

HMG-COA REDUCTASE INHIBITORS/STATINS

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EXECUTIVE SUMMARY

Several drugs are currently available for the treatment of hyperlipidemia, but the most potent agents are known as HMG CoA reductase inhibitors or statins. Currently available statins include: atorvastatin (Lipitor); fluvastatin (Lescol); lovastatin (Mevacor); pravastatin (Pravachol); simvastatin (Zocor); and, rosuvastatin (Crestor). All are effective in modifying low-density lipoproteins (LDL), high-density lipoproteins (HDL, total cholesterol (TC) and triglycerides (TG). All agents lower LDL in a dose dependent manner, approximately 20-38% with initial doses and 35-61% with maximal doses¹. The newest statin, rosuvastatin has been called a “superstatin” because it appears to have the ability to reduce low-density lipoprotein cholesterol (LDC-C) and increase HDL cholesterol (HDL-C) to a greater degree than the other approved statins, providing a 63% LDL-C reduction at a dose of 40 mg. Atorvastatin lowers elevated triglyceride levels more effectively than do the other statins.

The Third Expert Report of the National Cholesterol Education Program (NCEP)² recognizes LDL-C to be the primary target in the management of hyperlipidemia. Reducing elevated LDL-C levels has been shown to reduce the incidence of cardiovascular events, including transient ischemic attacks and stroke, and to reduce all-cause mortality. As a result, recommendations for initiation of treatment and goals of therapy are based primarily upon LDL-C. Several primary and secondary clinical trials have demonstrated that lovastatin, pravastatin, and simvastatin can reduce the occurrence of coronary heart disease death and nonfatal myocardial infarction. Most authorities believe that these benefits may well be a class effect shared by other statins.

Adverse effects are uncommon and usually mild. The most common adverse effects include headache, myalgias (without CPK changes) and GI symptoms (dyspepsia, flatus, constipation, and abdominal pain). More serious but rare side effects include hepatotoxicity and myopathy. Statins have been associated with elevated transaminases in approximately 1-2% of patients, usually occurring 3 to 12 months after initiation of therapy. Elevated transaminases are defined as being greater than three times the upper limit of normal.

The majority of statins depend on the P450 3A4 enzyme system for metabolism and can interact with other drugs using this pathway (common drugs include macrolides, calcium channel blockers, azole antifungals, and nefazodone), resulting in higher statin blood levels and possible myositis. Lovastatin and simvastatin are most vulnerable to this interaction. Other statins have less dependence on this enzyme pathway and theoretically are less likely to encounter this interaction. Pravastatin is not metabolized by this enzyme system.

To summarize, evidence from clinical trials, the NCEP Guidelines, and the increasing focus on aggressively lowering LDL-C all position the statins as having an important role in both the primary and secondary prevention of coronary heart disease, myocardial infarction, stroke, and peripheral artery disease.

I. INDICATION

Labeled Indications for Statins						
Indication	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Primary hypercholesterolemia	✓ ¹	✓ ¹	✓ ¹	✓ ¹	✓ ¹	✓ ¹
Mixed dyslipidemia	✓ ²	✓ ²		✓ ²	✓ ²	✓ ²
Hypertriglyceridemia	✓ ³			✓ ³	✓ ³	✓ ³
Primary dysbetalipoproteinemia	✓ ⁴			✓ ⁴		✓ ⁴
Homozygous familial hyperlipidemia	✓				✓	✓
Primary prevention coronary events			✓	✓		✓
Secondary prevention cardiovascular event(s)		✓	✓	✓		✓

¹Includes heterozygous familial and nonfamilial hypercholesterolemia.

²Includes Fredrickson types IIa and IIb.

³Includes Fredrickson type IV.

⁴Includes Fredrickson type III.

II. MECHANISM OF ACTION

All statins competitively inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early precursor of cholesterol. This leads to a compensatory increase in the number of LDL receptors, primarily in the liver, an increase in LDL plasma clearance and a reduction in LDL production. Although the most pronounced effect of statins is the lowering of LDL-C levels, these agents also increase HDL-C and decrease total-C and plasma triglycerides.

III. PHARMACOKINETICS

The bioavailability for atorvastatin, fluvastatin, pravastatin, and rosuvastatin range from 14-34%, whereas the bioavailability for lovastatin and simvastatin are only ~5% because of an extensive first-pass effect. Atorvastatin, lovastatin, and simvastatin are transformed by the cytochrome P450 system to active and/or inactive metabolites. Fluvastatin is primarily metabolized by CYP2C9 and may interact with CYP2C9 inhibitors. Pravastatin is not significantly metabolized by the cytochrome P450 system and may be less likely to be involved in drug interactions. Statins and their metabolites are eliminated mainly by biliary excretion and to a much lesser extent by the kidneys. Renal impairment may involve initial lower doses for lovastatin, pravastatin, and rosuvastatin. Atorvastatin and fluvastatin do not require any dose adjustment. Statin therapy is not recommended in patients with active liver disease.

Pharmacokinetics of Statins						
Drug	Bioavailability	Excretion	t _{1/2} (hrs)	Major metabolites	Protein binding	Effects of renal/hepatic impairment
Atorvastatin	≈14% absolute bioavailability; first-pass metabolism (CYP3A4)	< 2% (urine)	≈14 ¹	Metabolized to ortho- and parahydroxylated derivatives (active)	≥ 98%	Plasma levels not affected by renal disease but markedly increased with chronic alcoholic liver disease.
Fluvastatin	98% absorbed; absolute bioavailability 24%; extensive first-pass metabolism (CYP2C9)	< 6% (urine) ≈90% (feces)	< 1	Hydroxylated metabolites (active, do not circulate systemically)	98%	Potential drug accumulation with hepatic insufficiency.
Lovastatin	≈35% absorbed; extensive first-pass metabolism (CYP3A4); < 5% of oral dose reaches general circulation	10% (urine) 83% (feces)	3 to 4	Beta-hydroxyacid; 6'-hydroxy derivative; 2 additional metabolites	> 95%	Increased plasma concentration with severe renal disease.
Pravastatin	34% absorbed; absolute bioavailability 17%; extensive first-pass metabolism; plasma levels may not correlate with efficacy	≈ 20% (urine) 70% (feces)	1.8	Major degradation product: 3 α-hydroxyl isomeric metabolite	≈ 50%	Mean AUC varied 18-fold in cirrhotic patients; peak values varied 47-fold. Initial doses decreased in severe renal impairment
Rosuvastatin	20% absorbed; not extensive first-pass metabolism	10% (urine) 90% feces)	19	N-desmethyl derivative	88%	Increased plasma concentration with severe renal disease. (CrCl<30ml/min)
Simvastatin	60% to 80% absorbed; extensive first-pass metabolism (CYP3A4); < 5% of oral dose reaches general circulation	13% (urine) 60% (feces)	3	Beta-hydroxyacid; 6'-hydroxy, 6'-hydroxymethyl, 6'-exomethylene derivatives	≈95%	Increased plasma concentration with hepatic and severe renal insufficiency.

¹For unmetabolized atorvastatin only. The t_{1/2} is 20 to 30 hours for the active metabolites.

IV. CLINICAL TRIALS

All of the statins lower cholesterol and raise HDL-C in a dose-dependent manner. If the needed LDL-C reduction is in the 35% range, any of the statins should be effective. If the LDL-C reduction is greater than 42%, simvastatin, atorvastatin, or rosuvastatin are the recommended agents because of their greater potency. The comparative cholesterol lowering effects of the statin drugs are noted below.

Comparison of Lipid-Lowering Properties of Statins (adapted from reference 1)						
	Mean Percentage Change from Baseline (%)					
	Atorvastatin 10 - 80 mg	Fluvastatin 10 - 80 mg ¹	Lovastatin 10 t - 80 mg	Pravastatin 10 - 40 mg	Rosuvastatin 5 - 40mg	Simvastatin 10 - 80 mg
TC*	↓ 28.2 - 45	↓ 14.6 - 19.5 ²	↓ 16 - 29	↓ 16 - 25	↓ 10 - 35	↓ 23 - 36
LDL-C	↓ 26.5 - 60	↓ 18.9 - 35	↓ 21 - 40	↓ 22 - 34	↓ 43 - 62	↓ 14 - 47
Apo-B	↓ 32 - 50	NA	NA	NA	↓ 38 - 54	NA
TG	↓ 19 - 51.8	↓ 2.7 - 10.6 ²	↓ 6 - 10	↓ 11 - 24	↓ 10 - 35	↓ 10 - 36
HDL-C	↑ 5 - 13.8	↑ 2.5 - 7.8 ²	↑ 2 - 9.5	↑ 7 - 12	↑ 8 - 14	↑ 8 - 12

*TC = total cholesterol, LDL-C = low-density lipoprotein cholesterol, Apo-B = apolipoprotein B, TG = triglyceride, HDL-C = high-density lipoprotein cholesterol, NA = not available, ↑ = increase, ↓ = decrease.

¹Fluvastatin 10 mg is below recommended starting doses.

²Information from placebo controlled trials using fluvastatin 10 to 40 mg.

V. CONTRAINDICATIONS

Contraindications include active liver disease or unexplained persistent elevated baseline liver function tests to above three times the upper limit of normal. They are also contraindicated in patients with hypersensitivity to a statin, in pregnancy and lactation. Statins are categorized in pregnancy category X; animal studies have shown that statins may cause fetal harm. Because of the potential for serious adverse reactions in nursing infants, women should not breastfeed when taking statins.

VI. WARNINGS

Muscle Effects: Transient, mildly elevated creatine phosphokinase (CPK) levels are commonly seen and are usually of no clinical consequence. Uncomplicated myalgia has been reported in atorvastatin- and fluvastatin-treated patients. Myopathy should be considered especially if it is in conjunction with increases in CPK values greater than ten times the upper limit of normal, diffuse myalgias, muscle tenderness, and/or weakness. Rhabdomyolysis may occur with this class of agents with renal dysfunction or acute renal failure secondary to myoglobinuria. Concomitant therapy with cyclosporine, erythromycin, gemfibrozil, fibric acid derivatives, azole antifungals, or lipid-lowering doses of nicotinic acid have been shown to increase the risk of myopathy (see Drug Interactions). Because fibrates may occasionally be associated with myopathy, avoid the combined use of statins and fibrates.

If markedly elevated CPK levels occur or if myopathy is diagnosed or suspected, it is recommended that the statin be discontinued. It is important to advise patients to promptly report muscle pain, tenderness or weakness, particularly associated with malaise or fever.

Hepatic Effects: Marked persistent increases (> 3 times the upper limit of normal occurring on ≥ 2 occasions) in serum transaminases have been reported with all the statins. When the drug was interrupted or discontinued or the dosage was reduced, transaminase levels usually fell slowly to pretreatment levels. Increases usually appeared 3-12 months after starting lovastatin therapy and were not associated with jaundice or other clinical signs or symptoms. In pravastatin-treated patients, abnormalities did not appear to be related to treatment duration and were not associated with cholestasis.

It is recommended that liver function tests (LFTs) be performed before the initiation of statins, 6 and 12 weeks after initiation of therapy or increase in dose, and periodically, i.e., semiannually thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin, or fluvastatin and within 3-12 months of starting lovastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve.

If an increase in ALT or AST > 3 times the upper limit of normal persists after a repeated test, reduce dose or discontinue statin.

Children: Safety and efficacy in individuals < 18 years of age have not been established. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited, treatment in this age group is not recommended.

VIII. DRUG INTERACTIONS

Statin Drug Interactions		
Precipitant drug	Object drug*	Description
Alcohol	<i>Fluvastatin</i> ↑	Daily intake of 20 g alcohol > 2 hours after the evening meal and within 1 hour of fluvastatin increases fluvastatin AUC by 30% and t_{max} by > 40%.
Antacids	<i>Atorvastatin</i> ↓	Coadministration with Maalox TC suspension decreased atorvastatin levels by \approx 35%; LDL-C reduction was not altered.
Azole antifungals Itraconazole Ketoconazole	All statins ↑	Coadministration increased lovastatin levels \approx 20-fold in healthy volunteers. Temporarily interrupt/consider reducing the dose of HMG-CoA reductase inhibitors if systemic azole antifungals are needed. The risk of myopathy is increased.
Bile acid sequestrants (BAS)	All statins ↓	A decrease in pravastatin (40% to 50%) and lovastatin bioavailability may occur. Take pravastatin 1 hour before or 4 hours after BAS. Coadministration of cholestyramine with fluvastatin resulted in decreased AUC and C_{max} . Take fluvastatin 4 hours after cholestyramine. Taking cholestyramine before the evening meal and cerivastatin at bedtime would not be expected to result in a significant decrease in the clinical effect of cerivastatin. Plasma levels of atorvastatin decreased \approx 25% with coadministration with colestipol.
Cyclosporine	All statins ↑	Concurrent administration increases risk of severe myopathy or rhabdomyolysis.
Erythromycin	All statins ↑	Coadministration increases the risk of severe myopathy or rhabdomyolysis. Atorvastatin plasma levels increased by \approx 40%.
Fibric acid derivatives Gemfibrozil	All statins ↑	Severe myopathy or rhabdomyolysis reported with lovastatin. Urinary excretion and protein binding of pravastatin may be decreased. Avoid concurrent use.
Cimetidine Ranitidine Omeprazole	<i>Fluvastatin</i> ↑	Coadministration results in a significant increase in fluvastatin C_{max} (43% to 70%) and AUC (24% to 33%), with an 18% to 23% decrease in plasma clearance.
Isradipine	<i>Lovastatin</i> ↓	Isradipine may increase clearance of lovastatin and its metabolites by increasing hepatic blood flow.
Nicotinic Acid	All statins ↑	Concurrent administration increases risk of severe myopathy or rhabdomyolysis.
Propranolol	<i>Simvastatin</i> ↔	Concomitant administration resulted in a significant decrease in C_{max} .
Rifampin	<i>Fluvastatin</i> ↓	Coadministration may cause a decrease in fluvastatin C_{max} and AUC and an increase in plasma clearance.
Atorvastatin	Oral contraceptives ↑	Coadministration increased AUC for norethindrone and ethinyl estradiol by \approx 30% and 20%, respectively.
All statins	Digoxin ↑	Slight elevation in digoxin levels possible. Concomitant multiple doses of atorvastatin and digoxin increased steady-state digoxin levels by \approx 20%. A 40 mg fluvastatin dose demonstrated an 11% increase in digoxin C_{max} and a slight increase in digoxin urinary clearance. Monitor digoxin patients appropriately.
Lovastatin Simvastatin	Warfarin ↑	Increased prothrombin time has been demonstrated with concomitant use of lovastatin and simvastatin. Bleeding has also been reported in a few patients concomitantly receiving lovastatin.

* ↑ = Object drug increased. ↓ = Object drug decreased. ↔ = Undetermined clinical effect.

Drug/Food Interaction: Administration of lovastatin, atorvastatin and simvastatin with grapefruit or grapefruit juice has shown decreased metabolism of the statin, resulting in higher drug levels, sometimes with increases in clinical effects and/or side effects, such as rhabdomyolysis. Studies have shown that separation of grapefruit and statins by 12 hours may minimize the interaction.

IX. ADVERSE EFFECTS

These agents are generally well tolerated; adverse reactions are usually mild and transient. In placebo controlled trials, less than 2% of atorvastatin-, 1% of fluvastatin-, and 1.7% of pravastatin-treated patients discontinued treatment because of adverse events; the most common reasons for discontinuation of pravastatin were asymptomatic serum transaminase increases and mild, non-specific GI complaints.

X. DOSAGE

Statins should be used in conjunction with other appropriate lifestyle modifications such as diet and exercise. The dose of the statin should be based mainly on target lipid levels, e.g. LDL-C. Generally, the lowest dose that produces and maintains the desired levels should be used. Additional factors such as alcohol intake and concurrent drug therapy may influence the initial dose. Advanced age is generally not a factor in determining initial doses of statins, although some have recommended a lower initial dose as a precaution. Maximum therapeutic benefit is usually seen after 4 weeks of therapy at a given dose. Dose adjustments should be made at intervals of no less than 4 weeks

Statins are usually taken in one daily dose in the evening, presumably to coincide with cholesterol synthesis, which is thought to peak in the early morning hours.

Depending on the statin used, patients should take this class of medication consistently with or without food. Under fasting conditions, lovastatin levels are $\approx 2/3$ of those found when given immediately after meals; therefore, it is recommended that patients take lovastatin with meals; simvastatin, fluvastatin, atorvastatin and pravastatin may be taken without regard to meals.

XI. PATIENT EDUCATION

- May cause photosensitivity, e.g. sensitivity to sunlight). Avoid prolonged exposure to the sun and other ultraviolet light. Use sunscreens and wear protective clothing until tolerance is determined.
- This group of medications has been shown to cause certain birth defects. If you are pregnant or think you may be pregnant, stop taking the drug immediately to avoid harmful effects in the developing fetus.
- Promptly report unexplained muscle pain, tenderness, or weakness, especially if accompanied by fever or malaise.
- Follow recommendations regarding therapeutic lifestyle changes, e.g. diet changes and exercise regimens.
- Take lovastatin with meals; fluvastatin, pravastatin, simvastatin, and atorvastatin may be taken without regard to meals.

XII. References

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