

Defining the Pharmacological Profile of Rosuvastatin: A Look at Statin Therapy for Dyslipidemia

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Abstract

Several statins are currently available for use in managing patients who require lipid-lowering therapy. These statins provide effective LDL-C lowering and proven long-term safety. However, the therapeutic potential of these agents may not be maximized. Rosuvastatin, currently under investigation, is a potent inhibitor of HMG-CoA reductase, which in clinical studies demonstrates a superior lowering of LDL-C and non-HDL-C levels compared with leading statins. The specificity of rosuvastatin, in addition to its tissue selectivity, long half life, modest bioavailability, low potential for drug interactions, and limited renal elimination will make it an attractive addition to the lipid lowering therapeutic armamentarium.

Background

- Statin with demonstrated long-term safety and lipid-lowering efficacy have been available for more than a decade; type 1 agents are fungus-derived; (eg, simvastatin, lovastatin, pravastatin) and type 2 agents are synthetic; (eg, fluvastatin, atorvastatin)
- Although all the statins are effective at lowering LDL-C, new research indicates that the magnitude of this effect can be enhanced
- In spite of their LDL-C lowering efficacy, only 30-70% of patients can achieve their LDL-C treatment goals with currently available statins even with use of maximum doses
- Rosuvastatin (formerly ZD4522) is a synthetic statin that provides greater LDL-C lowering than statins currently on the market. Research indicates that it is capable of achieving treatment goals in the majority of patients, even with starting doses and even in patients with a CHD or CHD risk equivalent who have the lowest LDL-C treatment goal

Objective

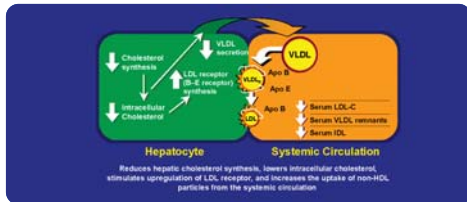
- To review the pharmacological properties of rosuvastatin, alongside other statins currently on the market

Pharmacological Profile

Mechanism of Action

- Statin act by reversibly inhibiting HMG-CoA reductase (HMGR), an enzyme involved in the biosynthesis of cholesterol
- By reducing hepatic cholesterol synthesis, statins lower intracellular cholesterol, stimulate up-regulation of LDL receptors, and increase the uptake of apolipoprotein-B-containing particles (ie, VLDL-C and LDL-C) from the circulation (Figure 1)

Figure 1. Statins: Mechanism of Action



- The more potent statins also reduce the liver secretion of VLDL, thereby providing another mechanism for lowering LDL-C levels

Differences Between Inhibitors of HMGR

- Statin inhibit HMGR by binding to the catalytic domain of the enzyme and thereby blocking access of HMG-CoA and inhibiting its conversion to mevalonic acid. The number and type of bonds between the statin and the HMG-binding pocket of HMGR determine the extent of the inhibition
- All statins exhibit a similar number of van der Waals interactions (about 8) between the HMG-CoA moiety on the statin structure and the binding pocket of the HMGR
- Type 2 statins exhibit another polar bond between the fluorine atom on their fluorophenyl group and an amino acid in the binding domain of HMGR
- Atorvastatin and rosuvastatin uniquely form an additional hydrogen bond between the carbonyl oxygen atom (atorvastatin) or sulfone oxygen atom (rosuvastatin) and the enzyme
- Rosuvastatin forms an additional, unique polar bond between the electronegative sulfone group and the HMGR structure. It is likely that the greater number or strength of bonds between rosuvastatin and the HMGR enzyme account for its superior cholesterol lowering effect (Figure 2a and b)

Figure 2a. 2-Dimensional Chemical Structures of Statins

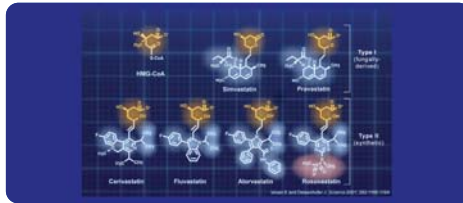
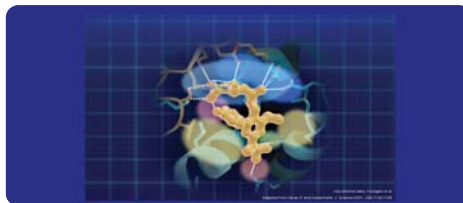


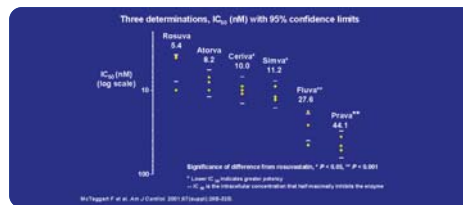
Figure 2b. Rosuvastatin Binding



Potency of HMGR Inhibition by Statins

As indicated by the concentration required to inhibit 50% of the activity of the HMGR enzyme in an *in vitro* study, rosuvastatin is determined to be a more potent inhibitor of the enzyme than other statins (Figure 3)

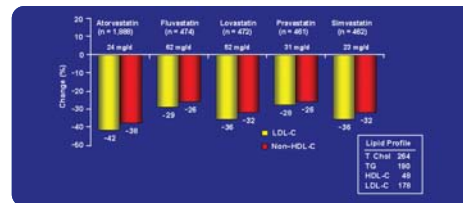
Figure 3. Potency* of Inhibition of HMG-CoA Reductase by Statins



LDL-C and non-HDL-C Lowering

- The National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) has reaffirmed the importance of lowering LDL-C to reduce the risk of coronary heart disease (CHD)
- NCEP ATP III has also established non-HDL-C as a secondary target of treatment for patients who have triglyceride levels over 200 mg/dL
- Statin are the most effective way of lowering LDL-C. The greatest LDL-C lowering is produced with the recommended starting dose; thereafter, LDL-C is reduced only about 6% with each doubling of the daily dose
- The effect of statins on non-HDL-C follows closely their LDL-C lowering efficacy; that is, the more potent LDL-C lowering statins are also the most potent non-HDL-C lowering statins
- In an open-label, randomized, parallel-group, 54-week study (the Atorvastatin Comparative Cholesterol Efficacy and Safety Study [ACCESS]), atorvastatin treatment yielded greater reductions in LDL cholesterol and non-HDL cholesterol than with the other currently available statins (Figure 4)

Figure 4. Change in LDL-C and non-HDL-C in Patients at 54 Weeks



- In a randomized, double-blind, placebo-controlled trial comparing the effects of rosuvastatin with atorvastatin in hypercholesterolemic patients, rosuvastatin 10 mg/day lowered LDL-C and non-HDL-C significantly more than atorvastatin 10 mg/day (Table 1)

Table 1. Effect of Rosuvastatin Versus Atorvastatin: On LDL-C and non-HDL-C

	Rosuvastatin 10 mg	Atorvastatin 10 mg
LDL-C	-43%	-35%
Non-HDL-C	-43%	-34%

Raising HDL-C

- Most statins produce a modest, but perhaps important raising effect on HDL-C, which is accompanied by an increased production of ApoA-1.
- There are differences between statins in their effect on HDL-C.¹
 - Most statins and most doses increase HDL-C 5-10%
 - The HDL-C raising effect of atorvastatin appears to diminish as doses are increased to 80 mg/d
 - The HDL-C raising effect of rosuvastatin is often between 10-15%

Pharmacokinetics of Statins

- The pharmacokinetic properties of rosuvastatin and other statins are summarized in Table 2

Table 2. Statin Pharmacokinetics and Bioavailability¹⁻¹¹

Characteristic	Rosuvastatin	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Prodrug, +/-	-	-	+	+	-	+
Active metabolites, +/-	-	-	+	-	+	+
Elimination half-life, h	20	14	<1	3-4	1.8	3
Bioavailability, %*	20	12	24	<5	17	<5
Excretion, %						
Urine	10	<2	5	10	20	13
Feces	90	>98	90	83	70	60
Protein binding, %	88	90	98	>95	50	95
Mechanism of hepatic metabolism (minor)	CYP2C9	CYP3A4	CYP2C9	CYP3A4	Sulfation	CYP3A4
Increased concentration with 3A4 inhibitors, +/-	Not expected	+	-	+	-	+

CYP=cytochrome P450; 3A4= cytochrome P450 3A4 isozyme.

*Percentage of active drug appearing in systemic circulation

- The ideal statin would have a
 - Long half-life (supporting once daily dosing)
 - Modest bioavailability (limiting systemic exposure)
 - Little renal excretion (limiting accumulation in renal impairment)
 - Low protein binding (limiting drug interactions)
 - Little or no metabolism via CYP 450 3A4 (limiting drug interactions)

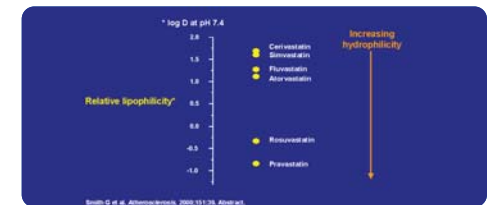
Bioavailability of Statins

- Most statins are subject to extensive first-pass metabolism by the cytochrome P450 enzyme system (Table 2)
- Notable exceptions include:
 - Pravastatin, which is eliminated through sulfation
 - Rosuvastatin, which undergoes metabolism via 2C9 of 10% of its dose
- Plasma concentrations may be higher in patients with renal disease for those statins which are eliminated in part through the kidneys¹²

Tissue Selectivity

- The hydrophilicity of statins may affect their selectivity for hepatic or nonhepatic tissues¹³
- Hydrophilicity favors hepatic selectivity
- The relative hydrophilicities of the statins are shown in Figure 5
 - Pravastatin is the most hydrophilic statin
 - Rosuvastatin is relatively hydrophilic, but is intermediate between pravastatin and other statins

Figure 5. Statin Octanol-Water Coefficients



Summary

- Rosuvastatin has demonstrated the important features of an ideal statin:
 - Potent inhibitor of HMG-CoA reductase
 - Liver selectivity
 - Attractive pharmacokinetic profile
 - Greater reductions in LDL-C and non-HDL-C and increases in HDL-C than currently available statins
 - Low potential for drug-drug interactions
- Based on these features, availability of rosuvastatin as a treatment option should improve the ability of patients to achieve established target goals for lipid lowering

References

- Ishtvan ES, Desseinerhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science*. 2001;292:1160-1164.
- Balantyne CM, Andrews TC, Hsia JA, et al. Correlation of non-high-density lipoprotein cholesterol with apolipoprotein B: effect of 5-hydroxytryptophan/tryptophan coenzyme A reductase inhibitors on non-high-density lipoprotein cholesterol levels. *Am J Cardiol*. 2001;88:265-269.
- Davidson M, Ma P, Stein EA, et al. Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. *Am J Cardiol*. 2002;90:268-275.
- Schaefer JR, Scheewe H, Ikwawaki K, et al. Metabolic basis of high density lipoproteins and apolipoprotein A-I increase by HMG-CoA reductase inhibition in healthy subjects and a patient with coronary artery disease. *Atherosclerosis*. 1999;144:177-184.
- Larsen ML, Illingworth DR. Drug treatment of dyslipoproteinemia. *Med Clin North Am*. 1994;78:225-245.
- McTegart F, Buckle L, Davidson R, et al. Preclinical and clinical pharmacology of rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Am J Cardiol*. 2001;87(suppl):29B-32B.
- Martin PD, Daise AL, Schneck DW, et al. Disposition of new HMG-CoA reductase inhibitor ZD4522 following dosing in healthy subjects [abstract]. *J Clin Pharmacol*. 2000;40:1056. Abstract 48.
- Simonson SG, Martin PD, Mitchell PD, et al. Pharmacokinetics and pharmacodynamics of rosuvastatin in hepatically impaired subjects [abstract]. *Clin Pharmacol Ther*. 2001;69(PB). Abstract P11-88.
- Prescribing information for Lipitor®, Zocor®, Mevacor®, Pravachol®, Lescol®, Physician's Desk Reference (PDR). 56th ed. Montvale, NJ: Medical Economics Co Inc; 2002.
- Lenzen H, Fager F. Pharmacokinetics and pharmacodynamics of the HMG-CoA reductase inhibitors. *Clin Pharmacokinet*. 1997;32:403-425.
- Blum CB. Comparison of properties of four inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. *Am J Cardiol*. 1994;73(suppl):3D-11D.
- Knapik RH. Treatment of lipid disorders. *N Engl J Med*. 1999;341:498-511.
- Buckle L, Ballard P, Davidson R, et al. Selectivity of ZD4522 for inhibition of cholesterol synthesis in hepatic versus non-hepatic cells [abstract]. *Atherosclerosis*. 2000;151:141. Abstract MoP29-166.

NCEP ATP III Guidelines: Getting the Most Patients to Goal

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Abstract

The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults has issued periodic reports outlining a strategy for prevention of coronary heart disease. In the most recent Adult Treatment Panel update, ATP III, emphasis is placed on reduction of low-density lipoprotein (LDL) cholesterol to specific target levels that vary according to the presence or absence of other risk factors: the higher the overall heart disease risk, the more aggressive the recommended LDL-C-lowering therapy. Recent controlled clinical trials have demonstrated dramatic reductions in risk of coronary heart disease with lipid-lowering therapy, including statin treatment. However, despite the availability of effective treatments, many patients do not attain the recommended treatment goals. Adherence to guidelines by both patients and providers is essential to maximizing the benefits of cholesterol lowering as demonstrated in clinical trials.

Background

- The third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) reflects observational and experimental data from key studies indicating that elevated LDL-C is a major cause of coronary heart disease (CHD). Thus, ATP III continues to identify LDL as the primary target of cholesterol-lowering therapy
 - Cholesterol is strongly associated with CHD mortality
 - A 10% reduction in total cholesterol results in a 15% reduction in CHD mortality risk and an 11% reduction in total mortality risk, according to a meta-analysis of 8 statin trials¹
- In the updated NCEP ATP III guidelines,¹ continuity is maintained with previous reports; however, emphasis is placed on the presence of CHD, CHD risk equivalents, and global risk assessment; consequently, more patients are considered candidates for intensive low-density lipoprotein cholesterol-lowering therapy than in previous recommendations
 - Three categories of risk are identified, for which different LDL cholesterol-lowering goals and intensities of therapy are proposed:
 - CHD and CHD risk equivalents
 - Multiple risk factors (2 or more)
 - 0 to 1 risk factors
- Risk assessment has become the first step in the selection of LDL-lowering therapy and requires measurement of LDL-C as well as other lipoprotein analyses and importantly, the identification of accompanying risk factors
- To maximize adherence to the ATP III guidelines, the NCEP Expert Panel provides recommendations directed at the patient, healthcare provider, and healthcare system to help achieve the effectiveness of the guidelines for primary and secondary prevention of CHD

Objective

- To review guidelines of the NCEP and summarize approaches to maximize the proportion of patients achieving the goals established by the guidelines

NCEP Guidelines¹

Patient Evaluation

- Initial evaluation of patients should include a complete lipoprotein profile after a 9- to 12-hour fast. ATP III guidelines suggest interpretation of profile results as summarized in Table 1

Table 1. Determination of Lipoprotein Levels After 9- to 12-Hour Fast

Lipoprotein Concentration Range (mg/dL)	Assessment
LDL Cholesterol	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
240	High
HDL Cholesterol	
<40	Low
60	High

- Patients should be evaluated for the presence of clinical atherosclerotic disease conferring high risk for coronary heart disease (CHD) events (CHD risk equivalents)
 - Clinical CHD
 - Symptomatic carotid artery disease
 - Peripheral arterial disease
 - Abdominal aortic aneurysm
 - Diabetes mellitus
- Presence of major risk factors other than LDL should be determined
 - Cigarette smoking
 - Hypertension (BP 140/90 mm Hg or on antihypertensive medication)
 - Low HDL cholesterol (<40 mg/dL)
 - HDL cholesterol 60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count
 - Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
 - Age (men 45 years; women 55 years)
- If 2+ risk factors other than LDL are present without CHD or CHD risk equivalent, 10-year (short-term) CHD risk should be determined using Framingham tables. The three levels of 10-year risk are:
 - >20%—CHD risk equivalent
 - 10-20%
 - <10%

Risk Category Determination

- LDL goals should be established, and the need for therapeutic lifestyle changes (TLC) or drug therapy should be considered (Table 2)

Table 2. LDL Cholesterol Goals and Cutoff Levels for Therapeutic Lifestyle Changes and Drug Therapy According to Risk Category

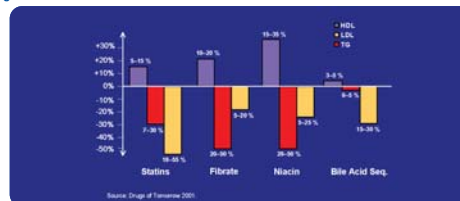
	LDL-cholesterol goal	LDL cholesterol level at which to initiate therapeutic lifestyle changes	LDL cholesterol level at which to consider drug therapy
CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL	100 mg/dL	130 mg/dL (100-129 mg/dL: drug optional)
2+ risk factors (10-year risk 20%)	<130 mg/dL	130 mg/dL	10-Year Risk 10%-20%: 130 mg/dL 10-Year Risk <10%: 160 mg/dL
0-1 risk factor	<160 mg/dL	160 mg/dL	190 mg/dL (160-189 mg/dL: LDL cholesterol-lowering drug optional)

- Initiate therapeutic lifestyle changes (TLC) if LDL is above goal; features of TLC include:
 - TLC diet
 - Saturated fat <7% of calories
 - Cholesterol <200 mg/day
 - Consider increased viscous (soluble) fiber (10-25 g/day) and plant stanols/sterols (2 g/day) as therapeutic options to enhance LDL lowering
 - Weight management
 - Increased physical activity

- Consider adding drug therapy if LDL exceeds cutoff levels (from Table 2)
 - Consider drug simultaneously with TLC for CHD and CHD equivalents
 - Consider adding drug to TLC after 3 months for other risk categories
- Drugs affecting lipoprotein metabolism include:
 - HMG-CoA reductase inhibitors (statins)
 - Lovastatin (20-80 mg)
 - Pravastatin (20-80 mg)
 - Simvastatin (20-80 mg)
 - Fluvastatin (20-80 mg)
 - Atorvastatin (10-80 mg)

- Bile acid sequestrants
 - Cholestyramine (4-16 g)
 - Colestipol (5-20 g)
 - Colesevelam (2.6-3.8 g)
- Nicotinic acid
 - Immediate release (crystalline) nicotinic acid (1.5-3.0 g)
 - Extended release nicotinic acid (Niaspan)[®] (1-2 g)
 - Sustained release nicotinic acid (1-2 g)
- Fibric acids
 - Gemfibrozil (600 mg BID)
 - Fenofibrate (200 mg)
 - Clofibrate (1000 mg BID)
- Lipid/lipoprotein effects of the different classes are summarized in Figure 1

Figure 1.



The Metabolic Syndrome

- The metabolic syndrome may be identified by the presence of any 3 of the factors listed in Table 3; if present after 3 months of TLC, the metabolic syndrome should be treated

Table 3. Clinical Identification of the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal obesity*	Waist circumference†
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	130/ 85 mm Hg
Fasting glucose	110 mg/dL

*Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.
†Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, eg, 94-102 cm (37-39 in). Such patients may have a strong genetic predisposition to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

- Treatment of the metabolic syndrome consists of:
 - Treatment of underlying causes (overweight/obesity and physical inactivity)
 - Intensification of weight management
 - Increase in physical activity
 - Treatment of lipid and non-lipid risk factors, if they persist despite lifestyle therapies
 - Treatment of hypertension
 - Use of aspirin for CHD patients to reduce thrombotic state
 - Treatment of elevated triglycerides and/or low HDL

Treatment of Elevated Triglycerides

- Triglycerides are considered to be elevated at levels of 150 mg/dL (Table 4)

Table 4. ATP III Classification of Serum Triglycerides

<150	Normal
150-199	Borderline high
200-499	High
500	Very high

- Treatment of triglyceride levels 150 mg/dL
 - The primary aim of therapy is to reach LDL goal
 - Weight management should be intensified
 - Physical activity should be increased
 - If triglycerides are 200 mg/dL after LDL goal is reached, a secondary goal should be set for non-HDL cholesterol (total minus HDL) that is 30 mg/dL higher than LDL goal

Table 5. Comparison of LDL-C and non-HDL-C Goals in the 3 risk categories

Risk Category	LDL-C Goal (mg/dL)	Non-HDL-C Goal (mg/dL)*
CHD and CHD risk equivalent (10-year risk for CHD >20%)	<100	<130
Multiple (2+) risk factors and 10-year risk 20%	<130	<160
0-1 risk factor	<160	<190

*Secondary goals for patients with TG 200 mg/dL.

- If triglyceride level is 200-499 mg/dL after LDL goal is reached, consider adding drug if needed to reach non-HDL goal
 - Intensify therapy with LDL-lowering drug, or
 - Add nicotinic acid or fibrate to further lower VLDL
- If triglyceride level is 500 mg/dL, first lower triglycerides to prevent pancreatitis:
 - Very low-fat diet (15% of calories from fat)
 - Weight management and physical activity
 - Fibrate or nicotinic acid
 - When triglycerides <500 mg/dL, turn to LDL-lowering therapy

Treatment of Low HDL Cholesterol (<40 mg/dL)

- First, reach LDL goal, then:
 - Intensify weight management and increase physical activity
 - If triglycerides 200-499 mg/dL, achieve non-HDL goal
 - If triglycerides <200 mg/dL (isolated low HDL) in CHD or CHD equivalent, consider nicotinic acid or fibrate

Conclusions

- NCEP ATP III guidelines suggest that the population eligible for lipid-lowering treatment should be increased due to recognition of additional risk factors for CHD
- Many patients do not achieve the recommended goals for LDL cholesterol, despite the availability of useful dietary and lifestyle modifications and pharmacologic agents with demonstrated lipid-modifying properties
- With greater utilization of treatment guidelines and increased attention to measures for improved adherence, the proportion of patients achieving goals for lipid-lowering treatment should be maximized
- Multiple recommendations have been made to improve overall treatment adherence; these include measures (patient-focused, provider-focused, and healthcare system-focused) to be taken at several different levels
- More aggressive approaches and new therapeutic options are needed to help patients achieve their specified goals

References

- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
- Gould AL, Rossouw JE, Santanello NG, Heysse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. *Circulation*. 1998;97:946-952.

Overview of the Safety of Statin Treatment: An Update on Rosuvastatin

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Abstract

Background: Undertreatment with statins is common, despite the demonstrated lipid-lowering properties of these agents. The greater efficacy of the newest of the statins, rosuvastatin, was demonstrated in previous trials, and early results also suggested that rosuvastatin had a safety profile similar to other statins. The present analysis was conducted to update the safety assessment of rosuvastatin based on adverse events (AEs) and laboratory results from phase II and III trials to date.

Methods: Patients included in the analysis were enrolled in placebo- and statin-controlled and uncontrolled phase II and III trials worldwide. The record of patients experiencing at least one AE was used as an indicator of safety. The rates of incidence of AEs, including liver and skeletal muscle effects, were tabulated.

Results: The types of AEs were similar in patients receiving rosuvastatin compared to other statins. Rates of incidence of all AEs, AEs considered related to study drug, AEs leading to death, nonfatal serious AEs, and AEs leading to withdrawal were similar in rosuvastatin and other study groups.

Conclusion: Rosuvastatin therapy was well tolerated, and the safety profile was similar to that of other statins. The present analysis of the safety of rosuvastatin treatment indicates that this newest statin has a favorable risk-benefit profile and is a valuable option in lipid-lowering therapy.

Background

- The beneficial effects of rosuvastatin treatment have been demonstrated in recent clinical studies;^{1,2} these effects include profound reductions in unfavorable lipid levels significantly greater than those achieved with other available statins
- Recent guidelines of the National Cholesterol Education Program recommend more intensive lowering of low-density lipoprotein cholesterol (LDL-C), particularly in individuals at high risk of coronary heart disease (CHD);³ statins are currently underutilized in efforts to achieve these goals
- Concern regarding possible side effects of statins is an important cause of undertreatment; statin therapy carries some risk of myositis, myalgias, and elevated hepatic transaminases⁴
 - Among statins on the current US market, fatal rhabdomyolysis is extremely rare; less than one death/million prescriptions; the highest rate is associated with cerivastatin, which was withdrawn from the market⁵ (16–80 times more frequent as compared to any other statin)
- Cardiovascular disease causes 1 in every 2.5 deaths in the US⁶, and the potential for statins to save or extend lives must be considered in weighing costs and benefits of treatment with these agents
- Early clinical data suggest that rosuvastatin is as safe as other statins;^{1,2,9} however, continued assessment of risks and benefits of this newest statin is warranted to accurately determine its therapeutic ratio

Objective

- To assess the safety of rosuvastatin from AEs and laboratory measurements in phase II and III trials

Materials and Methods

- Controlled trials included those comparing rosuvastatin with placebo (n = 647 for rosuvastatin; n = 289 for placebo) or statin comparators (n = 2579 for rosuvastatin; n = 1275 for atorvastatin, simvastatin, or pravastatin); overall, controlled and uncontrolled trials included 3747 patients treated with rosuvastatin
 - These groups were not mutually exclusive; some trials were represented in more than one data pool

AEs

- AEs were identified using Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) terminology.

Liver and Skeletal Muscle Effects

- In controlled and uncontrolled trials, clinically significant elevations in alanine aminotransferase (ALT) were defined as increases >3 x the upper limit of normal (ULN) on 2 consecutive occasions 4–10 days apart
- In controlled and uncontrolled trials, myopathy was defined by a creatine kinase (CK) elevation >10 x ULN, accompanied by muscle symptoms

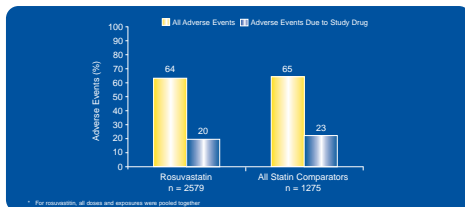
Results

- The demographic characteristics and lipid profiles of patients included in the analysis varied widely

AEs in Statin-Controlled Phase III/III Trials

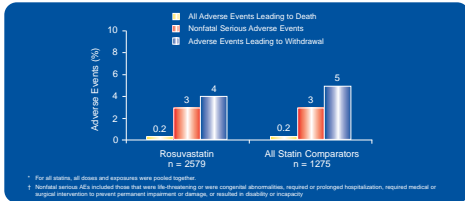
- Proportions of patients experiencing AEs were similar in the rosuvastatin treatment group and in patients treated with statin comparators (Figure 1)
 - AEs attributed to study medication also were similar across treatment groups

Figure 1. Percentage of patients with any AE and those with AEs attributed to trial medication in controlled phase III/III trials**



- No differences were observed in AEs resulting in death, nonfatal serious AEs, or AEs leading to study withdrawal (Figure 2)
 - No deaths occurring on the AEs were considered related to statin treatment

Figure 2. AEs leading to death, nonfatal serious AEs, and AEs leading to withdrawal in statin-controlled trials**



AEs in Placebo-Controlled Phase III/III Trials

- Proportions of patients experiencing AEs were similar in the rosuvastatin and placebo groups (Figure 3)

Figure 3. Total AEs and AEs attributed to study drug in placebo-controlled trials**

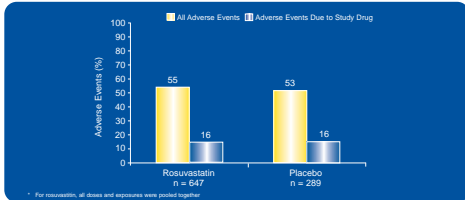
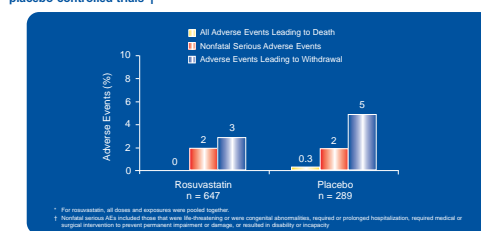


Figure 4. AEs leading to death, nonfatal serious AEs, and AEs leading to withdrawal in placebo-controlled trials**



Summary of AEs by COSTART Term

- AEs occurring in 5% of patients receiving statin treatment are summarized in Table 1

Table 1. AEs occurring in 5% of statin-treated patients in controlled phase III/III trials**

COSTART term	RSV (n=2579) %	ATV (n=773) %	SIM (n=250) %	PRA (n=252) %	All Statin Comparators (n=1275) %
Pharyngitis	12.2	12.7	15.6	14.7	13.6
Pain	6.7	5.6	7.6	8.7	6.6
Headache	6.6	7.8	6.8	5.2	7.1
Flu syndrome	5.3	6.9	8.4	5.6	6.9
Myalgia	5.1	4.5	4.4	1.6	3.9
Back pain	4.4	5.0	4.0	2.4	4.3
Abdominal pain	4.1	3.6	6.8	6.0	4.7
Accidental injury	2.6	2.5	6.0	4.0	3.5
Constipation	2.6	3.6	3.6	6.0	4.1
Urinary tract infection	2.1	1.0	5.6	2.0	2.1

* For all statins, all doses and exposures were pooled together.
 RSV=rosuvastatin; ATV=atorvastatin; SIM=simvastatin; PRA=pravastatin

- In the placebo-controlled trials, the most frequent AEs in rosuvastatin-treated patients were pharyngitis (8.3% vs 8.0% with placebo), headache (7.0% vs 5.2% with placebo), and pain (5.6% vs 4.5% with placebo); these were the only AEs reported in 5% of rosuvastatin-treated patients

Liver and Skeletal Muscle Effects

- In patients who received rosuvastatin in controlled and uncontrolled trials (pooled doses), clinically significant elevations in ALT occurred in 0.5% of patients; in cases where elevations were possibly related to rosuvastatin therapy, all were corrected or reduced with continuation or withdrawal of rosuvastatin
- In patients who received rosuvastatin in controlled and uncontrolled trials (pooled doses), myopathy occurred in 0.2% of patients; all cases were in patients receiving an 80-mg dose, irrespective of LDL-C level
 - CK elevations resolved in all patients following drug discontinuation, with or without hydration

Conclusions

- Rosuvastatin was well tolerated in phase II and III trials worldwide
- In placebo-controlled trials, the rate of incidence of AEs was similar in rosuvastatin and placebo groups
- In statin-controlled trials, the type and frequency of AEs observed were similar for rosuvastatin and other statins, and a low rate of withdrawal due to AEs was observed
 - ALT elevations and myopathy also were within the range reported for other statins^{10–13}
- These updated results suggest that the safety profile of rosuvastatin is comparable to that of atorvastatin, simvastatin, and pravastatin; the superior efficacy of rosuvastatin compared to other statins indicates that the therapeutic ratio of rosuvastatin should be highest among the statins; therefore, rosuvastatin may have an important role in lipid-lowering strategies as current guidelines are implemented

References

- Davidson M, Ma P, Stein E, Hutchinson H, Chitra R, Raza A, Gotto A Jr. Rosuvastatin is superior to atorvastatin in decreasing low-density lipoprotein cholesterol and increasing high-density lipoprotein cholesterol in patients with type IIa or IIb hypercholesterolemia. *J Am Coll Cardiol*. 2001;37(suppl A):292A. Abstract 1261-175.
- Paoletti R, Fahmy M, Mahla G, Mizan J, Southworth H. Rosuvastatin is superior to pravastatin and simvastatin in reducing low-density lipoprotein cholesterol, enabling more hypercholesterolemic patients to achieve low-density lipoprotein cholesterol targets. *J Am Coll Cardiol*. 2001;37(suppl A):291A. Abstract 1261-174.
- Stein E, Strutt K, Miller E, Southworth H. Rosuvastatin is superior to atorvastatin in the treatment of patients with heterozygous familial hypercholesterolemia. *J Am Coll Cardiol*. 2001;37(suppl A):292A. Abstract 1261-176.
- Olsson A, Southworth H, Wilpshar J. A 52-week trial of rosuvastatin versus atorvastatin in patients with primary hypercholesterolemia. *Eur Heart J*. 2001;22(suppl):253. Abstract 1410.
- Brown W, Zedler B, Bays H, Hassman H, Chitra R, Miller E, et al. The American Rosuvastatin Trialists Group. Long-term efficacy and safety of rosuvastatin: results of a 52-week comparator-controlled trial versus pravastatin and simvastatin. *Eur Heart J*. 2001;22(suppl):270. Abstract P1526.
- Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
- Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis [letter to the editor]. *N Engl J Med*. 2002;346:539-540.
- American Heart Association. 2002 Heart and Stroke Statistical Update. Dallas, Texas: American Heart Association; 2002.
- Knopp R. Drug treatment of lipid disorders. *N Engl J Med*. 1999;341:498-511.
- Shepherd J, Hunninghake D, Harris S, Hutchinson H, Pears J. A review of the safety profile of rosuvastatin in an international phase III/III clinical trial programme. *Int J Clin Pract*. 2002;(suppl 124):15.
- Shepherd J, Hunninghake D, Harris S, Hutchinson H, Pears J. A review of the safety profile of rosuvastatin in an international phase III/III clinical trial programme. Poster presentation at XIV International Symposium on Drugs Affecting Lipid Metabolism. New York. Sept 9–12, 2001.
- Black D, Bakker-Arkema R, Nawrocki J. An overview of the clinical safety profile of atorvastatin (Lipitor), a new HMG-CoA reductase inhibitor. *Arch Intern Med*. 1998;158:577-584.
- Insull W Jr, Isaacsohn J, Kwiterovich P, Ra P, Brazg R, Dujovne C, Shan M, Shugrue-Crowley E, Ripa S, Tota R. Efficacy and safety of cerivastatin 0.8 mg in patients with hypercholesterolemia: the pivotal placebo-controlled clinical trial. Cerivastatin Study Group. *J Int Med Res*. 2000;28:47-58.
- Zocor (simvastatin). In: *Physicians' Desk Reference*. 55th ed. Montvale, NJ: Medical Economics Co, Inc; 2001:2054-2056.
- Bradford R, Shear C, Chremos A, Dujovne C, Downton M, Franklin F, Gould A, Hesney M, Higgins J, Hurley D, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. *Arch Intern Med*. 1991;151:43-49.

Benefits of Cholesterol-Lowering Treatment in High-Risk Individuals. The Heart Protection Study (HPS): A Large, Randomized, Placebo-Controlled Trial of Simvastatin Treatment

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Abstract

Background: Risk of coronary heart disease (CHD) appears to decrease continuously with decreasing blood low-density lipoprotein (LDL) cholesterol concentration even beyond the normal concentration range in patients with established CHD. The risk reduction associated with lowering LDL cholesterol may be determined more by an individual's overall risk of cardiovascular disease than by initial blood lipid concentrations. The MRC/BHF Heart Protection Study was designed to assess the long-term effects of cholesterol-lowering therapy on all-cause and cause-effect mortality and major morbidity in a wide range of patient categories with increased risk of CHD (past myocardial infarction, peripheral vascular disease, diabetes, hypertension), as well as elderly with decreased blood cholesterol.

Methods: Men and women 40 to 80 years of age with nonfasting blood total cholesterol concentrations of ≥ 135 mg/dL were eligible if they were at substantial 5-year risk of death from coronary heart disease due to a prior medical history.

Results: Significant reductions in all-cause mortality were observed among subjects receiving simvastatin versus placebo, due to a highly significant ($P = 0.0005$) 18% proportional reduction in coronary death rate and reductions in deaths due to other causes, vascular and nonvascular. Treatment with simvastatin also resulted in a 38% proportional reduction in the incidence rate of first nonfatal myocardial infarction following randomization ($P < 0.0001$). Proportional reductions in the incidence rates of first stroke and first revascularization procedure with simvastatin treatment were 25% and 24%, respectively, and were highly significant ($P < 0.0001$).

Conclusion: Risk of heart attack, stroke, and revascularization was reduced by about one-third in patients taking simvastatin 40 mg daily. Cholesterol lowering therapy for 5 years can be expected to prevent new vascular events independently of age, sex, or other therapy.

Objective

- To assess the long-term effects of cholesterol-lowering therapy on vascular and nonvascular mortality and major morbidity in a broad range of patients

Materials and Methods

- A randomized, placebo-controlled trial involving medical collaborators from 69 UK hospitals. Patients were randomized from July 1994 to May 1997, and follow-up in the study continued until final visits between May and October 2001

Inclusion Criteria—Patients age 40–80 years with increased risk of coronary heart disease (CHD) death due to prior disease: myocardial infarction (MI) or other CHD; occlusive disease of noncoronary arteries; diabetes mellitus or treated hypertension; and total cholesterol > 3.5 mmol/L (> 135 mg/dL). **Exclusion Criteria**—chronic liver disease or abnormal liver function; severe renal disease or impaired renal function; and muscle disorders.

Outcomes

- Primary outcomes included mortality (in overall analyses) and fatal or nonfatal vascular events (in subcategory analyses)
- Subsidiary assessments included monitoring of cancer and other major morbidity; myopathy and elevated liver enzymes were also monitored

Statistical Methods

- Comparisons involved logrank analyses of the first occurrence of particular events during the treatment period among subjects randomized to simvastatin 40 mg daily versus those receiving placebo
- Primary comparisons were of effects on deaths from all causes, from coronary heart disease, and from all other causes
- Secondary comparisons included assessment of effects on specific noncoronary causes of death; on major coronary events (nonfatal MI or death from coronary disease); and on nonfatal or fatal strokes of any kind

- Additional secondary assessments were of effects on major vascular events and effects in different subcategories (eg, populations with specific prior diseases)

Results

- Subject characteristics are summarized in Tables 1 and 2

Table 1. Characteristics of Subjects at Baseline

Characteristic	n (%)
Gender, M/F	15,454/5082 (75/25)
Age, y	
< 65	9839 (48)
65–69	4891 (24)
≥ 70	5806 (28)
Prior disease	
Any MI	8510 (41)
Other CHD	4876 (24)
No CHD ¹	7150 (35)
Cerebrovascular	1820
Peripheral vascular	2701
Diabetes	3962
All patients	20,536 (100)

¹Categories within "No CHD" group are overlapping

- Mean lipid concentrations at baseline were as follows:
 - Total cholesterol: 228 mg/dL
 - LDL cholesterol: 131 mg/dL
 - HDL cholesterol: 41 mg/dL
 - Triglycerides: 186 mg/dL

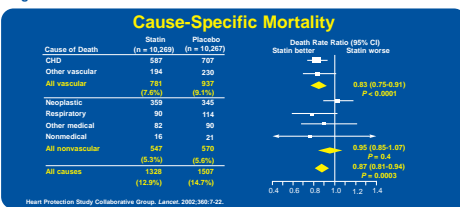
Table 2. Lipid Profile at Baseline

Lipid	n (%)	Lipid	n (%)
LDL-C (mg/dL)		Total cholesterol (mg/dL)	
< 116	6793 (33)	< 193	4072 (20)
116–134	5063 (25)	193–231	7883 (38)
≥ 135	8680 (42)	≥ 232	8581 (42)

Effects on Mortality

- During the scheduled treatment period, 1328 deaths occurred among the 10,269 subjects receiving simvastatin 40 mg/day, compared with 1507 deaths among 10,267 subjects receiving placebo ($P = 0.0003$; Figure 1)

Figure 1

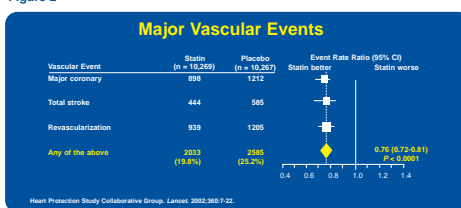


- Differences in mortality included a highly significant ($P = 0.0005$) 18% (SE 5) reduction in the coronary death rate and a marginally significant ($P = 0.07$) 16% reduction in the death rate from other vascular causes

Effects on Coronary and Other Vascular Events

- Treatment with simvastatin 40 mg daily resulted in a definite 24% (SE 3; 95% confidence interval [CI]: 19–28) proportional reduction in major vascular events (Figure 2)

Figure 2



- A pronounced 27% (SE 4; 95% CI: 21–33) proportional reduction was observed in major coronary events, consisting of first nonfatal MI or coronary death; the proportional reduction in incidence rate of first nonfatal MI was 38% (SE 5; 95% CI: 30–46)
- A highly significant 25% (SE 5; 95% CI: 15–34) proportional reduction in the incidence rate of first stroke was observed following randomization; this effect was mainly due to a 30% (SE 6; 95% CI: 19–40) proportional reduction in the incidence rate of stroke attributed to ischemia; a significant reduction was also observed in the incidence of transient cerebral ischemia in the absence of overt stroke
- Treatment with simvastatin also resulted in a highly significant 24% (SE 4; 95% CI: 17–30) proportional reduction in revascularization procedures; these included coronary bypass surgery, coronary angioplasty, and noncoronary procedures (eg, carotid endarterectomy, angioplasty)

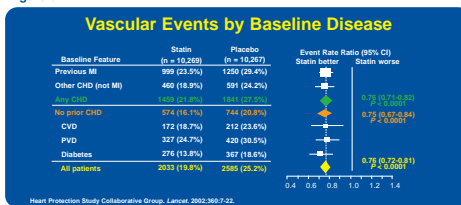
- During the first year, the reduction in major vascular events was not significant, but it was highly significant during each subsequent year ($P < 0.0001$ in years 2–4; $P = 0.0002$ in year 5+)

- In addition to reductions in major vascular events, significant ($P = 0.0003$) reductions were observed in numbers of participants who were hospitalized at least once for unstable or worsening angina

Vascular Event by Prior Disease

- Improvements with simvastatin treatment were observed not only in the overall population but also in subsets differentiated by prior medical history; when treatment benefits were assessed as a function of CHD (including previous MI), cerebrovascular disease (CVD), peripheral vascular disease (PVD), and diabetes mellitus, reductions in the rate of major vascular events were about one-quarter in each subcategory of participants studied (Figure 3)

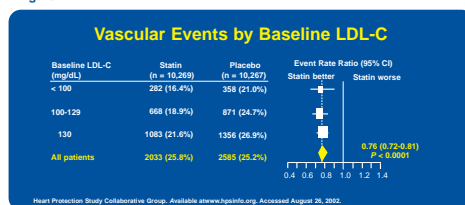
Figure 3



Vascular Event by LDL

- Proportional reductions in risk did not appear to be materially influenced by the pretreatment cholesterol or triglyceride concentrations
- When subjects were stratified by initial LDL-cholesterol level, reductions in risk ratio of nearly one-third were observed even in those with an initial level of < 100 mg/dL (Figure 4)

Figure 4



- Treatment benefits were attained irrespective of sex or age of subjects, and also were independent of blood creatinine concentrations at entry, cigarette smoking, treatment for hypertension, and use of aspirin, β -blockers, and angiotensin-converting-enzyme inhibitors; therefore, the benefits of simvastatin were additional to those of other cardioprotective treatments

Adverse Events: Myopathy and Elevated Liver Enzymes

Adverse Event, n	Study Group	
	Simvastatin	Placebo
Myopathy		
+ Rhabdomyolysis	5	3
- Rhabdomyolysis	5	1
CK 4–10 x ULN	19	13
CK >10 x ULN	11	6
ALT 2–4 x ULN	139	131
ALT >4 x ULN	43	32

CK = creatine kinase; ULN = upper limit of normal; ALT = alanine aminotransferase

Conclusions

- Cholesterol-lowering therapy reduced the risk of major vascular events in a wide range of high-risk individuals, even in patients with LDL-C below 100 mg/dL, who would not be considered for therapy by current US guidelines
- The risk of heart attack, stroke, and revascularization is reduced by approximately one-third in subjects who comply with daily treatment
- Maintenance of treatment for 5 years can prevent new vascular events in subpopulations of high-risk patients at the following rates: 10 of 100 events prevented in individuals who have experienced a prior MI; 9 of 100 events prevented in individuals with other CHD; and 7 of 100 events prevented in individuals with diabetes, prior stroke, or other PVD
- Initiation of statin therapy to lower LDL-C aggressively in high-risk patients provides marked benefits in reducing cardiovascular events with minimal risk that is less than with aspirin therapy

Reference

Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomized placebo-controlled trial. *Lancet*. 2002;360:7-22.

The Need for Better Lipid Control in Diabetes, Familial Hypercholesterolemia, and the Metabolic Syndrome

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Abstract

Several metabolic disorders, including diabetes, familial hypercholesterolemia, and the metabolic syndrome, predispose individuals to development of premature cardiovascular disease. The prevalence of diabetes is increasing, as overweight/obesity, a component of the metabolic syndrome and a risk factor for diabetes, becomes more common. Familial hypercholesterolemia is a relatively common genetic disorder that may result in early and severe coronary heart disease. Reduction of low-density lipoprotein (LDL) cholesterol is an important goal in the treatment of patients with these conditions. Despite the availability of multiple pharmacologic agents, many patients fail to achieve their target levels of LDL cholesterol, as established in recent guidelines for lipid-lowering therapy. A review of lipid-lowering treatment in patients with these metabolic disorders may be useful in evaluating newer treatment options.

Background

- Conditions that predispose individuals to cardiovascular disease are increasing in prevalence in the US; these conditions include diabetes and other metabolic disorders
 - Type 2 diabetes is associated with a 2- to 4-fold excess risk of coronary heart disease (CHD)¹
 - The metabolic syndrome is characterized by a constellation of overweight/obesity, hypertension, dyslipidemia, and impaired glucose tolerance, and has been compared to cigarette smoking as a major risk factor for premature CHD
 - Overweight/obesity is a characteristic of the metabolic syndrome and a risk factor for development of diabetes and CHD
 - According to results of the National Health and Nutrition Examination Survey (NHANES 1999-2000), 65% of adults (ages 20 to 74) are overweight or obese (with a body mass index [BMI] ≥ 25 kg/m²)
- Familial hypercholesterolemia (FH) is a relatively common genetic disorder; affected individuals are strongly predisposed to CHD
 - FH may be present in an estimated 500,000 people in the US
- Dietary and lifestyle changes alone may be inadequate to achieve goals of the American Diabetes Association (ADA) or the National Cholesterol Education Program (NCEP)
- Treatment with pharmacologic agents, including the statins, is an important component of lipid-lowering therapy for many of these patients, and optimization of this treatment should improve outcomes

Objective

- To summarize the importance of improved lipid control in patients with diabetes, FH, and the metabolic syndrome

Lipid Control in Diabetes

- Diabetic patients (especially those with type 2 diabetes) often have elevated levels of non-HDL cholesterol, and also may have diabetic dyslipidemia
- Diabetic dyslipidemia is characterized by the following features:
 - Elevated triglycerides
 - Smaller, denser LDL particles that have increased atherogenic potential
 - Low levels of HDL cholesterol²

Guidelines of the NCEP/ADA

- Recent guidelines of the NCEP elevate the status of diabetes (without CHD) to a level equivalent to CHD,³ as a risk factor for major coronary events
- Both ADA and NCEP guidelines recommend for diabetic patients an LDL cholesterol goal of <100 mg/dL
- In addition, the ADA recommends both medical nutrition therapy (MNT) and physical activity for lipoprotein status^{4,5}
 - However, MNT alone typically reduces LDL cholesterol by at most 15–25 mg/dL (0.40–0.65 mmol/L)
- Categories of risk in patients with diabetes have been proposed based on lipoprotein levels, as summarized in Table 1

Table 1. Category of risk based on lipoprotein levels in adults with diabetes⁶

Risk	Lipoprotein, mg/dL		
	LDL cholesterol	HDL cholesterol ^a	Triglyceride
High	130	<35	400
Borderline	100–129	35–45	200–399
Low	<100	>45	<200

^aFor women, the HDL cholesterol values should be increased by 10 mg/dL.

- Treatment of diabetic dyslipidemia is directed toward the following goals, in order of priority:
 - Lowering of LDL cholesterol
 - Raising of HDL cholesterol
 - Lowering of triglycerides
- The Scandinavian Simvastatin Survival Study (4S)⁷, the Cholesterol and Recurrent Events (CARE) study,⁸ and the Heart Protection Study,⁹ which included subjects with type 2 diabetes, showed that treatment with HMG-CoA reductase inhibitors (statins) significantly reduces CHD in diabetic patients
- Statins are the drugs of first choice for lowering LDL cholesterol, and higher doses are also moderately effective in hypertriglyceridemic subjects who also have elevated LDL cholesterol
- In combined hyperlipidemia (increased LDL cholesterol and triglycerides), statins may be used in combination with measures to improve glycemic control and other lipid-lowering agents (eg, fibric acid derivatives, nicotinic acid)

Lipid Control in Familial Hypercholesterolemia (FH)

- FH is a disorder that results from a mutation of the gene for the LDL receptor; FH may be heterozygous or homozygous (rare)¹⁰

Heterozygous FH

- In the more common, heterozygous form of FH (approximately 1 in 500 individuals are estimated to have heterozygous FH in the US),¹¹ half the normal number of LDL receptors are expressed
- Total cholesterol levels typically rise to 350–500 mg/dL
- Elevation of LDL cholesterol in FH may be early and severe, often leading to premature coronary artery disease
- Up to 90% of individuals with heterozygous FH may be undiagnosed or undertreated
 - When left untreated in men, the risk of developing symptoms of coronary artery disease increases from 5% at age 30 to 85% by age 60¹²
- Treatment of heterozygous FH may include:
 - Therapeutic lifestyle changes
 - Pharmacologic therapy
 - Statins^{13–15}
 - Bile acid sequestrants
 - Nicotinic acid
 - Cholesterol absorption inhibitors
 - Two-drug therapy (eg, statin + BAS or cholesterol absorption inhibitors); or
 - Three-drug therapy (eg, statin + BAS or cholesterol absorption inhibitors + nicotinic acid)

Homozygous FH

- In this rarer and more severe form of FH (occurring in 1 in 1 million individuals),¹⁶ LDL-receptor activity is essentially absent and total cholesterol levels are 700–1200 mg/dL
- Current therapy for homozygous FH may include the following measures:
 - High-dose statin treatment
 - Studies are beginning to evaluate the use of statins in younger patients,^{17,18} due to the early appearance and severity of the manifestations of homozygous FH
 - Nicotinic acid

- Plasmapheresis to selectively remove VLDL and LDL
 - Heparin-induced extracorporeal lipoprotein precipitation
 - Dextran sulfate cellulose absorption¹⁹
- Portacaval shunt surgery
- Treat lipid and non-lipid risk factors if they persist despite these lifestyle therapies:
 - Treat hypertension
 - Use aspirin for CHD patients to reduce prothrombotic state
 - Treat elevated triglycerides and/or low HDL

Lipid Control in the Metabolic Syndrome

- The metabolic syndrome is defined by
 - Abdominal obesity
 - Atherogenic dyslipidemia (high triglycerides, low HDL-C, small dense LDL)
 - Elevated blood pressure
 - Insulin resistance with or without glucose intolerance or impaired fasting glucose
- This syndrome is characterized by a prothrombotic state, as indicated by increased levels of fibrinogen and plasminogen activator inhibitor-1 (PAI-1)
 - A proinflammatory state, indicated by increased C-reactive protein (CRP)
- The incidence of the metabolic syndrome is increasing rapidly in the US, and is related to increasing obesity
- Factors contributing to the metabolic syndrome include:
 - Overweight/obesity
 - Physical inactivity
 - Genetics
- The metabolic syndrome is diagnosed when any 3 of the following are present (Table 2)

Table 2. Diagnosis of the Metabolic Syndrome²⁰

Risk Factor	Defining Level
Abdominal obesity	
Men	Waist circumference >102 cm (>40 in)
Women	Waist circumference >88 cm (>35 in)
Triglycerides	150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	130/85 mm Hg
Fasting glucose	110–125 mg/dL

^a For diagnosis of the metabolic syndrome, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III did not find adequate evidence to recommend routine measurement of insulin resistance (eg, plasma insulin), the proinflammatory state, or the prothrombotic state.²⁰

- Successful implementation of therapeutic lifestyle changes (TLC) may be most effective in patients who are diagnosed with the metabolic syndrome (Table 3)

Table 3. Essential components of Therapeutic Lifestyle Changes

Component	Recommendation
Restrict LDL-raising nutrients	
Saturated fats	Less than 7% of total calories
Dietary cholesterol	Less than 200 mg/day
Add LDL-lowering therapy	
Plant stanols/sterols	2 g/day
Increased viscous (soluble) fiber	10–25 g per day
Restrict total calories	Adjust caloric intake to maintain desirable body weight/prevent weight gain
Monitor physical activity	Include enough moderate exercise to expend at least 200 kcal/day

- Treatment of the metabolic syndrome should consider the following objectives:
 - Treat underlying causes (overweight/obesity and physical inactivity):
 - Intensify weight management
 - Increase physical activity

Conclusions

- Dyslipidemia is commonly associated with diabetes, and the metabolic syndrome
- Diabetes, obesity, and the metabolic syndrome are rapidly increasing in prevalence
- FH is a genetic disorder of the LDL receptor that causes severe hypercholesterolemia and often early coronary disease
- Recent guidelines have established goals for lipid-lowering therapy, but many patients with these metabolic disorders do not achieve these goals, despite the availability of effective pharmacologic and lifestyle interventions
- With optimized use of drug therapy, including the statins, improved treatment outcomes should be possible in these patients

References

- American Diabetes Association. Management of dyslipidemia in adults with diabetes. *Diabetes Care*. 2002;25(suppl 1):S74–S77.
- Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA*. 2002;288:1723–1727.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
- American Diabetes Association. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications (Position Statement). *Diabetes Care*. 2002;25(suppl 1):S59–S60.
- American Diabetes Association. Diabetes mellitus and exercise (Position Statement). *Diabetes Care*. 2001;24:S51–S55.
- Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J, Pyörälä K. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med*. 1999;259:2687.
- Goldberg RB, Mellies MJ, Sacks FM, Moyé LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E, CARE Investigators. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: Subgroup analyses in the Cholesterol and Recurrent Events (CARE) Trial. *Circulation*. 1998;98:2513–2519.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
- Simon Broome Register Group. Mortality in treated heterozygous familial hypercholesterolemia: implications for clinical management. *Atherosclerosis*. 1999;142:105–112.
- Slack J. Risks of ischemic heart disease in familial hyperlipoproteinemic states. *Lancet*. 1969;2:1380–1382.
- Wierzbicki AS, Lumb PJ, Chik G, Crook MA. Comparison of therapy with simvastatin 80 mg and atorvastatin 80 mg in patients with familial hypercholesterolemia. *Int J Clin Pract*. 1999;53:609–611.
- Wierzbicki AS, Lumb PJ, Semra YK, Crook MA. High-dose atorvastatin therapy compared with traditional therapeutic regimes in severe heterozygous familial hypercholesterolemia. *QJ Med*. 1998;91:291–294.
- Kajinami K, Kotzumi J, Ueda K, Miyamoto S, Takagoshi T, Mabuchi H. Effects of NK-104, a new hydroxymethylglutaryl-coenzyme reductase inhibitor, on low-density lipoprotein cholesterol in heterozygous familial hypercholesterolemia. *Am J Cardiol*. 2000;85:178–183.
- Maraia AD, Firth JC, Bateman ME, Byrnes P, Marlers C, Mounthey J. Atorvastatin: an effective lipid-modifying agent in familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 1997;17:1527–1531.
- Stein E, Strutt KL, Miller E, Southworth H. ZD4522 is superior to atorvastatin in the treatment of patients with heterozygous familial hypercholesterolemia [abstract]. *J Am Coll Cardiol*. 2001;37(suppl):292A. Abstract 1281–178.
- Goldstein JL, Brown MS. Familial hypercholesterolemia. In: Scriver C, Beaudet A, Sly W, Valle D, eds. *The Metabolic and Molecular Basis of Inherited Disease*, 7th edition. New York: McGraw-Hill, 1995:198–203.
- Stein EA, Illingworth DR, Kivtorovich PO Jr, Liacouras CA, Siemes MA, Jacobson MS, Brewster TG, Hopkins P, Davidson M, Graham K, Arnsman F, Knopp RH, DuJovne C, Williams CL, Isaacsohn JL, Jacobson CA, Laakazawa FM, Ames S, Gormley CJ. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA*. 1998;281:137–144.
- Knipscheer HC, Boelen CC, Kastelen J, van Dieumen DE, Groenemeijer BE, van den Ende A, Buller HR, Bakker HD. Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia. *Pediatr Res*. 1996;39(suppl 5):867–871.
- Lambert M, Lupelin FJ, Gagne C, Levy E, for the Canadian Lovastatin in Children Study Group. Treatment of familial hypercholesterolemia in children and adolescents. *Pediatrics*. 1996;97:619–628.