation, following format is used throughout the whole section

- Question
- Question Significance and expected information to be obtained from Question
- Data obtained and analysis applied
- Inference

Q1. **As a 1st line therapy which statin do you normally prefer?**

a) Rosuvastatin **b)** Atorvastatin

Question Significance:

This question is included in the primary Research to find out the Doctors preference to prescribe Statin molecule as a first line therapy of Hyperlipidemia.

Data Obtained:

Graph-5.1: Preference of Doctors in First line therapy

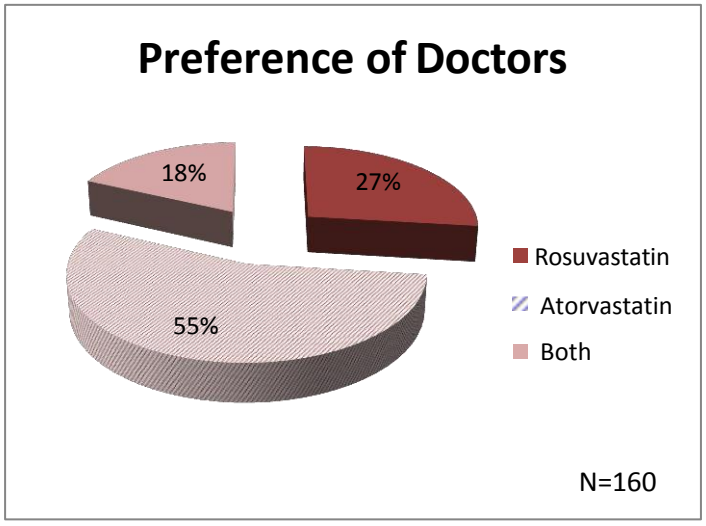


Table-5.1: Preference of Doctors as a First line therapy

Molecule	No of Response
Atorvastatin	88
Rosuvastatin	43
Both	29
Total response	160

- Atorvastatin is well studied molecule and Recommended by NCEP guidelines so most of the Doctors prefer to prescribe Atorvastatin.
- Rosuvastatin is a newer molecule compared to atorvastatin also less no of clinical data is available on the use of Rosuvastatin.
- 18 % doctors use both atorvastatin and Rosuvastatin as a first line agent.

***Q2.* In diabetic dyslipidaemic patients, where increase in TG is of concern, which medication you prefer?**

a) Atorvastatin
b) Rosuvastatin
c) Atorvastatin + Fenofibrate
d) Rosuvastatin + Fenofibrate

If others please specify:_____

Question Significance:

This question gives the information regarding the preference of doctors in Diabetic dyslipidaemic patients and to check whether the doctors prefer combination therapy or not.

Data Obtained:

Graph-5.2: Preference in treatment of Diabetic dyslipidaemia

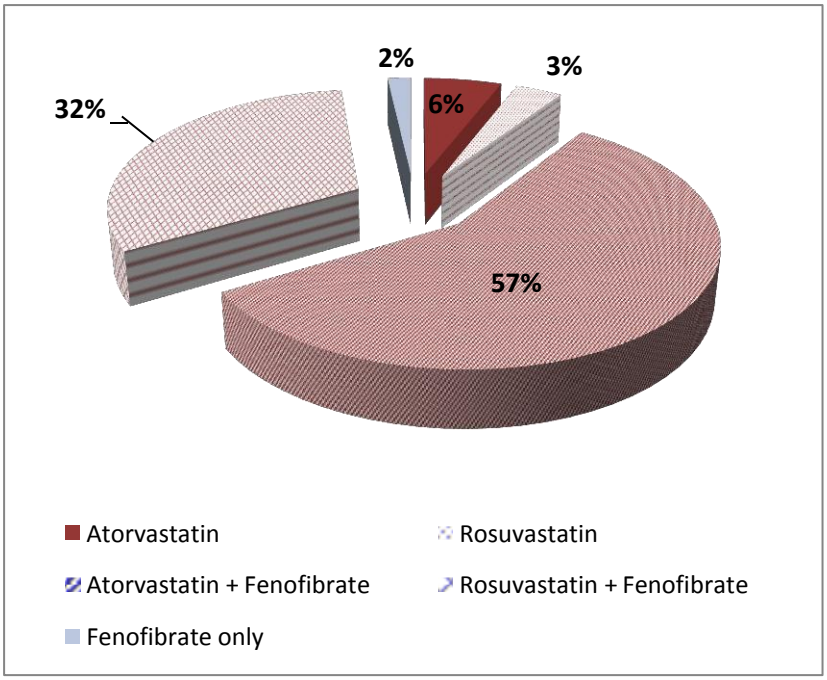


Table-5.2: Preferred Medication in Diabetic dyslipidaemia

Molecule	No of Response
Atorvastatin	10
Rosuvastatin	6
Atorvastatin + Fenofibrate	97
Rosuvastatin + Fenofibrate	54
Fenofibrate only	3
Total	170

- 57 % Doctors prefer Atorvastatin + Fenofibrate & 32 % prefer Rosuvastatin + Fenofibrate combination for the treatment of Diabetic dyslipidaemic patients.
- 2 % doctors use Only Fenofibrate for the treatment of diabetic dyslipidemia.
- From the result we can conclude that Atorvastatin with the combination with Fenofibrate significantly reduce the TG level compared to the monotherapy.so it is the best treatment option available for diabetic dyslipidemia.

- There are three reasons Doctors prefer Atorvastatin + Fenofibrate over Rosuvastatin + Fenofibrate.
  - New to the market
  - Expensive
  - Less clinical data

***Q3a.* Do you prescribe statins for the primary prevention of CVD? (In patients with normal cholesterol but having risk factors)**

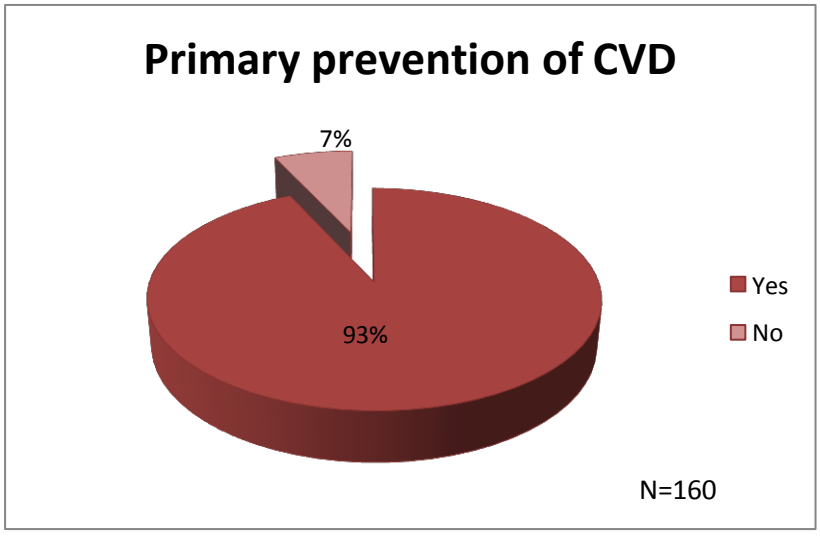
a) Yes b) No

Question Significance:

This Question is included in primary research to know whether Doctors prescribe statins for the primary prevention of cardiovascular diseases especially in those patients with normal cholesterol level.

Data Obtained:

Graph-5.3: Use in Primary prevention



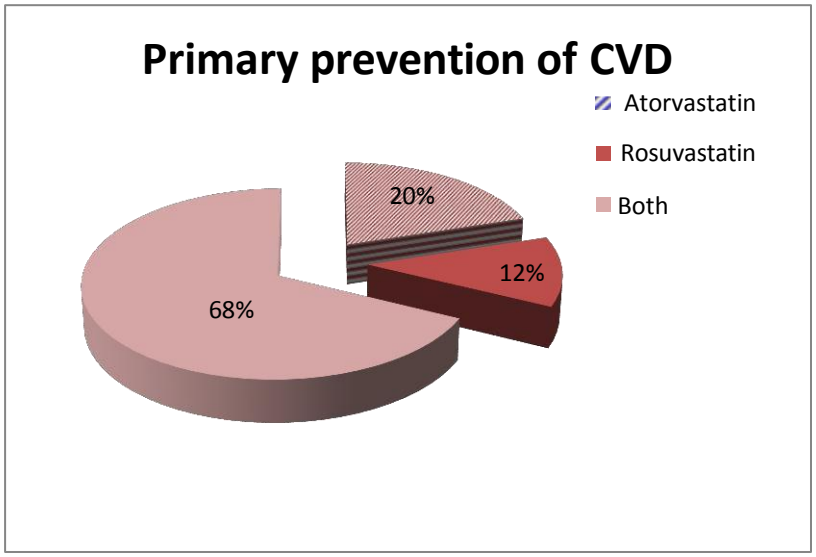
Row Labels	No of Doctor
Yes	149
No	11
Total	160

- This result shows that statins are used in primary prevention of various cardiovascular diseases. (i.e. ACS, Acute MI, Atherosclerosis)
- There is large opportunity for the atorvastatin molecule to be used in primary prevention of Acute MI, Atherosclerosis and other cardiovascular events.

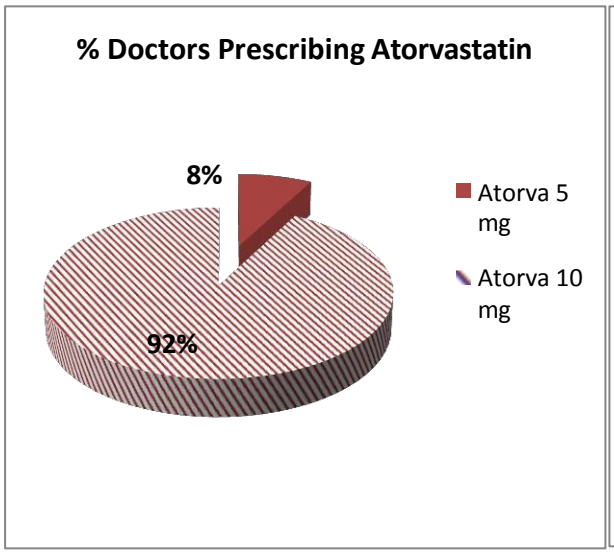
Q3b. If Yes which statin do you prefer and which strength? Please tick (□).

Strength	Atorvastatin	Rosuvastatin
5 mg		
10 mg		

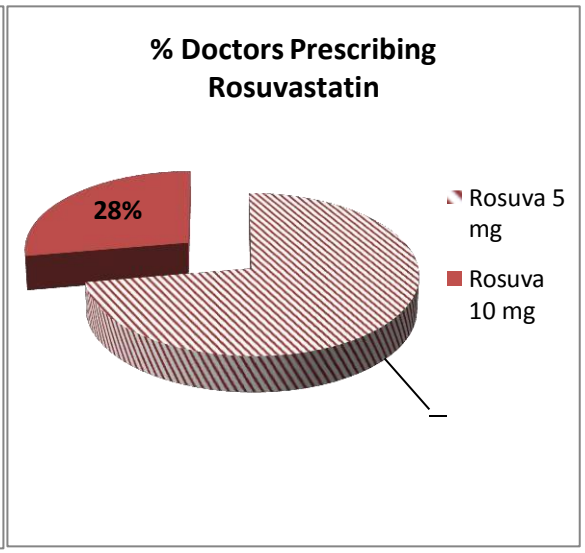
Graph-5.4: Preference in Primary prevention of CVD



Graph-5.5:preferred strength of Atorvastatin in Primary prevention



Graph-5.6: Preferred strength of Rosuvastatin in Primary prevention



- 92 % of the doctors prefer Atorvastatin 10 mg compared to only 8 % of Atorvastatin 5 mg.
- Whereas 72% % doctors prefer Rosuvastatin 5 mg compared to only 22 % of Rosuvastatin 10 mg.

***Q4.* With which strength of Atorvastatin or Rosuvastatin do you normally observe majority of patients achieving their LDL-C goals? Please tick (✍).**

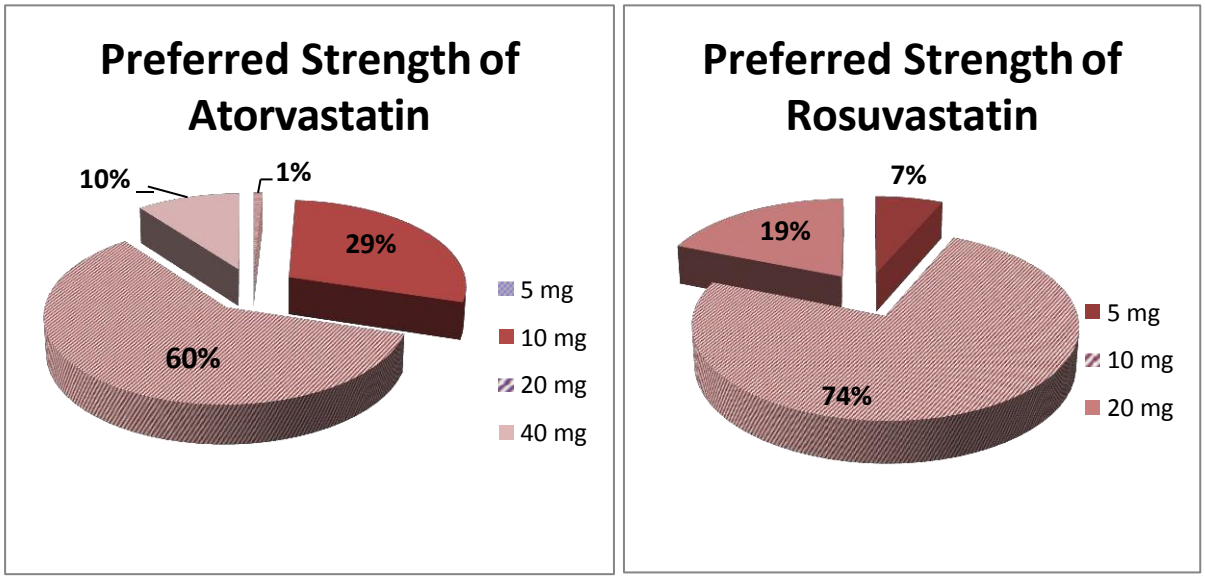
Strengths	Atorvastatin	Rosuvastatin
5 mg		
10 mg		
20 mg		
40 mg		
80 mg		

Question Significance:

This question gives the information regarding the strength preferred for achieving the LDL-C goals. This information is very helpful in deciding which strength is promoted aggressively.

Data Obtained:

Graph-5.7 & 5.8: Preferred strength for achieving LDL-C goals



- Most of the patients achieve their LDL-C goals with the strength of Atorvastatin 20 mg and Rosuvastatin 10 mg.
- Most of the doctors said that usually strength is decided after checking the LDL-C levels. If the LDL-C level is slightly high they usually start the treatment with Atorvastatin 20 mg or Rosuvastatin 10 mg.

***Q5*. In high risk patients who require lower cholesterol goals (LDL-C< 70mg/dl) which strength of the following statin do you prefer?**

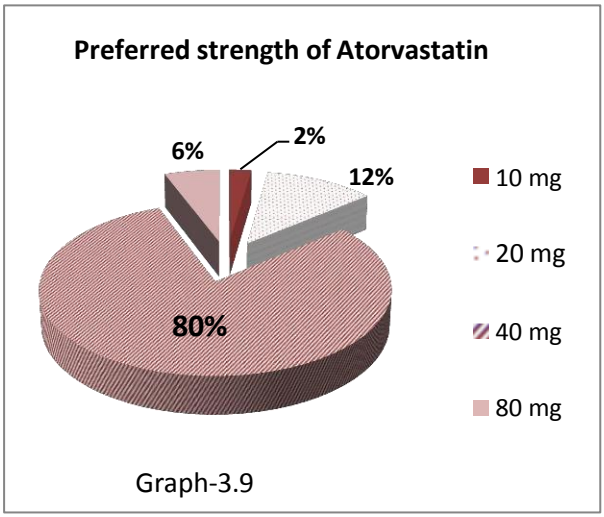
Strength	Atorvastatin	Rosuvastatin
10mg		
20mg		
40mg		
80mg		

Question Significance:

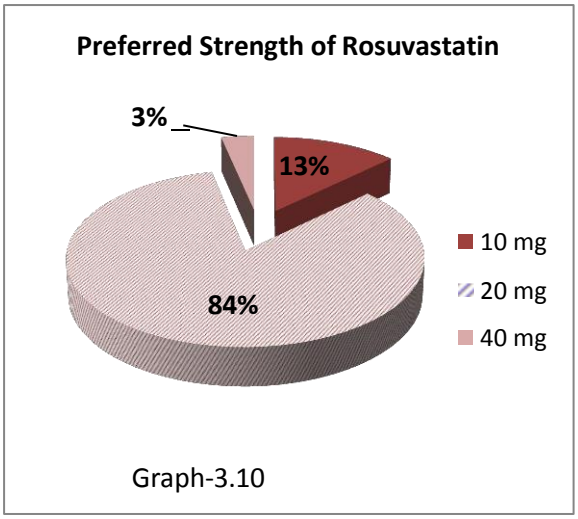
This Question gives the information regarding the preference of doctors for strength of two statin in high risk patients.

Data Obtained:

Graph-5.9 & 5.10: Preferred strength in high risk patients



Graph-3.9



Graph-3.10

- Only 6% doctors prescribe atorvastatin 80 mg which shows that less no of CPs prescribe atorvastatin 80 mg.
- CPs usually does not prescribe Atorvastatin 80 mg because of high risk of developing musculoskeletal side effects. They therefore prefer Atorvastatin 40 mg.
- Mostly Cardiologist prescribe Atorvastatin 80 mg when there is a patient with high risk factors and with high LDL-C levels however they usually switch to lower doses after 10-15 days.

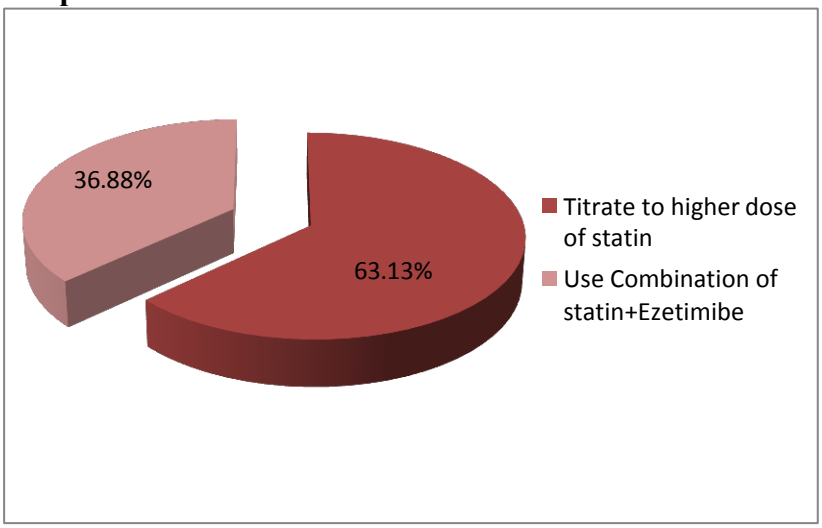
***Q6*. In patients at high risk do you titrate to higher doses of statin or prefer to use a combination with ezetimibe? (To attain LDL-C goals)**

a) Titrate to higher doses of statin

b) Use combination of statin + ezetimibe

Data Obtained:

Graph-5.11: Preference for combination with Ezetimibe



- 63.13 % doctors titrate to higher dose of statin to attain the LDL-C goals.
- 36.88 % doctors use combination of statin + ezetimibe.
- Less safety and pharmacokinetic data is available for the combination so doctors usually titrate to higher dose of statin rather to use combination.

Q7. What according to you are the major concerns in patients undergoing statin therapy?

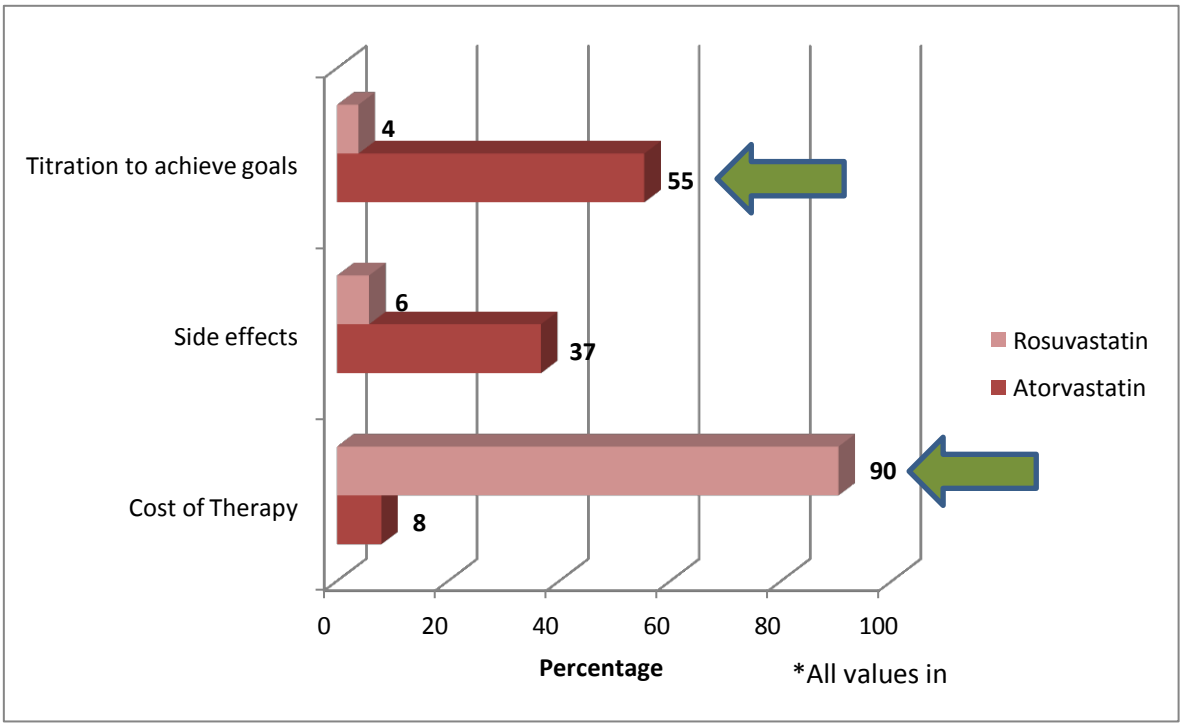
Concerns	Atorvastatin	Rosuvastatin
Cost of therapy		
Side effects		
Titration to achieve goals		
Any other		

Question Significance:

This question gives the information regarding the most influencing factors while prescribing atorvastatin or rosuvastatin.

Data Obtained:

Graph-5.12: Major factors affecting statin therapy



- Rosuvastatin is a costly molecule so main limiting factor experienced by the doctors to prescribe Rosuvastatin widely is cost.
- Atorvastatin is a cheap molecule compared to Rosuvastatin but titration is main concern to achieve the LDL-C goals.
- Side effects of atorvastatin and rosuvastatin are same but most of the doctors also concern about side effects while prescribing Atorvastatin.

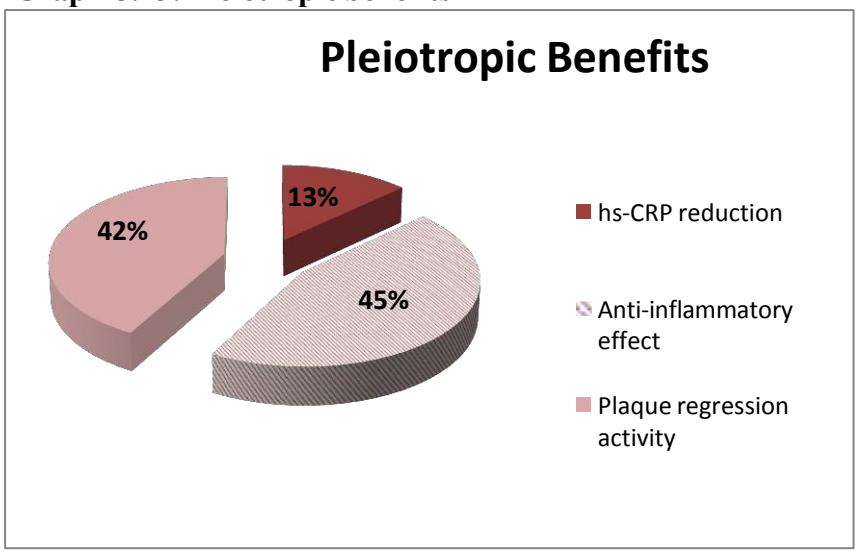
***Q8.* According to you, which pleiotropic benefits of Atorvastatin scores over Rosuvastatin?**

a) hs-CRP reduction b) Anti-inflammatory effect

c) Plaque regression activity Any other please specify _____

Data Obtained:

Graph-5.13: Pleiotropic benefits



- Most of the doctors said that pleiotropic benefits i.e. Anti-inflammatory effect and plaque regression activity of atorvastatin is good compared to rosuvastatin.

***Q9.* Please (□) your opinion on following statements. [1=Strongly Disagree, 5= strongly agree]**

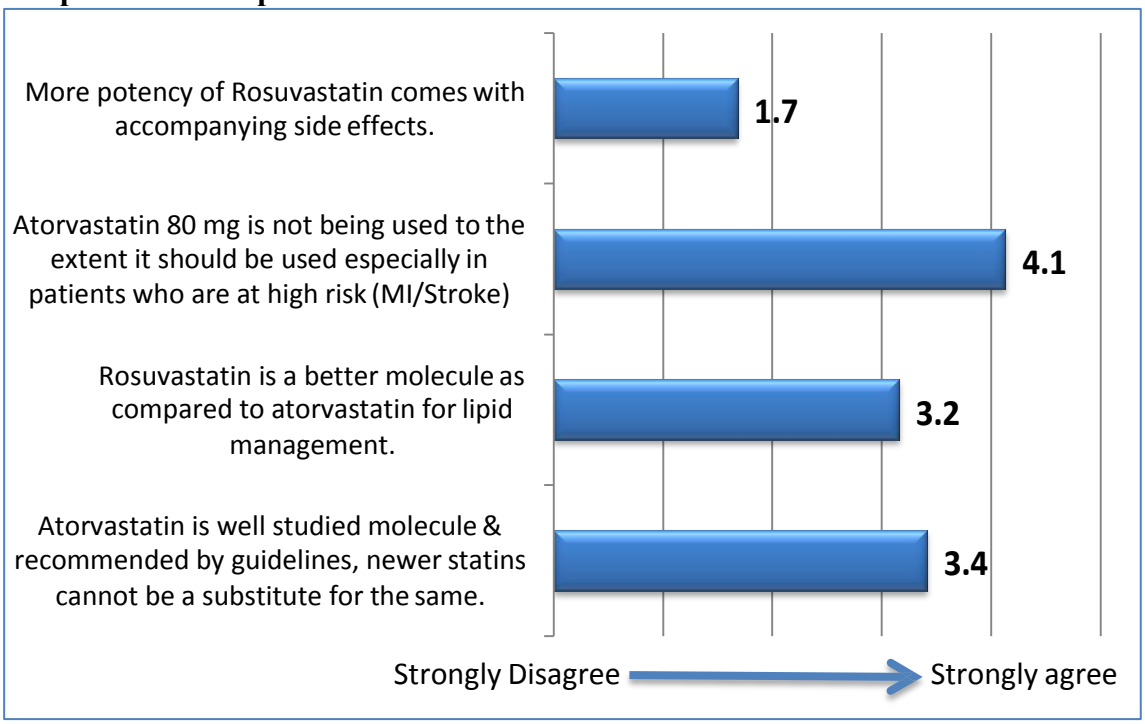
	1	2	3	4	5
Atorvastatin is well studied molecule & recommended by guidelines, newer statins cannot be a substitute for the same.					
Rosuvastatin is a better molecule as compared to atorvastatin for lipid management.					
Atorvastatin 80 mg is not being used to the extent it should be used especially in patients who are at high risk (MI/Stroke)					
More potency of Rosuvastatin comes with accompanying side effects.					

Question Significance:

To check the perception of doctors regarding the Atorvastatin therapy and Rosuvastatin therapy.

Data Obtained:

Graph-5.14: Perception of Doctors



- Most of the Doctors are somewhat agree to the statement that Atorvastatin is a well-studied molecule and newer statin cannot be the substitute for the same.
- 37 % doctors are agreed that atorvastatin is well studied molecule and cannot be a substitute for the same.
- Because of well-established clinical data most of the doctors don't want to shift from atorvastatin to rosuvastatin.
- Doctors are strongly agreed to the statement that Atorvastatin 80 mg is not being used to the extent it should be used in a patients who are at high risk.
- Doctors are not prescribing 80 mg due to the risk of developing musculoskeletal side effects.
- There is a neutral response for the statement that Rosuvastatin is a better molecule for lipid management.

***Q10*. Are there any unmet needs with the statins?**

***Q11*. IF yes then suggest the possible options to satisfy those unmet needs.**

Question Significance:

This question is included in the analysis to check if there are any gaps in the statin therapy and if there are gaps what can be the option to fill those gaps. These two questions are open ended questions and only 21 Doctors respond to these questions.

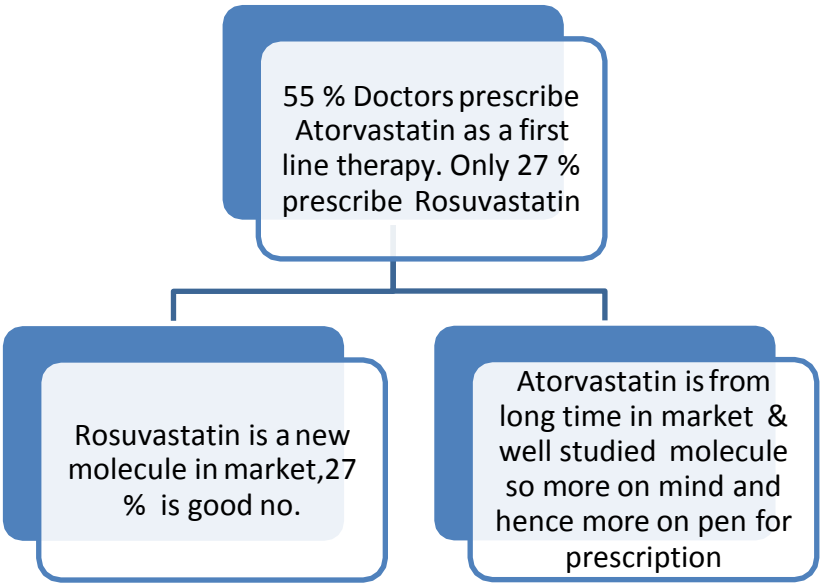
Data Obtained:

- Most of the doctors said that statins doesn't increase the HDL level up to the significant level. So try to find out the statin combination that will increase the HDL level significantly
- Some doctors said that statin cannot be given to the patients with active liver diseases. At present statin combination and dosages adjustment is the only viable option.
- Also statin cannot be given to the patients with musculoskeletal disorders. The remedy is combination with other drugs.

5.4 Key Research Findings

- Atorvastatin is leading molecule in current Statins market, whereas Rosuvastatin is growing at a tremendous rate which shows that by 2020 Rosuvastatin constitutes almost half of the total statin market. Thus high growth rate of Rosuvastatin poses a great threat to Atorvastatin market.

- 55 % doctors prescribe atorvastatin and 27 % doctors prescribe rosuvastatin. Rosuvastatin is a new molecule however its usage is increasing very fast.



- Most of the doctors prefer atorvastatin+ Fenofibrate combination (57%) to lower the TG level in a diabetic dyslipidaemic patients and less no of doctors use plain fenofibrate in diabetic dyslipidaemic patients.

- Majority of the Doctors prescribe Atorvastatin 10 mg (92%) and Rosuvastatin 5 mg (72%) for the primary prevention of CVD. This shows that Rosuvastatin is a potent molecule compared to atorvastatin.

- CPs usually prefers Atorvastatin 40 mg or Rosuvastatin 20 mg for High risk patients.

- Most of the Doctors usually titrate to higher dose of statin to achieve the LDL-C goals.

- 90 % of doctors said that they do not prescribe Rosuvastatin because it's a costly molecule so every patient cannot afford it. So cost of therapy is of main concern while prescribing Rosuvastatin.

- Majority of the patients agreed to the statements that Atorvastatin is a well-studied molecule and any newer statin cannot be the substitute for the same.
- Most of the doctors agreed to the statement that atorvastatin 80 mg is not being used to the extent it should be used in high risk patients.
- Although Rosuvastatin is a potent molecule but it doesn't have a more side effects

Fig- 5.1: Pros and Cons of Atorvastatin molecule

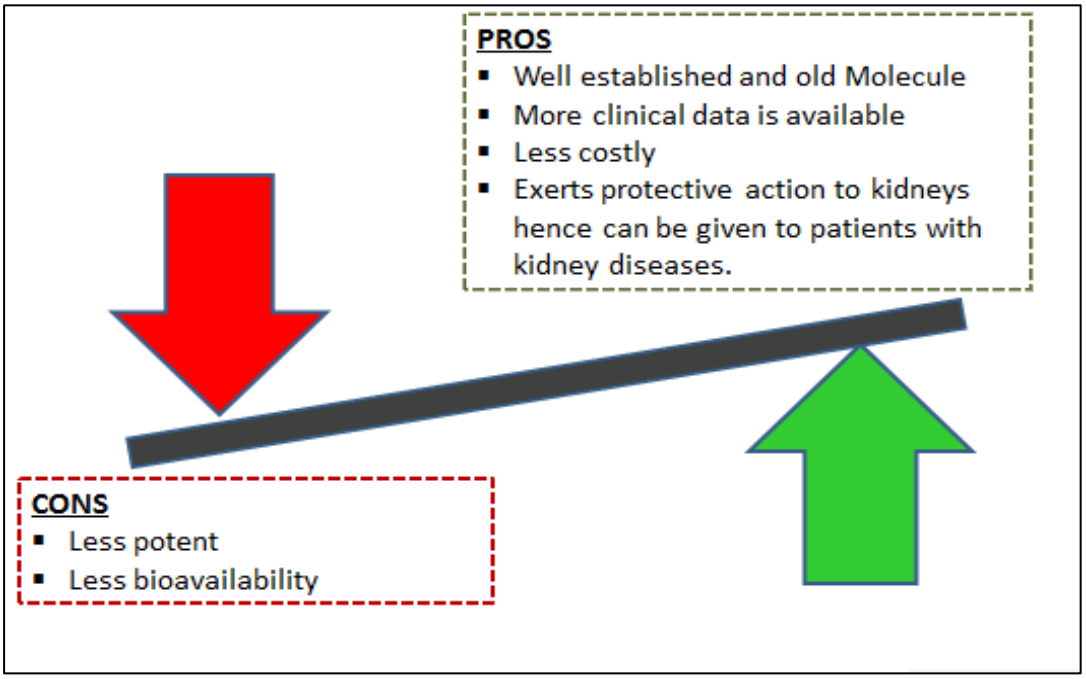
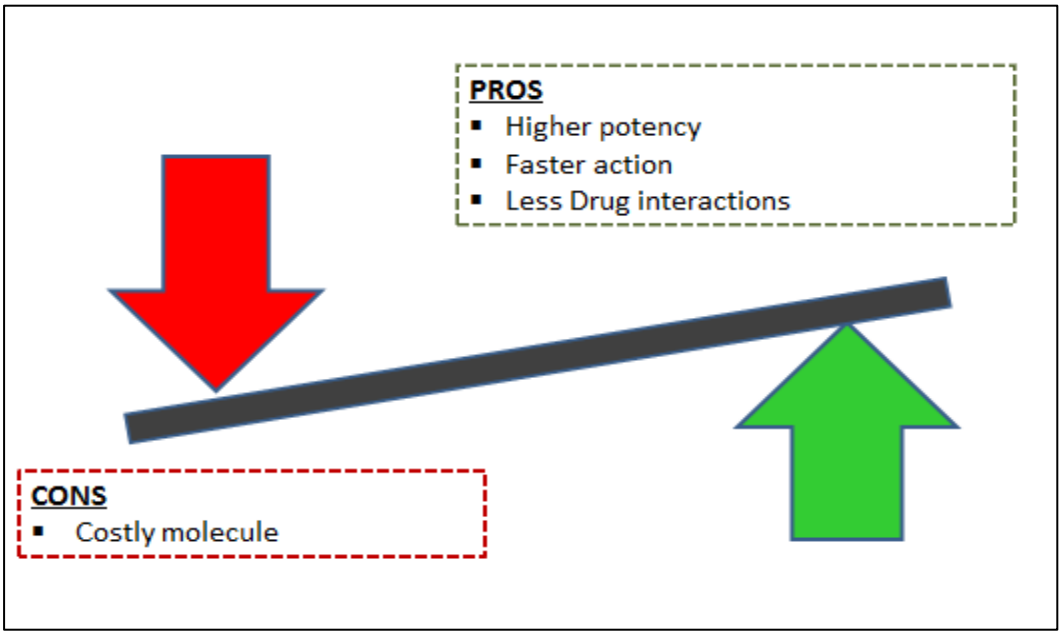


Fig-5.2: Pros and Cons of Rosuvastatin molecule



5.5 Suggestions

- Since Atorvastatin is the leading molecule with the highest market share in the current statin market newly launched Rosuvastatin molecule is gaining acceptance in the market which will be a greater threat to atorvastatin market in India.
- **Conduct Continuous Medical Education** to maintain the market share of atorvastatin molecule
- The campaign should be chiefly targeted to **KOL's** in the field of **Cardiology, Diabetology** and then should be gradually extended to remaining **Consulting cardiologist** and physicians.
- As a part of Continuous Medical Education (CME) doctors should be made aware of the fact that atorvastatin is a widely studied molecule with more than 400 clinical studies.
- Atorvastatin + Fenofibrate combination should be strongly promoted to the doctors those uses **only Fenofibrate** in the treatment of Diabetic dyslipidaemic patients.
- Promotion should be based on cost because atorvastatin + fenofibrate combination is less costly compared to Rosuvastatin + fenofibrate combination.
- Try to increase the usages of atorvastatin 10 mg for the primary prevention of CVD by providing sufficient clinical evidence to the doctors.
- **Build up the confidence** into the mindset of Consulting physicians and cardiologists to prescribe higher strength of atorvastatin (i.e. **Atorvastatin 80mg**) by providing sufficient clinical evidences.
- Atorvastatin is mostly prescribed due to its lower cost if in future cost of rosuvastatin molecule decreases that will create major threat to atorvastatin molecule so to remain in the competition try to cut down the cost.
- Statin combination therapy will be a better option in the future. So focus more on the combination therapy.

6. Reference

1. www.sciencedirect.com
2. www.healthscout.com/ency/68/366/main.html
3. NCEP ATP III classification of cholesterol
4. Cha-23, Pharmacotherapy: A Pathophysiologic Approach ,The McGraw-Hill Companies
5. http://www.thedrugmonitor.com,
6. www.lipitor.com
7. www.medicinenet.com
8. http://pharmacologywindow.blogspot.com/
9. www.rxlist.com
10. www.micromedex.com/products/ptquik/.../Rosuvastatin.html