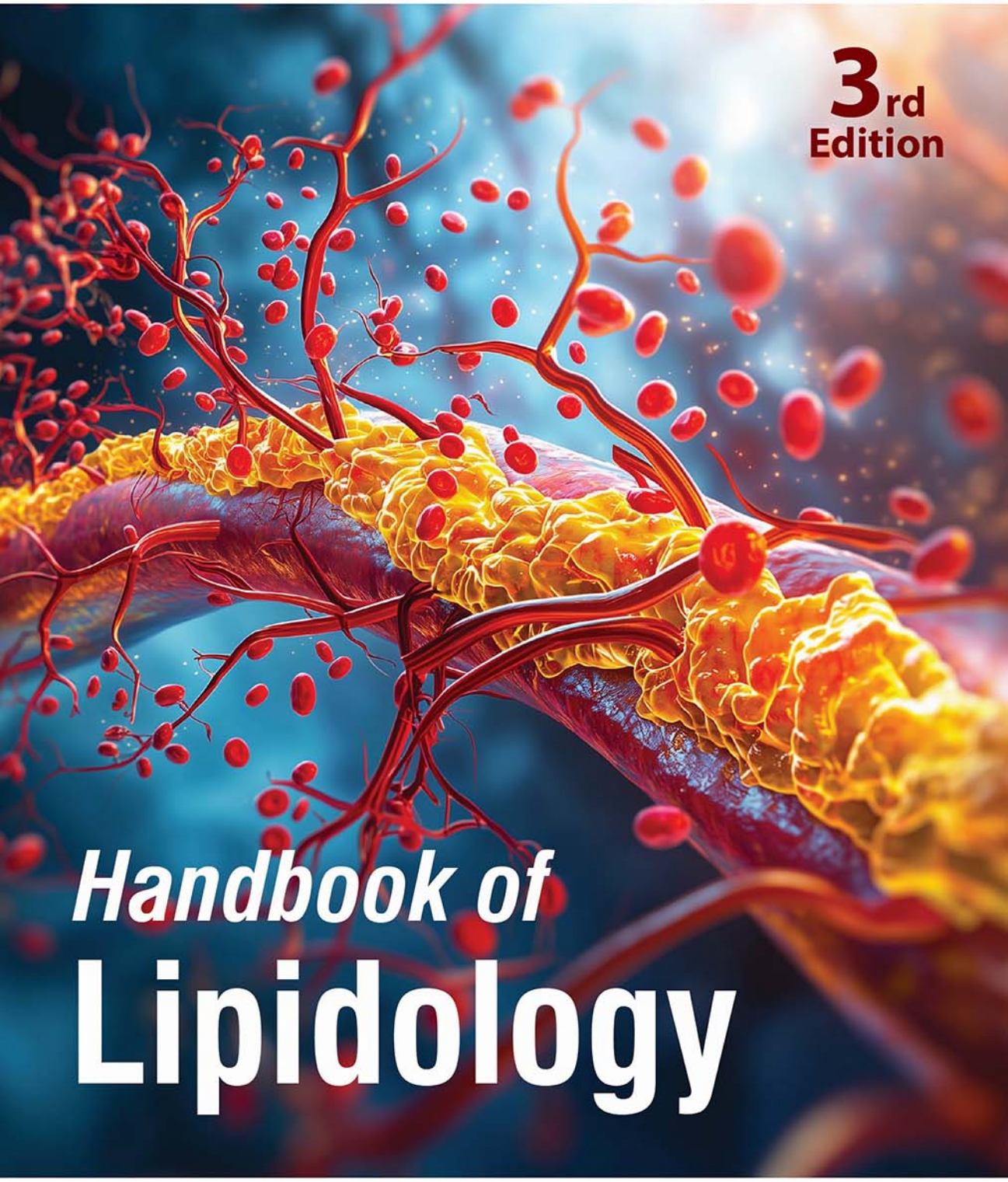
ed information on cardiology books, visit our website www.ejaypee.com, for detailed information on cardiology books, visit our website www.ejaypee.com



Handbook of Lipidology

Tapan Ghose

JAYPEE

Contents

1. History of the Dyslipidemia Research 1
Tapan Ghose

The Beginning *1*; Model of Atherosclerosis: Early Works *2*; Lipoprotein Particles *2*; Cholesterol—Genetic and Dietary Connection *2*; Epidemiological Evidence *3*; Recent Past Works on Cholesterol *3*; Lipid-Modifying Therapeutic Agents *3*; Statins: A Landmark Molecule in Atherosclerosis Management *4*; Ezetimibe *5*; Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies and Antisense Oligonucleotides *6*; Newer Nonstatin Therapeutic Oral Agents *6*; The Future *7*

2. Epidemiology of Lipid Disorders 12
Baridalyne Nongkynrih

Global Burden of Dyslipidemia *12*; Epidemiology of Dyslipidemia in India *15*; Preventive Measures *21*; Risk Assessment in Primary Prevention *21*

3. Biochemical Basis of Dyslipidemia 27
Moushumi Lodh, Ashok Kumar Parida

Apolipoproteins *27*; Small Dense Low-density Lipoprotein *30*; Lipoprotein Metabolism *31*; Hyperlipoproteinemia *33*; Dysfunctional High-density Lipoprotein *34*; Oxidized Low-density Lipoprotein and Atherosclerosis *35*; Current Guidelines and Expert Panel Recommendations *36*

4. Pathogenesis of Atherosclerosis 43
Sekhar Chakravarty

Pathophysiology *44*; Susceptibility, Atherogenic Stimuli, and Protective Factors *44*; Role of Inflammation *46*; Role of Infection *46*; Role of Growth Factors *47*

5. High-density Lipoprotein Metabolism, Mutation, and Targeting 51
Aijaz H Mansoor, Tapan Ghose

Classification of High-density Lipoproteins *51*; Biochemical Impact of High-density Lipoprotein Atherosclerosis *52*; Clinical Impact of High-density Lipoprotein Manipulation *52*; High-density Lipoprotein Mutations *54*; Dyslipidemia Associated with Low Level of High-density Lipoprotein *55*; Dyslipidemia Associated with a High Level of High-density Lipoprotein *56*; High-density Lipoprotein Targeting *56*; Recent Advances *57*

6. Clinical Approach to Lipid Disorders 60
Dheeraj Deo Bhatt, Tapan Ghose

Primary Lipid Disorders *60*; Secondary Lipid Disorders *65*; Clinical Features of Dyslipidemias *66*; Investigations *72*; Treatment *73*

7. Lipoprotein(a) and Atherosclerosis 81
Dipankar Deb, Hari S Nair

Structure of Lipoprotein(a) *81*; Plasma Level of Lipoprotein(a) *81*; Lipoprotein(a) and Atherosclerosis *81*; Clinical Implications of Lipoprotein(a) *84*; Future Needs *85*

8. Guidelines for the Management of Dyslipidemias 90
Vineet Bhatia, Tapan Ghose

Identification of Individuals at Risk *90*; Risk Stratification *91*; Current Guidelines *93*; Continuation and Monitoring *101*

9. Diet in Dyslipidemia 104
Jaideep Dey, Tapan Ghose

Basics of Human Nutrition *104*; Ideal Diet in Dyslipidemia *106*; Dietary Regimen for Dyslipidemia in Indian Context *109*; Additional Dietary Considerations in Dyslipidemia Management *112*

10. Lifestyle Modifications for the Management of Dyslipidemia 122
SC Manchanda, Kushal Madan

Role of Physical Exercise *122*; Effects of Physical Exercise on High-density Lipoprotein Cholesterol *122*; Effects of Physical Exercise on Triglycerides *123*; Effects of Physical Exercise on Low-density Lipoprotein Cholesterol *123*; Role of Smoking Cessation on Lipids *125*; Effects of Alcohol on Lipids *125*; Effect of Yoga on Lipids *125*

11. Obesity, Weight Loss, and Lipid Disorders 131
Harsh Wardhan, Gaurav Singhal, Suchitra Garhwal

Obesity and Dyslipidemia *131*; Management *132*; Future Directions *139*

12. Statins in Dyslipidemia 145
Tapan Ghose

Classification of Statins *145*; Pharmacology of Statins *147*; Biochemical Impact of Statin Therapy *148*; Clinical Impact of Statin Therapy *149*; Primary Prevention Trials *152*; Statin in Chronic Heart Failure *159*; Statin Rebound or Statin Withdrawal *162*; Statins in the Prevention of Contrast-induced Nephropathy *167*; Prescribing Information of Various Statins *169*

13. Bile Acid Sequestrants 178
Anjali Arora

Development of Bile Acid Sequestrant Drugs *178*; Physiology of Bile Acids *179*; Synthesis of Bile Acids *179*; Bile Acid Mechanism: At Molecular Level *179*; Obesity and Diabetes Mellitus *182*; Action of Bile Acid Sequestrants *182*; Plasma Lipoproteins and Bile Acid Sequestrants *183*

14. Cholesterol Absorption Inhibitors 187
Sudhir S Shetkar, Nirmal Ghati, Sandeep Singh

Intestinal Cholesterol Absorption *187*; Agents Affecting Cholesterol Absorption *189*; Intraluminal Cholesterol Processing Targets *189*; Intracellular Cholesterol Processing Targets *191*

15. Fibrates and Nonfibrates for Hypertriglyceridemia 201
Saurabh Mehrotra, Krishna Prasad, Sundeep Mishra
Management of Hypertriglyceridemia *201*

16. Acid Citrate Lyase Blocker: Bempedoic Acid..... 215
Tapan Ghose, Sutapa Chaudhuri
Bempedoic Acid *215*

17. Familial Combined Hyperlipidemia..... 229
DJ Dutta
Genetic Basis of Familial Combined Hyperlipidemia *229*; Prevalence of Familial Combined Hyperlipidemia *229*; Diagnostic Criteria of Familial Combined Hyperlipidemia *230*; Structure and Metabolism of Lipoproteins in Familial Combined Hyperlipidemia *230*; Clinical Presentation *231*; Differential Diagnosis of Familial Combined Hyperlipidemia *231*; Principles of Management *231*

18. Dyslipidemia in Children and Adolescents 237
Rahul Nagpal, Roohi Khan
Blood Lipids and Atherogenesis *237*; Measurement of Cholesterol and Lipoproteins *237*; Selected Primary Lipoprotein Disorders *239*; Hyperlipoproteinemias *239*; Hypercholesterolemia with Hypertriglyceridemia *245*; Clinical Identification of the Metabolic Syndrome in Adults *245*; Proposed Definition of the Metabolic Syndrome in Adolescents *246*; Hypertriglyceridemias *246*; Disorders of High-density Lipoprotein Metabolism *247*; Disorder Associated with Low Cholesterol *248*; Disorders of Intracellular Cholesterol Metabolism *249*; Lipoprotein Patterns in Children and Adolescents *250*; Fetal Origin for Adult Disease *252*; Secondary Dyslipoproteinemia *252*; Rationale for Lipid Screening *252*; Approach for Screening *254*; Management *254*; Physical Activity *261*

19. Dyslipidemia in Diabetes Mellitus..... 274
Suchitra Behl, Anoop Misra
Definition and Mechanism *274*; Dyslipidemia in Asian Indians *275*; Dyslipidemia and Macrovascular Complications of Diabetes Mellitus *276*; Diabetic Dyslipidemia and Microvascular Complications of Diabetes Mellitus *278*; Diagnosis and Management of Dyslipidemia *278*; Management *279*; Guidelines for Initiating Therapy *279*; Other Medications and Supplements *282*; Newer Medications *282*

20. Lipids and Kidney Disease 287
Upendra Singh, Sanjeev Gulati
Pathophysiology of Dyslipidemia in Chronic Kidney Disease and Dialysis-dependent Patients *287*; Evidence of Association between Lipid Disorders and Cardiovascular Outcome in Chronic Kidney Disease *291*; Management of Lipid Disorders in Chronic Kidney Disease *291*; Therapeutics for Dyslipidemia in Chronic Kidney Disease *292*

21. Dyslipidemia in Women 302
Neema Sharma, Tapan Ghose

Lifetime Variation of Lipid Parameters in Women *302*; Management of Dyslipidemia in Women before Planning Pregnancy *303*; Dyslipidemia in Pregnancy *303*; Dyslipidemia in Polycystic Ovary Syndrome *306*; Dyslipidemia in Menopausal Women *307*

22. Genetic Testing in Lipid Disorders 312
Pratishtha Mehra, Vimal Mehta, Jamal Yusuf

Lipoproteins *313*; Diagnosis of Lipid Disorders *314*; Genetic Dyslipidemias *314*; Familial Hypercholesterolemia *316*; Prevalence of Familial Hypercholesterolemias *317*; Familial Hypercholesterolemia Genetics *317*; Diagnosis of Familial Hypercholesterolemia *318*; Impact of Genetic Testing on Management of Genetic Dyslipidemia *319*; Genetic Testing Methods *320*; Genetic Testing for Hypertriglyceridemia *322*; Role of Routine Genetic Testing *322*

23. Dyslipidemia in Retroviral and Nonretroviral Infection 326
Ranjan Kachru, Tapan Ghose

Lipid Alterations in Human Immunodeficiency Virus Infection *326*; Risk Stratification *328*; Management of Dyslipidemia in Human Immunodeficiency Virus-infected Population *329*; Drugs for the Lipid Management *330*; Lipid Lowering in Nonretroviral Infection *334*; COVID-19 Infection *334*

24. Lipoprotein Apheresis 341
Sutapa Chaudhuri

Current Indications of Lipoprotein Apheresis *343*; Miscellaneous Uses of Lipoprotein Apheresis *343*

25. Newer and Evolving Therapeutic Targets and Agents in Lipid Management 349
Tapan Ghose, Satya Nand Pathak

Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor *350*; Cholesteryl Ester Transfer Protein Inhibitors *351*; Squalene Synthase Inhibitor *352*; Inhibitor of Apolipoprotein B100 Expression *352*; Microsomal Triglyceride Transfer Protein Inhibitor *352*; Diacylglycerol Acyltransferase Inhibitors *353*; Thyromimetics or Tiromes *353*; Apolipoprotein E Mimetic Peptides *353*; Apolipoprotein A-I Synthesis Inducer *353*; High-density Lipoprotein-Mimetic Peptide *353*; Nuclear Receptors *353*; Phospholipase Inhibitors *354*; Lipoprotein(a)-Lowering Agents *354*; High-density Lipoprotein Infusion Therapy *355*; Angiopoietin-like Protein Inhibitor *355*; Gene Therapy *355*

Index 365

12

CHAPTER

Statins in Dyslipidemia

Tapan Ghose

INTRODUCTION

Statins are chemicals that inhibit the rate-limiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) in the cholesterol biosynthesis. In early 1970, a Japanese microbiologist, Dr Akira Endo, discovered mevastatin, formerly called compactin, from fungus *Penicillium citrinum*. Pravastatin is the first available statin manufactured by Sankyo, Japan (1979). This was commercially launched in 1989 in Japan. It received Food and Drug Administration approval in 1991. Subsequently, lovastatin (Mevacor) was launched by Merck. Pitavastatin (Livalo) was discovered in Japan by Nissan Chemical Industries in 2005.

The discovery of statin is a landmark in human history. For the first time, it was shown that all manifestation of atherosclerotic vascular disease, starting from subclinical to clinical, can be prevented by an oral agent.[1,2]

CLASSIFICATION OF STATINS

Broadly, the statins can be classified into two groups based on their sources: (1) Type 1 or naturally derived statins and (2) type 2 or synthetic. The naturally derived statins are obtained from fungus. Type 1 or naturally derived statins are: (1) Lovastatin, (2) simvastatin, (3) pravastatin, and (4) pitavastatin. Synthetic statins or type 2 statins are: (1) Fluvastatin, (2) atorvastatin, and (3) rosuvastatin. Statins can be classified by their solubility also. Water-soluble or hydrophilic statins are pravastatin, pitavastatin, and rosuvastatin. Fat-soluble or hydrophobic statins are simvastatin, lovastatin, fluvastatin, and atorvastatin **(Box 1)**.[3,4]

Mechanism of Action of Statins

Low-density Lipoprotein-dependent Mechanism of Action

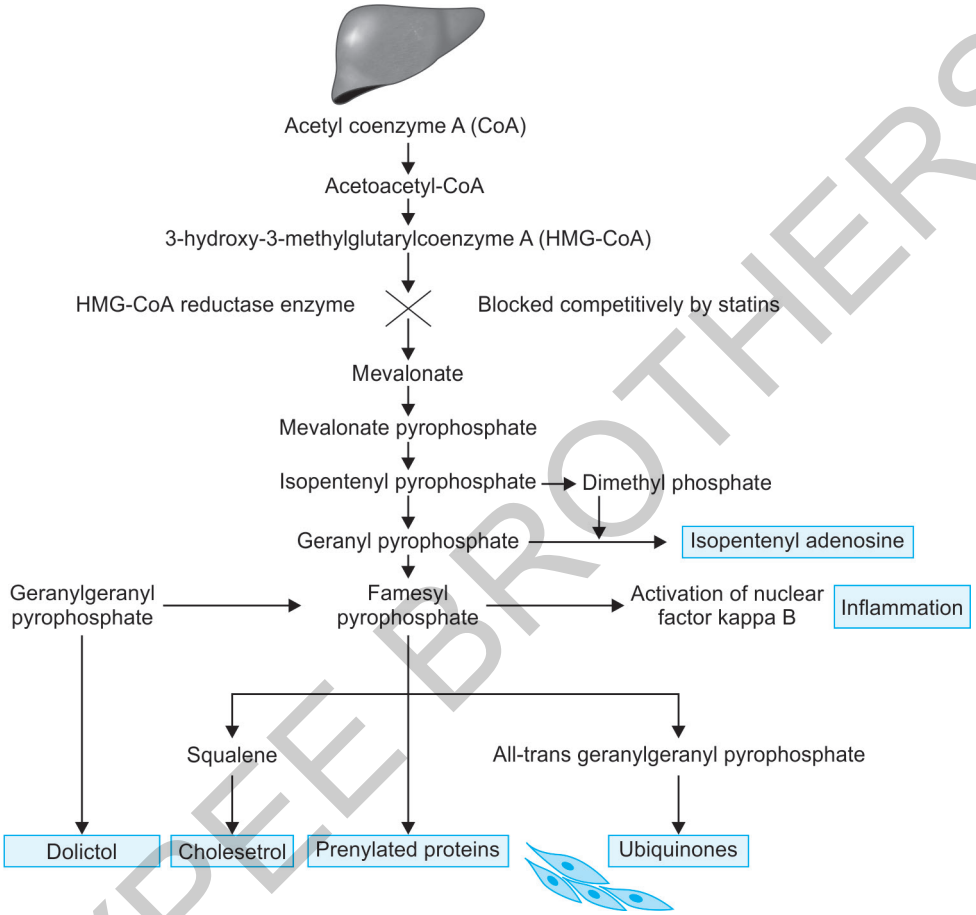
Statins competitively inhibit the rate-limiting enzyme HMG-CoA reductase. This results in

BOX 1: Classification of statins.

- *Classification of statins based on the manufacturing method:*
  - *Type 1 (fermentation derived):* Simvastatin, lovastatin, pravastatin, and pitavastatin
  - *Type 2 (synthetic):* Fluvastatin, atorvastatin, and rosuvastatin
- *Classification of statins based on the solubility:*
  - *Water soluble (hydrophilic):* Pravastatin and rosuvastatin
  - *Fat soluble (lipophilic):* Simvastatin, lovastatin, fluvastatin, atorvastatin, and pitavastatin
- *Classification of statins based on the development:*
  - *First-generation statins:* Lovastatin, pravastatin, and fluvastatin
  - *Second-generation statins:* Simvastatin and atorvastatin
  - *Third-generation statins:* Cerivastatin (withdrawn from the market), rosuvastatin, and pitavastatin

JAYPEE BROTHERS

Flowchart 1: Blockade of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase results in inhibition of mevalonate biosynthesis that results in upregulation of low-density lipoprotein (LDL) receptor synthesis, reduction in cholesterol biosynthesis, and reduction in the formation of prenylated proteins and isoprenoids (isoprenyl adenosyl, dolichols, and ubiquinone).



the blockage of conversion of HMG-CoA to mevalonate that leads to a number of changes in the liver cells. The total cholesterol (TC) synthesis and cholesterol pool are reduced. The sterol-regulatory element-binding proteins are upregulated. There is an increase in the number of low-density lipoprotein (LDL) receptor synthesis in liver. The LDL receptors bind with apolipoprotein (Apo) B and ApoE and very-low-density lipoprotein (VLDL) particles. This results in the increased clearance of these particles by hepatocytes.

The reduction in mevalonate biosynthesis also results in reduction in dolichols, ubiquinones, and isoprenoids. These have varying effects on the lipogenesis and adverse events of statins **(Flowchart 1)**.[3]

Low-density Lipoprotein-independent (Pleiotropic) Mechanism of Action

Some of the observed beneficial effects are independent of LDL lowering. They are termed pleiotropic effects of statins

JAYPEE BROTHERS

(Greek: pleion—more, tropos—direction). Statins act as anti-inflammatory agents and stabilize the atherosclerotic plaque. The serum C-reactive protein (CRP) is lowered. Endothelial function improves. This occurs much earlier than LDL reduction. Statins also improve endothelial function in smokers with normal LDL levels. Statins led to the reduction in atheroma volume and lipid pool, and this leads to regression of atherosclerosis. Statin therapy leads to increased endothelial nitric oxide level and reduction in several factors such as smooth muscle cell proliferation, inflammation, vasoconstriction, thrombosis, cell migration, and changes in actin cytoskeleton. It causes reduction in endothelin-1 level. Inhibition of Rho/Rho kinase signaling pathways by statins is one of the proposed hypotheses to explain these pleiotropic effects. Decreased protein prenylation in peripheral tissues leads to decrease in release of growth hormone. This also reduces platelet aggregation. This could be another possible mechanism of the pleiotropic benefit **(Fig. 1)**.[5-7]

PHARMACOLOGY OF STATINS

All statins are absorbed rapidly when orally administered. The peak absorption is by 4 hours. Lovastatin and simvastatin are prodrugs, and they are highly lipid soluble. Fluvastatin and atorvastatin are next lipid-soluble drugs. More lipid-soluble drugs penetrate all membranes easily. Pravastatin and rosuvastatin are more hydrophilic. They are transported across all membranes by organic anion-transporting polypeptide. Pravastatin, fluvastatin, and rosuvastatin are more bioavailable. Less than 20–25% of the drug reaches circulation. Pitavastatin has the highest bioavailability (51%). Mostly 75–80% of the orally administered drug is eliminated by liver and gastrointestinal tract and minimal amount by the kidneys. Pravastatin and simvastatin have maximum renal elimination (20 and 30%, respectively). In the presence of severely impaired renal function, these statins are to be avoided.

Elimination half-life of older statins such as lovastatin, simvastatin, fluvastatin, and pravastatin ranges between 1 and 3 hours. Atorvastatin has a half-life of 17 hours, whereas rosuvastatin has a half-life of 19 hours. Pitavastatin has a half-life of 12 hours. Because of longer half-lives, these three statins can be administered at any time of the day as opposed to bed-time dosing of other statins. This is required because the HMG-CoA enzyme activity is highest at night. The statins are converted to water-soluble salts for elimination. Simvastatin and lovastatin are eliminated by cytochrome P450 3A (CYP3A) enzymes. Atorvastatin also (to a lesser extent) undergoes metabolism by the same pathway. Fluvastatin and rosuvastatin are largely excreted unchanged. Pitavastatin undergoes hepatic glucuronidation and minimal metabolism by CYP2C9 and CYP2C8. Most are excreted in the feces; 10% of the dose is excreted unchanged in the urine. Several clinically important drug interactions need attention. Azole antifungals, macrolide antibiotics, human immunodeficiency virus (HIV) protease inhibitors, and grapefruit juice increase the plasma level of statins metabolized by CYP3A pathway, and coadministration of these agents may increase the chances of rhabdomyolysis. In general, fibrates increase the plasma levels of statins. Gemfibrozil has the highest tendency to increase statin blood concentration by interfering with OATP1B1-mediated transport of statins to hepatocytes and inhibition of CYP2C8. Fenofibrate statin combination avoids these interactions.

JAYPEE BROTHERS

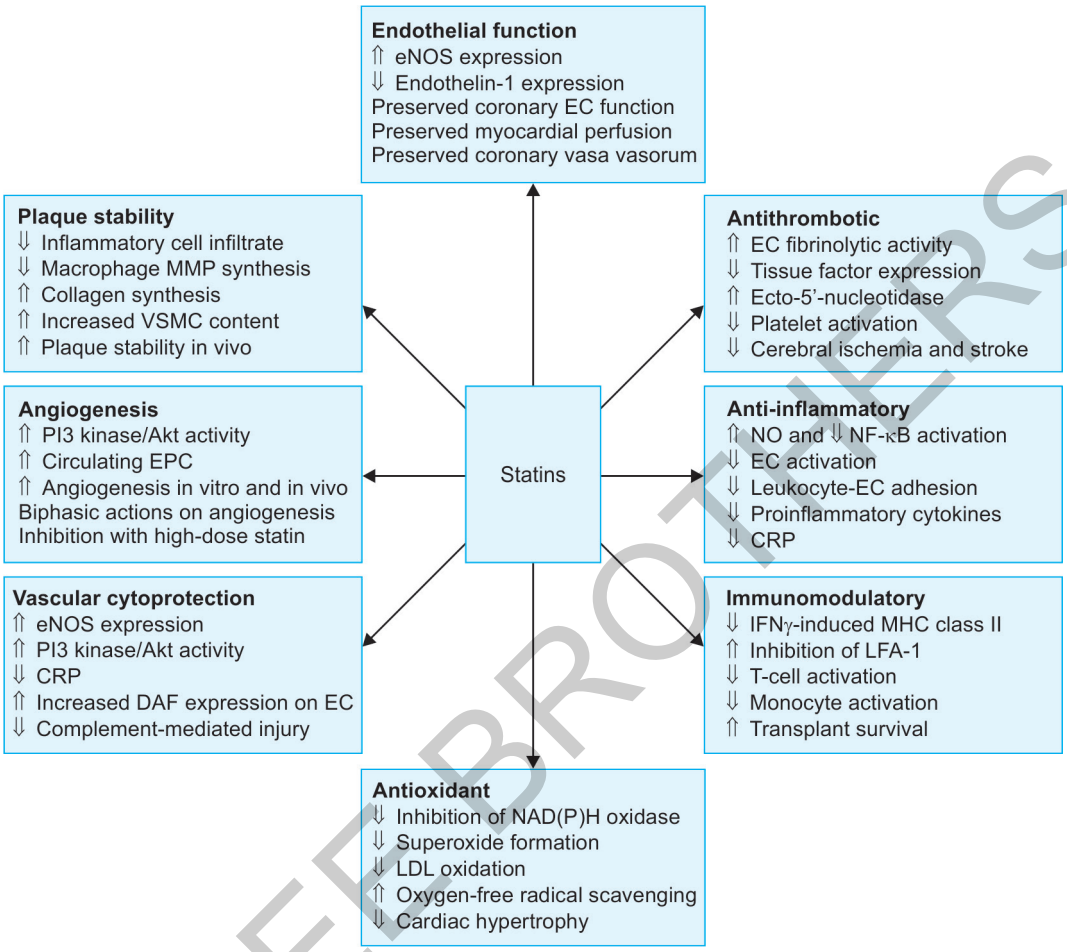


Fig. 1: Pleiotropic effects of statins on the vasculature. (CRP: C-reactive protein; DAF: decay-accelerating factor; EC: endothelial cell; eNOS: endothelial nitric oxide synthase; EPC: endothelial progenitor cell; IFN: interferon; LDL: low-density lipoprotein; LFA-1: lymphocyte function-associated antigen-1; MHC: major histocompatibility complex; MMP: matrix metalloproteinase; NAD(P)H: nicotinamide adenine dinucleotide phosphate; NF-κB: nuclear factor kappa B; PI3: phosphoinositide 3; VSMC: vascular smooth muscle cell)

Statins (with exception of pravastatin) are highly protein-bound molecules. They are likely to replace protein-bound drugs such as warfarin. Rosuvastatin or simvastatin coadministration with warfarin can increase prothrombin time (PT). However, warfarin has no clinically significant interaction with statins **(Box 2 and Table 1)**.[3,8]

BIOCHEMICAL IMPACT OF STATIN THERAPY

Significant reduction in LDL cholesterol (LDL-C) is seen with all the available statins. On milligram-to-milligram basis, the LDL-lowering potency is as follows. Rosuvastatin is the most potent statin followed by atorvastatin, pitavastatin, simvastatin, and

JAYPEE BROTHERS

BOX 2: Pharmacology of statins.

- Oral bioavailability—20–51%
- Absorption—absorbed rapidly, peak absorption at 4 hours
- Half-life—lovastatin, simvastatin, pravastatin, lovastatin, and pravastatin—1–3 hours
  - Pitavastatin 12 hours, atorvastatin 17 hours, and rosuvastatin 19 hours
- Metabolism—metabolized by cytochrome P450 pathway
  - CYP2C9—fluvastatin
  - CYP344—atorvastatin, lovastatin, and simvastatin
  - Non-P450—pravastatin
- Excretion—fluvastatin and rosuvastatin are largely excreted unchanged
  - 75–80% of the rest are excreted by liver and gastrointestinal tract
  - <10% excreted by kidneys

pravastatin. Pravastatin (10–40 mg) lowers LDL by 20–30%, simvastatin (10–80 mg) by 28–46%, atorvastatin (10–80 mg) by 37–51%, rosuvastatin (10–40 mg) by 46–55%, and pitavastatin (1–4 mg) by 33.6–47.2%.[9]

Rosuvastatin 10 mg, atorvastatin 20 mg, simvastatin 40 mg, and pravastatin 80 mg are comparable in clinical efficiency. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL goals achieved in various treatment groups were rosuvastatin (55%), atorvastatin (43%), simvastatin (31%), and pravastatin (11%). However, statin therapy alone may not be able to lower LDL to target levels in some patients.

Plasma triglyceride (TG) levels are decreased by 15–30% by various statins. Their effects follow the same pattern as the effect on LDL-C. Maximum reduction in TG is achieved by atorvastatin and rosuvastatin. Atherogenic dyslipidemia is characterized by high VLDL remnant particles, small dense LDL, low high-density lipoprotein cholesterol (HDL-C), and increase in particle number. Statins are highly efficacious in lowering the number and composition of these particles. Statins reduce LDL, VLDL, apolipoprotein CIII (ApoCIII), cholesterol, and TGs. They also reduce small dense LDL by 44%.

The NCEP ATP III non-HDL goal achieved by various statins is as follows: Atorvastatin (38%), simvastatin (32%), lovastatin (32%), fluvastatin (26%), and pravastatin (26%).

Most statins increase the HDL-C by 5–7%. This is done by upregulating the transport protein adenosine triphosphate (ATP)-binding cassette transporter A1. Rosuvastatin raises HDL by 8–10%. This also reduces the transfer of cholesteryl ester from HDL to VLDL and LDL via inhibition of cholesteryl ester transfer protein. Pitavastatin increases the HDL concentration to a maximum (24.6%) in patients with low HDL. Reduction in TC and TG and increase in HDL make this an ideal statin in atherogenic dyslipidemia.[10,11]

CLINICAL IMPACT OF STATIN THERAPY

Statins have shown to reduce cardiovascular (CV) and total mortality in various trials such as Scandinavian Simvastatin Survival Study (4S), Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID), and Heart Protection Study (HPS). They reduce coronary heart disease (CHD) death, nonfatal myocardial infarction (MI), and the first CV event. This has been shown in both primary prevention trials and secondary intervention trials involving more than 120,000 patients. In total, 1% reduction in LDL lowers the first major event by 0.88%. Statins reduce the events in all ages and genders. Various trials conducted with statins can be grouped into (1) primary prevention trials, (2) clinical outcome trials, (3) acute coronary syndrome (ACS) trials, (4) stroke trials, (5) high-dose

JAYPEE BROTHERS

TABLE 1: *Statin interactions:* Maximum recommended statin doses (mg) and cautions.[8-14]

	Simvastatin	Lovastatin	Pravastatin	Atorvastatin	Rosuvastatin	Fluvastatin	Pitavastatin
Itraconazole	0[h]	0[h]	—[i]	20 mg[a]	—[i]	—[i]	—[i]
Ketoconazole	0[h]	0[h]	—[i]	—[b]	—[i]	—[i]	—[i]
Posaconazole	0[h]	0[h]	—[i]	—[b]	—[i]	—[i]	—[i]
Fluconazole	—[i]	—[i]	—[i]	—[b]	—[i]	20 mg BD	—[i]
Erythromycin	0[h]	0[h]	—[i]	—[b]	—[i]	—[i]	1 mg
Clarithromycin	0[h]	0[h]	40 mg	20 mg[a]	—[i]	—[i]	—[i]
Telithromycin	0[h]	0[h]	—[i]	—[i]	—[i]	—[i]	—[i]
HIV protease inhibitors	0[h]	0[h]	—[i]	0–40 mg[c]	10 mg[c,d]	—[i]	—[i]
Telaprevir	0[h]	0[h]	—[i]	Avoid	—[i]	—[i]	—[i]
Boceprevir	0[h]	0[h]	—[i]	—[i]	—[i]	—[i]	—[i]
Nefazodone	0[h]	0[h]	—[i]	—[i]	—[i]	—[i]	—[i]
Gemfibrozil	0[h]	Avoid	Avoid	—[b,d]	Avoid or 10 mg	—[d]	—[d]
Other fibrates	—[d]	20 mg	—[d]	—[b,d]	—[d]	—[d]	—[d]
>1 g niacin/day	—[b,d]	20 mg	—[b]	—[b]	—[d]	—[b]	—[b]
Cyclosporine	0[h]	Avoid	20 mg	Avoid	5 mg	20 mg BD	0[h]
Danazol	0[h]	20 mg	—[i]	—[d]	—[i]	—[i]	—[i]
Amiodarone	10 mg	40 mg	—[i]	—[i]	—[i]	—[i]	—[i]
Dronedarone	10 mg						
Verapamil	10 mg	20 mg	—[i]	—[i]	—[i]	—[i]	—[i]
Diltiazem	10 mg	20 mg	—[i]	—[i]	—[i]	—[i]	—[i]
Amlodipine	20 mg	—[i]	—[i]	—[i]	—[i]	—[i]	—[i]

Contd...

JAYPEE BROTHERS

Contd...

	Simvastatin	*Lovastatin*	*Pravastatin*	*Atorvastatin*	*Rosuvastatin*	*Fluvastatin*	*Pitavastatin*
Ranolazine	20 mg	—[i]	—[i]	—[i]	—[i]	—[i]	—[i]
Digoxin	—[i]	—[i]	—[i]	—[e]	—[i]	—[i]	—[i]
Warfarin	—[f]	—[f]	—[i]	—[i]	—[d]	—[f]	—[f]
Rifampicin	—[i]	—[i]	—[i]	—[g]	—[i]	—[i]	—[b]
Phenytoin	—[i]	—[i]	—[i]	—[i]	—[i]	—[d]	—[i]
Colchicine	—[d]	—[i]	—[d]	—[i]	—[i]	—[i]	—[i]

[a]Caution should be used at doses above this dose (lowest dose necessary should be used).
[b]Consider statin dose reduction when coadministering this drug.
[c]Refer to the section "Statin Dosage."
[d]Coadminister with caution.
[e]Coadministration of atorvastatin and digoxin can increase digoxin level by 20%, and these patients should be monitored appropriately.
[f]Monitor international normalized ratio (INR) when statin started.
[g]Administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g., rifampicin and efavirenz) can lead to variable reduction in plasma concentration of atorvastatin. Thus, atorvastatin should be administered simultaneously with drugs that are 3A4 inducers since delaying the statin administration can result in reduced statin plasma concentration.
[h]Not to be used in this particular combination.
[i]No specific United States Food and Drug Administration (USFDA) recommendation.
(BD: twice a day; HIV: human immunodeficiency virus)

JAYPEE BROTHERS

versus low-dose statin trials, (6) chronic heart failure (CHF) trials, (7) trials in borderline high lipid situation, (8) trials in low HDL and LDL, (9) atheroma reduction trials, and (10) trials in elderly **(Box 3)**.[12,13]

PRIMARY PREVENTION TRIALS

These are the trials conducted in individuals without overt CHD. Various trials under this category are: (1) West of Scotland Coronary Prevention Study (WOSCOPS),[14] (2) Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),[15] (3) HPS,[16] (4) Collaborative Atorvastatin Diabetes Study (CARDS),[17] (5) Anglo-Scandinavian Cardiac Outcomes Trial: Lipid-Lowering Arm (ASCOT-LLA),[18] (6) Atorvastatin Study for Prevention of CHD End Point in Non-insulin-Dependent Diabetes Mellitus (ASPEN),[19] (7) Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA)[20] trial, and (8) Justification for the Use of Statin in Prevention and Intervention Trial Evaluating Rosuvastatin (JUPITER).[21]

In the WOSCOPS trial, 40 mg pravastatin (n = 3,302) was compared with placebo (n = 3,293) in men with elevated lipid (LDL 155 mg/dL; TC 252 mg/dL). Pravastatin lowered plasma cholesterol by 20% and LDL by 26%. There were fewer deaths and nonfatal MI in pravastatin arm, 174 versus 248 [relative risk (RR) 31%; 95% confidence interval (CI) 17–43; $p \leq 0.001$]. The adverse events were comparable, and there was no increase in non-CV mortality.[14]

The AFCAPS/TexCAPS trial was designed to study the role of lovastatin (20–40 mg) for the prevention of first coronary event in individuals with average cholesterol level without having clinically evident atherosclerotic vascular disease. A total of 5,608 men and 997 women with mean cholesterol level 222 ± 21 mg/dL and LDL-C

BOX 3: Various trials with statins.

- *Primary prevention trials*:
  - WOSCOPS
  - AFCAPS/TexCAPS
  - HPS
  - CARDS
  - ASCOT-LLA
  - ASPEN
  - MEGA
  - JUPITER
- *Clinical outcome trials*:
  - 4S
  - LIPID
  - TNT
  - IDEAL
  - SEARCH
  - BIP
- *ACS trials*:
  - MIRACL
  - PROVE IT-TIMI 22
  - FLORIDA
  - PACT
  - A to Z Trial (Z phase)
  - ARMYDA-ACS
- *High-dose atorvastatin versus angioplasty*:
  - AVERT
- *Borderline high lipids:*
  - CARE
- *Congestive heart failure*:
  - CORONA
- *Atheroma volume reduction*:
  - ASTEROID
  - REVERSAL
  - REGRESS
  - SATURN
  - MARS
  - ORION
- *Postmarketing study*:
  - LIVES
  - ROSUVEES
  - CHIBA
- *Stroke*:
  - SPARCL
- *Statins in dementia*:
  - ROSPER
  - LEADe
  - CLASP
  - ADCLT
- *New trials*:
  - REAL-CAD
  - J-PREDICT
  - DIALYSIS

JAYPEE BROTHERS

level 150 ± 17 mg/dL were randomized to lovastatin versus placebo. After average follow-up for 5.2 years, lovastatin reduced ACS (183 vs. 116; RR 0.63; 95% CI 0.50–0.79; $p \leq 0.001$) and MI (95 vs. 57; RR 0.60; 95% CI 0.43–0.83; $p = 0.002$). Safety outcomes were comparable to placebo.[15]

In HPS, 20,536 adults (aged 40–80 years) with coronary artery disease (CAD) or other vascular disease or diabetes mellitus (DM) were included. The study addressed the benefit of lowering cholesterol with simvastatin in a high-risk population with average cholesterol. Primary outcome measures were mortality (overall analysis) and fatal and nonfatal vascular events (prespecified subcategory with subsidiary cancer) and other morbidity analyses. All-cause mortality was reduced by simvastatin (1,328, 12.9%) compared with placebo (157, 14.7%; $p = 0.0003$). Coronary death was reduced significantly [simvastatin 587 (5.7%) vs. placebo 707 (6.9%); $p = 0.0005$]. Other vascular deaths and nonvascular deaths were not significantly different. Nonfatal MI, coronary death, stroke, and revascularization were reduced with simvastatin. The benefit was seen even in patients with LDL <116 mg/dL (3.0 mmol/L) on average and TC below 193 mg/dL (5.0 mmol/L). There was no impact on cancer incidence or hospitalization for any nonvascular cause. In total, 5-year treatment of 1,000 patients having high-risk features would prevent 70–100 events irrespective of the initial cholesterol.[16]

The CARDS addressed the benefit of atorvastatin (10 mg) treatment in patients with DM without having prior vascular events and without having high LDL-C concentration. A total of 2,838 patients were randomized to atorvastatin ($n = 1,428$) versus placebo ($n = 1,410$). The mean duration of follow-up was 3.9 years. At baseline, the mean TC was 207 mg/dL (5.35 mmol/L) in placebo arm versus 207 mg/dL (5.36 mmol/L) in atorvastatin arm. The mean LDL was 117 mg/dL (3.02 mmol/L) versus 118 mg/dL (3.04 mmol/L) in these two groups. TC and LDL-C were reduced by 26 and 40%, respectively, by atorvastatin treatment. The primary end point of major CV events, including stroke, was reduced by 37% (95% CI 17–52; $p = 0.0001$, placebo 127 events vs. 83 events in atorvastatin arm). There was no excess of adverse events.[17]

The ASCOT-LLA was one of the arms of the ASCOT trial where the effect of lipid lowering was studied, in which 19,257 patients were randomized to blood pressure lowering (ASCOT BPLA beta-blocker ± diuretic vs. calcium channel blocker ± angiotensin-converting enzyme inhibitor). Of these, 10,305 patients were again randomized to either atorvastatin 10 mg or placebo. Atorvastatin administration reduced the primary end point (nonfatal MI and fatal CHD) by 36%. The secondary end points were reduced significantly. All coronary events reduced by 19%, fatal and nonfatal stroke by 27%, and all CV events and procedures by 21%.[18]

The ASPEN ($n = 2,410$) trial was designed to study the impact of 10 mg atorvastatin versus placebo in diabetic population with LDL-C below guideline targets. The primary end point was composite of CV death, nonfatal MI, nonfatal stroke, recanalization, coronary artery bypass graft (CABG) surgery, resuscitated cardiac arrest, and worsening or unstable angina leading to hospitalization. Over a period of 4 years, the primary end point rates were 13.7 and 15.6% [hazard ratio (HR) 0.90; 95% CI 0.73–1.12]. The composite end point was not significantly reduced.[19]

In MEGA trial, 7,832 men aged 40–70 years and postmenopausal women with TC 220–270 mg/dL (5.69–6.98 mmol/L) were

JAYPEE BROTHERS

randomized to pravastatin (10–20 mg/day) versus placebo. The primary end point was a composite of CAD events defined as sudden death, fatal and nonfatal MI, angina, or CV intervention. The secondary end points were stroke, cerebral infarction, or CHD composite of any CV event or mortality. Over a period of 5.3 years, mean TC was reduced by 2.1 versus 11.5% in placebo and active treatment group, respectively. Mean LDL-C was reduced by 3.2 and 18% in placebo and active group, respectively. This translated into lower events in the pravastatin arm (66 vs. 101 events; HR 0.67; 95% CI 0.49–0.9; p = 0.01). Malignant neoplasm and serious adverse events were not different in these two groups.[20]

The JUPITER trial tested the hypothesis that people with elevated high-sensitivity CRP as well as mildly elevated lipid level (LDL <130 mg/dL) might benefit from therapy with rosuvastatin. In total, 17,802 men and women with LDL <130 mg/dL (3.4 mmol/L) and high-sensitivity CRP levels of 2.0 mg/L or higher were randomized to rosuvastatin 20 mg daily versus placebo. The primary end point was the combination of MI, stroke, arterial revascularization, hospitalization for unstable angina, or CV death. The trial was stopped at 1.9 year (mean) and maximum 5-year follow-up. Treatment with rosuvastatin reduced LDL by 50% and CRP by 37%. The primary end points were 0.77 versus 1.36 per 100 person follow-up in rosuvastatin versus placebo arm, respectively (HR 0.56; 95% CI 0.46–0.69; $p \leq 0.0001$). MI was less (0.17 vs. 0.37%; HR 0.46; 95% CI 0.30–0.70; p = 0.0002). The rates of stroke were less with rosuvastatin (0.18 vs. 0.34%; HR 0.52; 95% CI 0.34–0.79; p = 0.002). Similarly, revascularization or unstable angina was less (0.41 vs. 0.77%; HR 0.53; 95% CI 0.40–0.70; $p < 0.00001$). The combined end points of MI, stroke, or CV death were less (p = 0.00001). All-cause mortality was less (1.0 vs. 1.25%; HR 0.80; 95% CI 0.67–0.97; p = 0.02). Myopathy or cancer incidence was not different. However, rosuvastatin arm had a higher incidence of DM.[21]

Clinical Outcome Trials

These are the trials conducted on patients with established CAD. Secondary prevention of the CV events was the end point. The trials under this category are: (1) 4S trial,[22] (2) LIPID,[22] (3) Treating to New Targets (TNT),[23] (4) A comparison of Intensive statin versus low moderate therapy in stable CAD patients with previous MI (IDEAL trial),[24] (5) Study of Effectiveness of Additional Reduction in Cholesterol and Homocysteine (SEARCH),[25] and (6) Early Intensive versus a Delayed Conservative Simvastatin Strategy in patients with ACS, phase Z of the A to Z (Aggrastat to Zocor) trial.[26]

In the landmark 4S trial, 4,444 patients with previous history of angina or MI with elevated cholesterol (5.5–8 mmol/L) were randomized to simvastatin (n = 2,221) and placebo (n = 2,223). Simvastatin reduced mean TC by 25%, mean LDL-C by 35%, and increased HDL-C by 8% over 5.4 years of median follow-up. This translated with reduction in death with simvastatin 182 (8%) versus 256 (12%) in placebo. There was 30% RR reduction in death with simvastatin (RR 0.70; 95% CI 0.58–0.85; p = 0.003). Coronary deaths were 111 in simvastatin group versus 189 in placebo group (RR 0.58; 95% CI 0.46–0.73). Non-CV causes of death were 46 and 49, respectively. Overall, 4,311 (19%) in the simvastatin group and 622 (28%) patients in the placebo group had a major coronary event (RR 0.66; 95% CI 0.59–0.75; $p < 0.00001$). There was 37% RR reduction for myocardial revascularization ($p \leq 0.00001$). The number needed to treat (NNT) was 30. There was no excess of adverse events.[22]

JAYPEE BROTHERS

In the LIPID trial, 9,014 patients aged between 31 and 75 years, who were admitted for unstable angina or acute MI and had cholesterol level between 155 and 271 mg/dL, were randomized to placebo or pravastatin 40 mg/day. The primary end point was mortality for CHD. Over a mean follow-up of 6.1 years, CHD death was 8.3% in placebo arm versus 6.4% in the pravastatin arm (RR 0.76; 95% CI 0.12–0.35; $p \leq 0.001$). Overall mortality was 14.1% in the placebo group versus 11.0% in the pravastatin group (RR 0.78; 95% CI 0.13–0.31; $p \leq 0.001$). The effects were consistent in all predefined subgroups. There were no clinically significant adverse events with pravastatin.[23]

The TNT trial addressed the efficacy and safety of lowering LDL below 100 mg/dL (2.6 mmol/L) in stable CAD patients. A total of 10,001 patients with clinically stable CAD with LDL level <130 mg/dL (34 mmol/L) were randomized to atorvastatin 10 mg versus atorvastatin 80 mg dosage. The primary end point was the occurrence of a major CV event, defined as death from CHD, nonfatal procedure-related MI, resuscitation after cardiac arrest, and fatal or nonfatal stroke. Over a mean follow-up of 4.9 years, LDL was lowered to mean 77 mg/dL (2.0 mmol/L) with 80 mg and to 101 mg/dL (2.6 mmol/L) with 10 mg atorvastatin. Primary event occurred in 434 (8.7%) patients on 80 mg dose versus 548 (10.9%) patients on 10 mg dose. Absolute reduction in risk was 2.2%. There was RR reduction with 22% (HR 0.78; 95% CI 0.69–0.89; $p < 0.007$). The overall mortality was not significantly different. Persistent liver aminotransferase elevation was seen in 0.2% in 10 mg group and 2.2% in 80 mg group ($p < 0.001$).[24]

The IDEAL trial assessed the high-dose atorvastatin (80 mg) versus standard dose simvastatin (20 mg) for secondary prevention of CAD following MI. A total of 8,888 patients aged 80 years or below were randomized to atorvastatin ($n = 4,439$) versus simvastatin ($n = 4,449$). The primary end point was major coronary event defined as coronary death, nonfatal MI, or resuscitation from cardiac arrest. Over a median follow-up of 4.8 years, mean LDL was lowered to 104 [standard error (SE) 0.3] mg/dL with simvastatin and to 81 (SE 0.3) mg/dL with atorvastatin. Major coronary events occurred in 463 (10.4%) patients in the simvastatin group as compared with atorvastatin group (411; 9.3%) (HR 0.89; 95% CI 0.78–1.01; $p = 0.07$). Intensive lipid lowering did not reduce the primary end point significantly. However, the composite secondary end point and nonfatal MI were reduced. Transaminase elevation was higher, 43 (1%) versus 5 (0.1%; $p < 0.001$) with 80 mg dose of atorvastatin.[25]

In the SEARCH trial, 12,064 patients with past MI were randomized to simvastatin 80 mg versus 20 mg dose regimen. This study also had a homocysteine-lowering arm. Overall, 6,031 patients received 80 mg and 6,033 patients received 20 mg dose of simvastatin. The 80 mg dosage caused a further reduction in TC (0.6 mmol/L), LDL-C (0.5 mmol/L), and TGs (0.2 mmol/L). Major vascular events occurred in 1,477 (24.5%) patients on 80 mg/dL versus 1,553 (25.7%) on 20 mg/dL (RR 0.94; 95% CI 0.88–1.01; $p = 0.010$). Hemorrhagic stroke and vascular or nonvascular deaths were not significantly different. Myopathy occurred in 2 (0.03%) with 20 mg versus 53 (0.9%) with 80 mg dosage.[26]

Trials of Statins in Acute Coronary Syndrome

Each and every patient with ACS, including patients with acute ST-elevation myocardial infarction (STEMI), non-ST elevation MI

JAYPEE BROTHERS

TABLE 2: Early statin trial in acute coronary syndrome.

Trials	*Drugs*	*Initiation*	*Duration*
MIRACL	Atorvastatin vs. placebo	96 hours	4 months
PROVE IT-TIMI 22	Pravastatin vs. atorvastatin and gatifloxacin vs. placebo	1–10 days	24 months
FLORIDA	Fluvastatin vs. placebo		
A to ZTrial (Z phase)	Tirofiban/simvastatin	1–10 days	12 months
PACT	Pravastatin vs. placebo	<24 hours	1 month
L-CAD	Pravastatin vs. placebo	<6 days	6 months
PRINCESS	Cerivastatin/placebo	96 hours	3 months

[A to Z TRIAL (Z phase): Aggrastat to Zocor; FLORIDA: Fluvastatin on Risk Diminishing after Acute; L-CAD: Lipid-Coronary Artery Disease; MIRACL: Myocardial Ischemia Reduction with Acute Cholesterol Lowering; PACT: Pravastatin ACS Treatment; PROVE IT-TIMI 22: Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22]

(non-STEMI), and unstable angina, should receive statin therapy at the earliest for secondary prevention of coronary events. The various trials of statins conducted in the setting of ACS are: (1) Myocardial Ischemia Reduction with Acute Cholesterol Lowering Trial (MIRACL),[27] (2) Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI-22) trial,[28] (3) Fluvastatin on Risk Diminishing After Acute MI (FLORIDA) trial,[29] (4) A to Z trial,[30] (5) Pravastatin Acute Coronary Syndrome Treatment (PACT),[31] and (6) LIPID-CAD [Lipid-Coronary Artery Disease (L-CAD)] study **(Table 2)**.[32]

In the MIRACL study, 3,806 patients were randomly assigned to receive 80 mg of atorvastatin or placebo within 24–96 hours of a non-Q-wave myocardial infarction (QMI) (54% patients) or unstable angina (46% patients). In all, 23% of patients had type 2 DM, 55% patients were hypertensive, and 28% of patients were smoking at the time of randomization. The follow-up period was 4 months. The composite end point of death, recurrent MI, cardiac arrest, and resuscitation or worsening angina with hospitalization had occurred in 14.8% of patients in the atorvastatin group versus 17.4% of the placebo group (RR 0.84; p = 0.048). Individually, symptomatic ischemia with objective evidence and emergency hospitalization was the only end point that was significant (6.2 vs. 8.4% for atorvastatin vs. placebo, respectively; $p = 0.02$). The rate of serious adverse events was similar (<1%) in both the groups.[27]

In the PROVE IT-TIMI 22 trial, 4,162 patients who had been hospitalized for ACS within preceding 10 days were randomized to either pravastatin 40 mg daily or atorvastatin 80 mg daily. The primary end point was a composite of all-cause mortality, MI, unstable angina requiring hospitalization, revascularization (performed at least 30 days after randomization), and stroke. The follow-up period was 18–36 months (mean 24 months). In the atorvastatin group, the median LDL was 62 mg/dL (1.60 mmol/L) compared with 95 mg/dL in the pravastatin group (2.46 mmol/L; $p \leq 0.001$). Kaplan–Meier estimates of the rates of the primary end point at 2 years were 26.3% in the pravastatin group

JAYPEE BROTHERS

for detailed information on cardiology books, visit our website www.ejaypee.com, for detailed information on cardiology books, visit our website www.ejay

Handbook of Lipidology

The third edition of *Handbook of Lipidology* has 25 chapters, which cover the complex subject of lipidology from the basics to bedside. Similar to the first and second editions, leading academicians and medical practitioners of the country have addressed the various aspects of lipidology in an easily understandable manner. The first chapter itself gives a reader a 360° idea of lipid biology. "Clinical Approach to Lipid Disorders" is a novel chapter that presents a step-by-step approach to lipid disorders. The chapter on "Statins" is a comprehensive updated document, which enriches the reader to have a solid foundation on statins. This book is a must-read for all the statin prescribers and clinicians in medicine and cardiology dealing with lipid management during daily practice. A new chapter on "Bempedoic Acid" has been added in this new edition. Key points at the end of each chapter are very helpful for the busy clinicians. Recently published multiple lengthy guidelines have been condensed in the chapter on "Guidelines". This book will be of immense help to the postgraduates for the preparation of National Board of Examination, Royal College of Physicians, Specialty Board Examinations, and exit examinations of various universities.

Tapan Ghose MD DNB (Medicine) DNB (Cardiology) FNB (Interventional Cardiology) MNAMS FCSI FIMSA FACC FSCAI is graduated in medicine with honors in Biochemistry and was awarded the Dr Anjan Chakravorty Memorial Medal in Medicine from Silchar Medical College and Hospital, Silchar, Assam, India. He has been trained in Medicine in Assam Medical College, Dibrugarh, and was awarded MD (Medicine) and DNB (Medicine) in 1993. After working at the Safdarjung Hospital, New Delhi, he joined the Batra Hospital and Medical Research Centre in 1997. He was awarded DNB (Cardiology) and FNB (Interventional Cardiology) by the National Board of Examinations. Subsequently, he worked at the Fortis Escorts Heart Institute and Paras Hospitals. Currently, he is the Senior Director and Head, Department of Cardiology, and Head, Department of Clinical Research and Academics, Fortis Flt Lt Rajan Dhall Hospital, New Delhi. He is the recipient of "Cardiologist of the Year 2014" at the India Health and Wellness Summit and Awards; Legends in Cardiology, Times Achievers Awards; Distinguished Service Award 2020; Rotary Club of Delhi Vasant Valley; Economic Times Inspiring Cardiologist Award 2021; Outstanding Clinician Awards 2021 by the National Diabetes, Obesity and Cholesterol Foundation, etc. He has a keen interest in clinical research and postgraduate teaching. He has contributed to more than 200 papers, abstracts, and chapters in various national and international journals, including multicenter clinical trials such as ASCEND HF, IMPROVE IT, and TUXEDO. The first research paper on atorvastatin in India was presented by him in 2000. He is a Task Group Member for guidelines for the management of cardiovascular diseases in India and a Member of the Writing Committee for the Cardiological Society of India (CSI) Clinical Practice Guidelines for Dyslipidemia, 2023.

Shelving Recommendation
CARDIOLOGY

ISBN 978-93-6616-520-2

Buy from ejaypee

JAYPEE BROTHERS