

How low should you go, and what's the best way to get there?

A practical review of current data on lipid-lowering therapy



The Alosa Foundation



Balanced data about medications

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These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.

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Introduction

Cardiovascular (CV) disease is the leading cause of death in the United States. Management of serum cholesterol levels is a key component of efforts to reduce the morbidity and mortality of CV disease, and numerous medications are effective.

However, despite the fact that more than 200 million prescriptions are written annually for lipid-lowering drugs at an annual cost of over \$19 billion¹, the adequacy of cholesterol management is often inadequate.² Less than half of people who require lipid-lowering therapies receive them, even among high risk patients, despite widely accepted guidelines for management and solid evidence to guide therapy.³ Of those who are treated, only about a third achieve their LDL goals.⁴ Some of the utilization shortfall is likely due to problems of affordability, poor patient adherence even when drugs are covered, and confusion about appropriate management. Recent studies reconsidering the optimal goals of cholesterol reduction and evaluating the comparative efficacy of lipid-lowering medications have added to the complexity of choosing the optimal therapy for each patient.

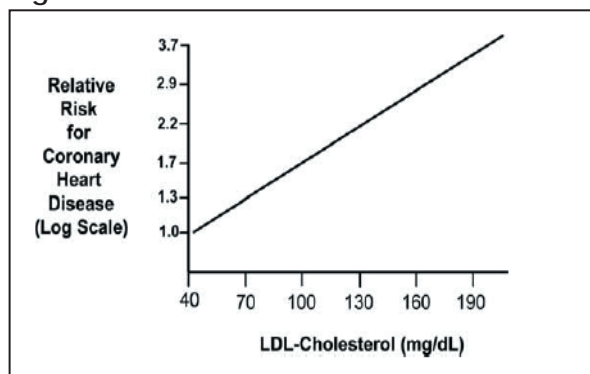
In this monograph, we synthesize the current evidence about the treatment of hypercholesterolemia. It covers five main topics:

- the official guidelines for cholesterol management, including the most recent updates;
- evidence on the benefit of more intense statin therapy, starting statins in the early post-acute coronary syndrome (ACS) period, and reducing LDL to very low levels;
- the role of statins in managing congestive heart failure;
- resources to help clinicians choose medications and reach cholesterol goals; and
- recent data on the use of statins for patients with normal lipid levels.

Epidemiology of hypercholesterolemia

Hypercholesterolemia is common in the U.S. While there has been some reduction in its prevalence in the last 20 years, about half of all adults have at least “borderline high-risk” cholesterol levels – total serum cholesterol concentration levels over 200 mg/dL.^{5, 6} High cholesterol is more common in men than in women (55% vs. 47%).⁵ There is a graded and continuous relationship between serum cholesterol concentration and cardiovascular mortality,^{7, 8} with a well-documented increase in the risk of death with rising cholesterol levels (Figure 1).⁷

Figure 1: CAD and cholesterol are related.⁷



The importance of treatment

Diet and exercise are the foundation of all lipid-management strategies, and are discussed in more detail below. When these lifestyle changes alone are inadequate to reach LDL goals, there is abundant evidence that treating hypercholesterolemia with statins reduces cardiovascular mortality in patients with and without known coronary artery disease.⁹⁻¹¹ Statins are the only class of medications shown to improve mortality in primary and secondary prevention of coronary artery disease (CAD), and its benefits also apply to elderly patients without life-threatening co-morbid conditions.^{10, 12} Meta-analyses of the effect of treatment in patients with known coronary artery disease have found a reduction in the absolute risk of death of about 15%.^{13, 14} A review of primary and secondary prevention trials found that every 10% decrease in serum cholesterol was associated with a 15% decrease in coronary heart disease mortality and an 11% decrease in total mortality risk, with no change in non-cardiac mortality.¹⁵ Finally, a meta-analysis of data from > 90,000 patients in 14 RCTs found that statin therapy can safely reduce the 5-year incidence of major coronary events, coronary revascularization, and stroke by about 20% per 40 mg/dL reduction in LDL levels.¹⁶ The absolute benefit relates mainly to the patient's absolute risk level and to the absolute reduction in LDL cholesterol achieved.¹⁶ Non-statin lipid-lowering drugs are also effective in reducing cholesterol, but only some of these medications have been shown to reduce mortality.^{17, 18}

Treatment options

While statins are by far the most widely used class of medications for lipid lowering, other classes of medications can be used as alternatives or in addition to statins. The classes and their mechanisms of action are listed below, and the clinical characteristics are listed in Table 1.¹⁹

Statins inhibit HMG-CoA reductase, an enzyme involved in cholesterol synthesis in the liver. They decrease serum LDL concentrations by reducing levels of cholesterol in the hepatocyte, causing it to up-regulate expression of LDL receptors. The statin class is the most effective in reducing LDL cholesterol (by 18-55%), and is first-line therapy for elevated LDL in patients without contraindications.

Bile acid sequestrants (e.g., cholestyramine) bind bile salts in the intestine, leading to conversion of cholesterol to bile acids, up-regulation of LDL receptors, and less circulating LDL. Bile acid sequestrants are moderately effective in reducing LDL (15-30% reduction), and are thought to be safer for use in pregnancy.

Fibrates (e.g., gemfibrozil) alter gene expression in target cells, and activate a gene that increases HDL levels and decreases triglyceride levels. Fibrates can reduce LDL cholesterol by 5-20%, and are the most effective medication for reducing triglycerides.

Nicotinic acid (niacin or vitamin B3) binds to a receptor on adipocytes, inhibiting lipolysis and release of fatty acids. It also decreases VLDL synthesis and secretion, and raises HDL levels. Niacin can reduce LDL cholesterol by 5-25% and triglycerides by 20-35%. It is the most effective medication for increasing HDL (15-35%).

Ezetimibe inhibits cholesterol absorption in the small intestine, reducing dietary intake of cholesterol and promoting excretion in the bile. Ezetimibe has been shown to reduce LDL cholesterol by an average of 18% and can be used concurrently with statins with similar additive effects,²⁰ but has not been shown to reduce cardiac events or other clinical outcomes.

Table 1: Efficacy and clinical characteristics of lipid-lowering medication classes^{19, 20}

Drug Class	LDL reduction	Triglyceride reduction	HDL increase	Major side effects	Contra-indications	Comments
Statins	18-55%	7-30%	5-15%	Myopathy, liver toxicity (very rare)	Liver disease, pregnancy, certain other drugs*	NCEP considers statins first-line therapy for LDL
Bile acid sequestrants	15-30%	May increase triglycerides	2-3%	GI distress, constipation, decreased absorption of other drugs	Dysbetalipoproteinemia, raised triglycerides (especially >400 mg/dL)	Can be used during pregnancy
Fibrates	5-20% (with normal triglycerides); may raise LDL (with high triglycerides)	25-50%	10-35%	Dyspepsia, gallstones, myopathy	Severe renal or hepatic disease	Drug of choice for triglycerides >500 mg/dL
Nicotinic acid	5-25%	20-35% (up to 50% in hypertriglyceridemic patients)	15-35%	Flushing, hyperglycemia, hyperuricemia, upper GI distress, hepatotoxicity	Liver disease and severe gout; peptic ulcer disease and diabetes are relative contraindications	The most effective drug at raising HDL
Ezetimibe	18%	8%	1%	Headache, GI distress, myopathy	Liver disease	Similar additive effects when prescribed in addition to a statin

* Cyclosporine, macrolide antibiotics, some anti-fungal agents, and cytochrome P-450 inhibitors (e.g., fibrates and niacin) should be used with caution in patients taking statins.

The ATP III Guidelines

The **Third Report of the Adult Treatment Panel (ATP III)** constitutes the National Cholesterol Education Program's (NCEP) updated clinical guidelines for cholesterol testing and management. It is based on a systematic review of the literature combined with input from an expert national panel about detection, evaluation and treatment of high cholesterol. ATP III was published in 2002¹⁹ and was updated in 2004.²¹ The guidelines are scheduled to be updated again in 2010/2011.

The guidelines are organized in a series of 9 steps; the first 5 focus on risk stratification, steps 6 and 7 focus on lowering LDL, and steps 8 and 9 address hypertriglyceridemia and the metabolic syndrome.

STEP 1: Determine lipoprotein levels

A fasting lipoprotein profile should be checked at least once every 5 years in all adults 20 years and older. Table 2 depicts classification of LDL results, prior to risk-stratification.

Table 2. LDL classification.

<100 mg/dL	Optimal
100-129 mg/dL	Near/above optimal
130-159 mg/dL	Borderline high
160-189 mg/dL	High
≥190 mg/dL	Very high

Total cholesterol (as opposed to LDL) is considered “desirable” if <200 mg/dL, “borderline high” if 200-239 mg/dL, and “high” if >240 mg/dL. HDL, the protective (“good”) cholesterol is considered low if <40 mg/dL and high if >60 mg/dL.

STEP 2: Identify CAD and CAD risk equivalents

Patients with CAD and those with clinical atherosclerotic disease have a greater than 20% risk of a coronary event (either MI or death) in the next 10 years. CAD “risk equivalents” are:

- Clinical CAD
- Symptomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm
- Diabetes

STEP 3: Determine presence of other risk factors

The guidelines identify the following 5 risk factors and 1 negative risk factor for CAD (see Table 3). The presence of the negative risk factor removes one risk factor from the count.

Table 3. CAD risk factors.

<ul style="list-style-type: none">• Cigarette smoking• Hypertension (BP ≥140/90 mm/Hg or on antihypertensive medication)• Low HDL-cholesterol (<40 mg/dL)<ul style="list-style-type: none">◦ HDL-cholesterol ≥60 mg/dL is a “negative” risk factor• Family history of premature CAD (in male first degree relatives <55 years, in female first degree relative <65 years)• Age (men: ≥45 years, women: ≥55 years)
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STEP 4: Calculate 10-year CAD risk in patients with 2 or more risk factors

If a patient has one or fewer CAD risk factors, risk does not need to be formally calculated because these patients have a 10-year risk of CAD of <10%. If 2 or more risk factors (other than LDL) are present without CAD or a CAD risk equivalent, the next step is to assess 10-

year CAD risk, using the Framingham tables (Appendix 1). These allow the clinician to easily insert risk factors and estimate a 10-year cardiovascular risk score. Based on this score, patients are classified into three risk levels: >20% (patients considered to have CAD risk equivalent), 10-20%, and <10%. An easy-to-use risk calculator can be found online at: <http://hp2010.nhlbihin.net/atpiii/calculator.asp>.

STEP 5: Determine risk category and LDL goal

The last step in risk assessment is to use a patient's risk to establish an LDL goal and to identify when to initiate therapeutic lifestyle changes and medication therapy (see Table 4).

Table 4: LDL goals and levels to initiate therapy, by risk category.

Risk category	LDL level at which to initiate therapeutic lifestyle changes (TLC)	LDL level at which to consider drug therapy	LDL goal
Low risk: 0-1 risk factors	≥160 mg/dL	≥190 mg/dL (optional for 160-189 mg/dL)	<160 mg/dL
Moderate risk: 2+ risk factors, 10 year risk <10%	≥130 mg/dL	≥160 mg/dL	<130 mg/dL
Moderately high risk: 2+ risk factors (10-year risk 10-20%)	≥130 mg/dL	≥130 mg/dL (optional for 100-129 mg/dL)	<130 mg/dL (consider <100 mg/dL)
High risk: CAD or CAD-risk equivalents, or 2+ risk factors with 10-year risk >20%	≥100 mg/dL	≥100 mg/dL (optional for selected patients 70-99 mg/dL)	<100 mg/dL (consider <70 mg/dL)

STEP 6: Initiate therapeutic lifestyle changes ("TLC") if LDL is above goal

For all patients with LDL levels above their goal, TLC should be instituted, with an aim of increasing physical activity, reducing weight when appropriate, cessation of smoking, and improving diet. Patients are advised to reduce intake of cholesterol-raising nutrients, limit saturated fat consumption to less than 7% of total calories, and reduce dietary cholesterol to less than 200 mg per day.

The guidelines suggest that clinicians provide counseling about TLC and perform follow-up cholesterol monitoring after 6 weeks. For patients who do not respond after 6 weeks, counseling should be reinforced, and certain foods that have been shown to reduce LDL, such as plant stanols/sterols (e.g., soybean or pine oil – found in many margarines) or viscous (soluble) fiber (e.g., psyllium), can be suggested. Cholesterol should be checked again in 6 weeks, and if goals are not met, medication considered.

STEP 7: Consider adding drug therapy if LDL exceeds targets

See Table 4 for LDL levels at which medical management is indicated. The guidelines recommend statins as first-line treatment for patients with elevated LDL and no contraindications, and do not offer guidance about which drug to choose.

STEPS 8 & 9: Identify and treat metabolic syndrome and hypertriglyceridemia

The primary goal in lipid management is to reduce LDL. But evidence is accumulating to suggest that CAD risk can be further reduced by modifying other risk factors such as hypertriglyceridemia or the metabolic syndrome, a constellation of lipid and non-lipid risk factors. Diagnosis of the metabolic syndrome is made when 3 or more of the following are present: abdominal obesity (waist circumference >40 inches for men and >35 inches for women), elevated triglycerides (≥ 150 mg/dL), low HDL (<40 mg/dL for men and <50 mg/dL for women), elevated blood pressure ($\geq 130/\geq 85$ mmHg), and elevated fasting glucose (≥ 110 mg/dL).

For patients with the metabolic syndrome, begin with risk factor modification. Obesity and physical inactivity should be addressed by improving diet and increasing exercise. If lipid and non-lipid risk factors persist despite lifestyle interventions, treat hypertension, elevated triglycerides and low HDL, and add aspirin (unless contraindicated) to reduce the prothrombotic state.

Triglyceride levels can be classified according to the values in Table 5. For patients with elevated triglycerides that do not fall into the "very high" range, the primary objective is still to reduce LDL. If triglycerides are elevated even after LDL is reduced to goal, medication management of the triglycerides should be considered. Triglyceride levels over 500 mg/dL raise the risk of pancreatitis and their reduction becomes a primary goal. Therapy includes a very low-fat diet ($\leq 15\%$ of calories from fat), weight management and physical activity, and a fibrate (drug class of choice) or nicotinic acid. When triglycerides are reduced to <500 mg/dL, focus should return to LDL-lowering therapy.

Table 5: Triglyceride classification.

<150 mg/dL	Normal
150-199 mg/dL	Borderline high
200-499 mg/dL	High
≥ 500 mg/dL	Very high

Bottom line: The ATP III guidelines recommend LDL management as the primary goal of cholesterol-lowering therapy. The approach stratifies patients in terms of cardiovascular risk to identify LDL goals and thresholds for treatment. There are 9 steps in the guidelines; 1-5 focus on risk stratification, 6-7 focus on lowering LDL, and 8-9 address hypertriglyceridemia and the metabolic syndrome.

The evidence for intensive lipid lowering

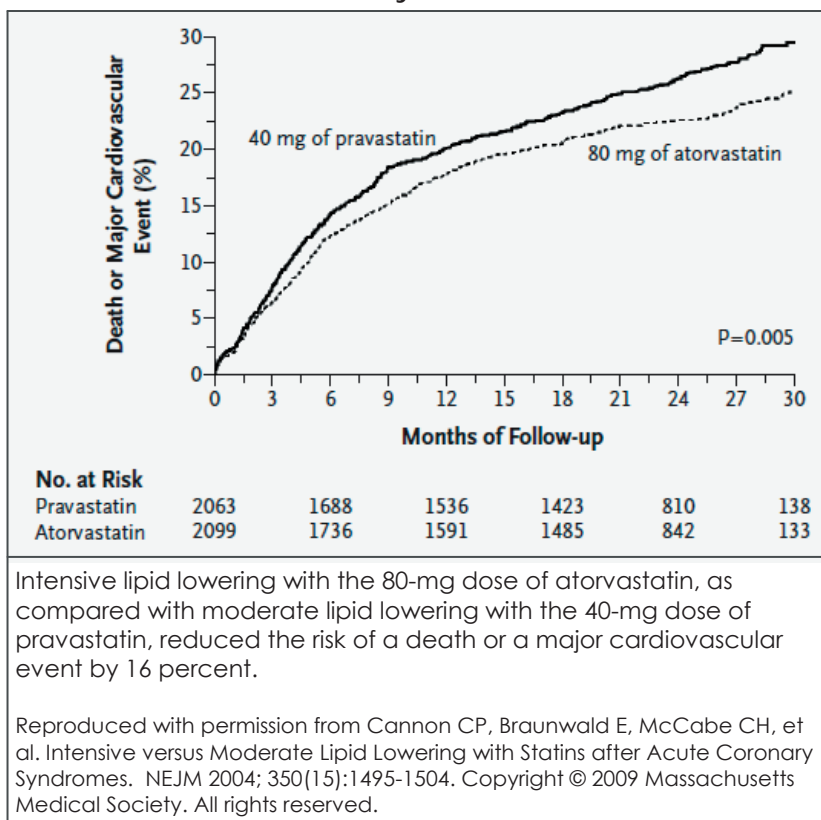
In the landmark clinical trials that established the value of statins in the late 1980s and early 1990s, patients required 1-2 years of therapy before showing a benefit over placebo.⁷ As a result, statins were typically started weeks to months after hospital discharge for patients with acute coronary syndromes (ACS), with the goal of lowering cholesterol moderately. However, patients have the highest rate of recurrent ischemic events and death shortly after an ACS event. While statins reduce the risk of ischemic events in all patients with CAD, statin-treated patients still frequently have these events.

Intensive lipid lowering for patients with acute coronary syndromes

The **MIRACL (Myocardial Ischemia Reduction with Acute Cholesterol Lowering)** study²² was the first to suggest the benefit of early, intensive statin therapy. It enrolled 3,086 patients with a mean age of 65 years and unstable angina or non-Q-wave acute MI. Patients were randomized to treatment with atorvastatin 80 mg daily or placebo between 24 and 96 hours after hospital admission, and followed for 16 weeks. In the atorvastatin group, the mean LDL level declined from 124 mg/dL at baseline to 72 mg/dL at study end; in the placebo group, the mean LDL increased from 124 mg/dL to 135 mg/dL. Primary outcome events were death, non-fatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalization. A primary outcome event occurred in 14.8% of patients in the atorvastatin group and 17.4% in the placebo group (absolute risk reduction (ARR), 2.6%; RR, 0.84; 95% CI, 0.70-1.00; p = 0.048). Patients in the atorvastatin group also had a reduced risk of death, non-fatal MI, and cardiac arrest, but these reductions were not statistically significant. Elevated liver enzymes (more than 3-times the upper limit of normal) occurred more commonly in the atorvastatin group than in the placebo group (2.5% vs. 0.6%; p<0.001).

The **A to Z (Aggrastat to Zocor)**²³ and **PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22)**²⁴ trials assessed patients hospitalized with ACS. In **A to Z**, patients were given intensive therapy (simvastatin 40 mg daily for 30 days, then 80 mg daily) or moderate therapy (placebo for 4 months, then simvastatin 20 mg daily). After about 2 years, cardiovascular-related death was significantly reduced with intensive therapy (5.4% vs. 4.1%). There was a non-significant reduction in the primary end-point (a composite of cardiovascular death, MI, readmission for ACS, or stroke) with intensive therapy (14.4% vs. 16.7%). In **PROVE IT-TIMI 22**, patients randomized to atorvastatin 80 mg daily (intensive therapy) were significantly less likely to have the primary end-point (a composite of death from any cause, MI, unstable angina requiring hospitalization, revascularization, and stroke) than patients given less intensive therapy with pravastatin 40 mg daily (22.4% vs. 26.3%), see Figure 2. In both trials, elevations of liver enzymes were more likely with intensive therapy, but no differences in muscle toxicity were noted.

Figure 2. Incidence of the Primary End Point in PROVE IT-TIMI 22.



A pooled analysis of 8,658 post-ACS patients from the [A to Z](#) and [PROVE IT-TIMI 22](#) trials found that by 8 months, LDL levels were significantly lower in the intensive statin therapy group (median 64 mg/dL) than in the moderate therapy group (median 87 mg/dL, $p < 0.001$). All-cause mortality was significantly reduced in the intensive therapy group compared with the moderate therapy group (3.6% vs. 4.9%; HR, 0.77; 95% CI 0.63 to 0.95; $p = 0.015$). This reduction in all-cause mortality with intensive statin therapy was consistent across key subgroups. One death was prevented for every 95 patients treated with high-dose statin therapy for 2 years.²⁵

Intensive lipid lowering in patients with stable coronary disease

The [TNT \(Treating to New Targets\)](#)²⁶ and [IDEAL \(Incremental Decrease in End Points Through Aggressive Lipid Lowering\)](#)²⁷ studies assessed patients with stable CAD. In TNT, patients with clinically evident CAD (previous MI, previous or current angina with evidence of CAD, history of revascularization) were randomized to atorvastatin 10 mg daily or 80 mg daily. Patients treated with atorvastatin 80 mg were less likely to have the primary end-point (a composite of death from coronary heart disease, nonfatal MI, resuscitation after cardiac arrest, fatal or non-fatal stroke) than patients treated with atorvastatin 10 mg daily (8.7% vs. 10.9%).

In [IDEAL](#), patients with previous MI were randomized to atorvastatin 80 mg daily or simvastatin 20 mg daily. The primary end-point (a composite of death from CAD, non-fatal MI, or resuscitation after cardiac arrest) was not significantly different between groups (atorvastatin 9.3%; simvastatin 10.4%), however, when stroke was included in the outcome (as

in the TNT trial) intensive therapy was superior. The safety profile of intensive therapy in IDEAL and TNT was similar to that seen in the A to Z and the PROVE IT-TIMI 22 trials.

The recently completed **SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine)** trial²⁸ enrolled 12,064 patients with a prior MI, and randomized them to simvastatin 80 mg daily or simvastatin 20 mg daily. The trial results were presented at the Scientific Sessions of the American Heart Association in November 2008 but have not been published as of the time of publication of this monograph. In that report, patients given 80 mg of simvastatin daily had a decrease of 14 mg/dL in their LDL compared with those receiving a 20 mg dose, a non-significant difference. There was a non-significant reduction in the primary end-point of major coronary events, stroke, and revascularization in the 80 mg group compared to the 20 mg group (24.5% and 25.7% respectively). The groups differed significantly in terms of adverse effects, with more cases of myopathy in the 80 mg simvastatin group compared to the 20 mg simvastatin group (53 vs. 3, including 7 cases of rhabdomyolysis vs. 0). There was no increased risk of cancer in the 80 mg daily group.

Intensive lipid lowering for patients after stroke

The **SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels)** trial²⁹ enrolled patients with stroke or TIA but no coronary artery disease, and randomized them to atorvastatin 80 mg daily or placebo. The primary end-point (fatal or non-fatal stroke) was significantly reduced by atorvastatin (11.2% vs. 13.1%). Whether high-intensity statins are superior to moderate-intensity statins for patients with stroke or TIA is presently unknown. In a further analysis of this study,³⁰ the primary outcome was significantly reduced by atorvastatin compared to placebo in patients aged <65 years (7.9% vs. 10.5%) but not in those aged ≥65 years (14.7% vs. 16.2%). However, the risk of stroke or TIA, a major coronary event, a CHD event, or a revascularization procedure were all significantly reduced compared to placebo in both age groups.

A recent **Cochrane review** examined the effect of lipid-lowering therapy for preventing stroke recurrence or subsequent vascular events in patients with a history of stroke or TIA.³¹ The review examined 8 studies (5 with statins, including SPARCL) involving about 10,000 patients. Active interventions involved pravastatin, atorvastatin, simvastatin, clofibrate, and conjugated estrogen. Only statin therapy reduced the risk of any subsequent stroke (OR, 0.88; 95% CI, 0.77 to 1.00). Statin therapy reduced the risk of subsequent serious vascular events (OR, 0.74; 95% CI, 0.67 to 0.82), but not of all-cause mortality (OR, 1.03; 95% CI, 0.84 to 1.25). Statins significantly reduced the risk of recurrent ischemic, but not hemorrhagic, stroke.

Table 6: Key trials of high-intensity statin therapy.

Trial name	Who was enrolled	What was studied and for how long?	Effect on cholesterol levels	Prevention of vascular events
A to Z trial <i>JAMA</i> 2004	4,497 patients hospitalized with ACS (STEMI or NSTEMI) within the past 5 days, with a total cholesterol <250 mg/dL and ≥1 high-risk feature (age >70, DM, prior CAD, peripheral artery disease, stroke, elevated cardiac enzymes, recurrent angina with ST changes, ischemia on pre-discharge stress test, or multi-vessel CAD on angiography).	Simvastatin 40 mg daily for 30 days, then 80 mg daily, or placebo for 4 months, then simvastatin 20 mg daily for 6-24 months.	Mean LDL at baseline was 111 mg/dL, and after 24 months was 66 mg/dL in the intensive group and 81 mg/dL in the moderate group.	There was a non-significant reduction in the primary end-point (composite of cardiovascular death, MI, readmission for ACS, or stroke) with intensive therapy (14.4% vs. 16.7%). Cardiovascular-related death was significantly reduced with intensive therapy (4.1% vs. 5.4%).
PROVE IT-TIMI 22 <i>NEJM</i> 2004	4,162 patients hospitalized with ACS (AMI with or without ST elevation or high-risk UA) within the preceding 10 days, with total cholesterol <240 mg/dL.	Atorvastatin 80 mg daily or pravastatin 40 mg daily for 18-36 months (average 24 months).	Mean LDL at baseline was 106 mg/dL, and at the end of the trial was 62 mg/dL in the intensive group and 95 mg/dL in the moderate group.	The primary end-point (a composite of death from any cause, MI, unstable angina requiring hospitalization, revascularization, and stroke) was reduced with intensive therapy (22.4% vs. 26.3%).
TNT <i>NEJM</i> 2005	10,001 patients with clinically evident CAD (previous MI, previous or current angina with evidence of CAD, history of revascularization). All patients had LDL 130-250 mg/dL at enrollment and had 8 weeks of atorvastatin 10 mg daily.	If LDL still >130 mg/dL after run-in, patients were randomized to atorvastatin 80 mg daily or 10 mg daily (median follow-up 4.9 years).	Median LDL level at randomization was 98 mg/dL, and at follow-up was 77 mg/dL in the high-intensity group and 101 mg/dL in the moderate group.	The primary end-point (a composite of death from coronary heart disease, nonfatal MI, resuscitation after cardiac arrest, fatal or non-fatal stroke) occurred in fewer patients treated with atorvastatin 80 mg than 10 mg (8.7% vs. 10.9%).

Table 6 (cont'd): Key trials of high-intensity statin therapy.

Trial name	Who was enrolled	What was studied and for how long?	Effect on cholesterol levels	Prevention of vascular events
IDEAL <i>JAMA</i> 2005	8,888 patients with documented previous MI and "who qualified for statin therapy according to national guidelines." 75% were on statin therapy prior to randomization.	After dietary counseling, atorvastatin 80 mg daily or simvastatin 20 mg daily (median follow-up 4.8 years).	Mean LDL at baseline was 121 mg/dL, and after treatment was 80 mg/dL with atorvastatin and 100 mg/dL with simvastatin.	The primary end-point (a composite of death from CAD, nonfatal MI, or resuscitation after cardiac arrest) was not significantly different between groups (atorvastatin 9.3% vs. simvastatin 10.4%). When stroke was included in the outcome (as in the TNT trial), intensive therapy was superior.
SEARCH 2008	12,064 patients with a prior MI, no admission in previous 3 months for MI, unstable angina, or revascularization (and none planned for the next 3 months).	After a 2-month run-in on simvastatin 20 mg, simvastatin 80 mg daily or simvastatin 20 mg daily (median follow-up 6.7 years).	Mean LDL at baseline was 97 mg/dL, and after treatment was 83 mg/dL in the 80 mg daily group (not significantly different to the 20 mg daily group).	The primary end-point of major coronary events, stroke, and revascularization was lower in the 80 mg group (24.5%) than the 20 mg group (25.7%), but this difference did not achieve statistical significance.
SPARCL <i>NEJM</i> 2006	4,731 patients who had stroke or TIA (as diagnosed by a neurologist) within 1-6 months before study entry and no coronary artery disease.	Atorvastatin 80 mg daily or placebo (median follow-up 4.9 years).	Mean LDL at enrollment was 133 mg/dL, and at follow-up was 61 mg/dL in the atorvastatin group and 128 mg/dL in the placebo group.	The primary end-point (fatal or non-fatal stroke) was significantly reduced by atorvastatin (13.1% vs. 11.2%).

Bottom line: High-intensity statin therapy appears to be more effective than moderate-intensity therapy for patients with ACS and stable coronary artery disease. High-intensity therapy may produce a higher incidence of adverse effects, although this was not seen in all studies. The LDL levels achieved with intensive treatment in these trials supports the NCEP "optional" goal of 70 mg/dL for patients with CAD. The SPARCL trial confirms that recent stroke and TIA should be treated as coronary disease equivalents. Data support the use of high-intensity statins in patients aged over 65 years.

Statins for patients with normal lipid levels and elevated high-sensitivity C-reactive protein

Inflammatory biomarkers, such high-sensitivity C-reactive protein (hs-CRP), are associated with elevated cardiovascular risk and have been proposed as targets (or as markers) for therapeutic intervention. Statins lower hs-CRP levels³², and these reductions correlate with the risk reduction seen with statins in patients with^{33, 34} and without³⁵ known cardiovascular disease. The **JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin)** trial examined whether men ≥ 50 years and women ≥ 60 years of age with hs-CRP ≥ 2.0 mg/L, but normal cholesterol levels (LDL cholesterol < 130 mg/dL), would benefit from treatment with a statin.³⁶ According to existing guidelines, statins would not be recommended for such patients. Study subjects were randomized to receive either rosuvastatin (Crestor) 20 mg/d or placebo.

The main outcome measure was a composite end-point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. Treatment with rosuvastatin significantly reduced LDL, hs-CRP and triglyceride levels. The trial was stopped early by its data safety monitoring board after a median follow-up of 1.9 years (maximum 5 years) because of marked benefit in the rosuvastatin group for all outcome measures.

Table 7. Results of the Jupiter trial.

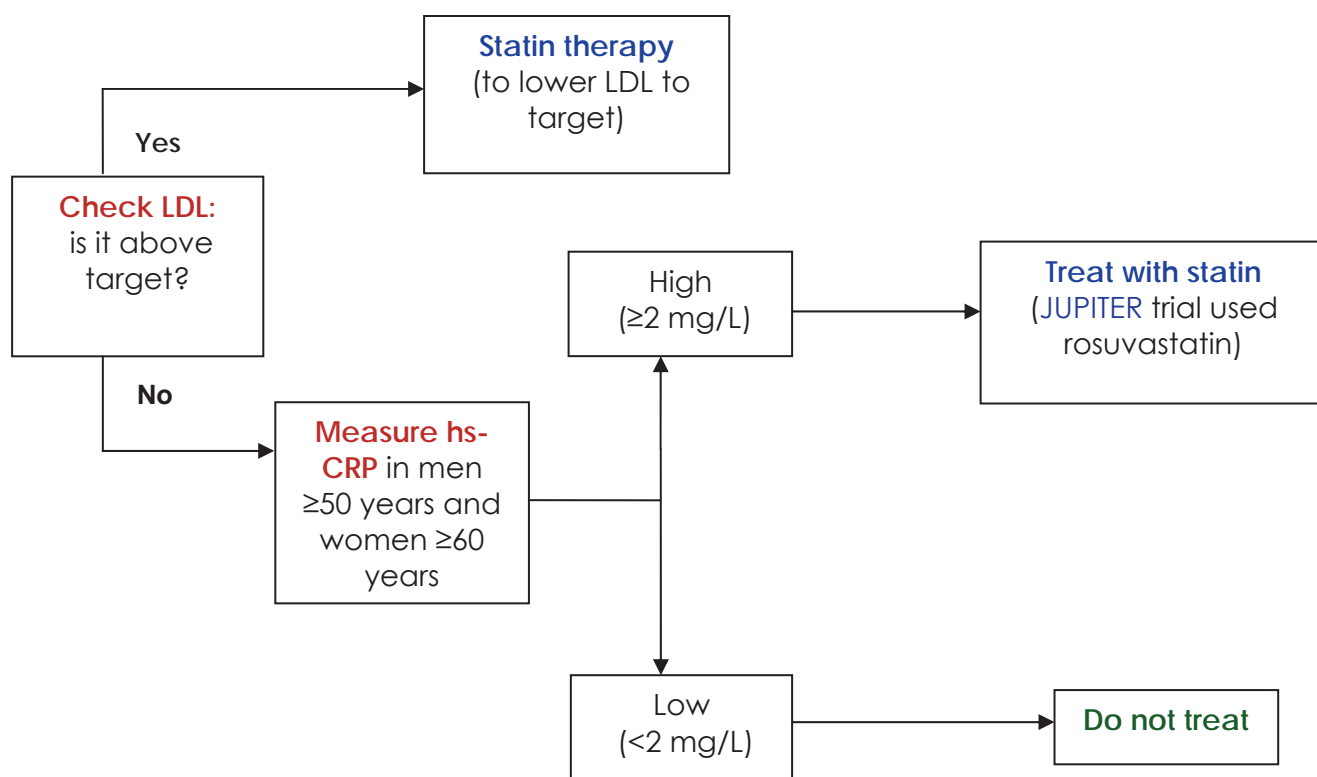
Clinical endpoint	Rosuvastatin group Rate per 100 person-years of follow-up	Placebo group Rate per 100 person-years of follow-up	Relative risk reduction (RRR)
primary end-point (MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from CV causes)	0.77	1.36	44%; p < 0.00001
any MI	0.17	0.37	54%; p = 0.0002
any stroke	0.18	0.34	48%; p = 0.002
arterial revascularization or hospitalization for unstable angina	0.41	0.77	47%; p < 0.00001
combined end-point of MI, stroke, or death from CV causes	0.45	0.85	47%; p < 0.00001
death from any cause	1.00	1.25	20%; p = 0.02

The rosuvastatin group did not have a significant increase in myopathy or cancer, but did have a higher incidence of physician-reported diabetes compared to the placebo group (3% vs. 2.4%; p = 0.01). This finding has also been observed in randomized trials of other statins.

Another analysis of JUPITER found that the rates of symptomatic venous thromboembolism (pulmonary embolism or deep vein thrombosis) were likewise significantly reduced in patients randomized to receive rosuvastatin (HR, 0.57; 95% CI, 0.37 to 0.86; $p=0.007$), suggesting that statins may also reduce the risk of venous thromboembolism, in addition to arterial thromboses, in patients with elevated hs-CRP.³⁷

The following figure provides one plausible evidence-based approach to statin use in light of the findings of JUPITER:

Figure 3. Use of statins for patients with elevated LDL or hs-CRP.



Bottom line: Prescribing a statin to patients with normal LDL levels but elevated hs-CRP may substantially reduce the risk of vascular outcomes. It is unknown whether the beneficial effects demonstrated in JUPITER are a class effect of statins or more closely related to rosuvastatin.

Are statins useful in heart failure?

Patients with congestive heart failure (CHF) have been excluded from many statin trials, so there has been a lack of data on statin use in this situation, and available data are conflicting.³⁸ Some studies have suggested that cholesterol in patients with CHF causes a worse prognosis,³⁹ while other studies (post hoc and observational) and a systematic review have suggested that statins may be beneficial in CHF.³⁸⁻⁴⁰

The **CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure)** trial^{41, 42} enrolled 5,011 patients with a mean age of 73 years, systolic heart failure, evidence of ischemic heart disease and an ejection fraction $\leq 40\%$. Patients were randomized to treatment with rosuvastatin 10 mg daily or placebo, and followed up for a median of 33 months. The primary end-point was a composite of CV death, non-fatal MI and non-fatal stroke. LDL levels declined from 137 mg/dL at baseline to 76 mg/dL at 3 months in the rosuvastatin group (a reduction of 44%), but did not change significantly in the placebo group (136 mg/dL at baseline and 138 mg/dL at 3 months). There was no significant difference in the primary outcome between the rosuvastatin and placebo groups (HR, 0.92; 95% CI, 0.83 to 1.02; $p=0.12$), nor in death from any cause (HR, 0.95; 95% CI, 0.86 to 1.05; $p=0.31$). There were fewer hospitalizations for CV causes in the rosuvastatin group (2,193) than in the placebo group (2,564), (HR, 0.92; 95% CI, 0.85 to 0.99; $p<0.001$).⁴¹

The **GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca – Heart Failure)** study⁴³ enrolled 4,574 patients with a mean age of 68 years, and chronic heart failure of NYHA class II-IV, irrespective of cause and left ventricular ejection fraction. Patients were randomized to treatment with rosuvastatin 10 mg daily or placebo, and followed for a median of 3.9 years. Primary outcomes were (1) death from any cause and (2) death from any cause or hospital admission for CV reasons. There was no significant difference in death from any cause between the rosuvastatin and placebo groups (HR, 1.00; 95% CI, 0.898-1.122, $p=0.943$).

Bottom line: Two large prospective trials designed to assess the role of statins in CHF have failed to demonstrate a reduction in mortality or CV events. Statins cannot be recommended as routine therapy in the management of CHF.

Ezetimibe (Zetia, Vytorin)

Since its introduction, ezetimibe has been widely promoted to manage hypercholesterolemia through a mechanism different from that of the statins, prescribed as a single product (Zetia) or in combination with simvastatin/Zocor (as Vytorin). Ezetimibe was approved by the FDA solely on the basis of its capacity to lower LDL cholesterol; unlike many statins, it has not been shown to reduce the risk of cardiac events.

The **ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression)** trial⁴⁴ was designed to determine whether ezetimibe in

combination with simvastatin might improve the cardioprotective effects of statin therapy alone. Nearly two years passed between completion of this study and release of its initial results. ENHANCE enrolled 720 patients with heterozygous familial hypercholesterolemia with baseline LDL cholesterol levels of approximately 318 mg/dL to receive combination ezetimibe + high-dose simvastatin (Vytorin), or simvastatin alone. In addition to cholesterol levels, the study measured the thickness of the arterial intima over a 24-month period. The study found that although the combination product lowered LDL more than a statin alone (141 mg/dL vs. 193 mg/dL), this was not accompanied by an advantage in the level of atherosclerosis.⁴⁵

Thus, while ezetimibe (alone or in combination with simvastatin) has been shown to lower LDL, there is no reliable data that it reduces the risk of cardiovascular events. Without this information, it is not clear that either Zetia or Vytorin offers a clinical advantage over optimizing dosages of well tested and proved statins.

Three recent trials have compared a statin with statin + ezetimibe.⁴⁶⁻⁴⁸

Table 8. Effects of statin + ezetimibe vs. statin alone on LDL levels.

Trial	Who was enrolled?	What was studied and for how long?	Reduction in LDL levels		Side effects
			Combination therapy	Monotherapy	
Leiter <i>AJC</i> 2008	579 patients with hypercholesterolemia, an LDL \geq 70 mg/dL and \leq 160 mg/dL at baseline, and a high risk of CHD. Median LDL at baseline was 90 mg/dL.	Atorvastatin 40 mg + ezetimibe 10 mg daily vs. atorvastatin 80 mg daily for 6 weeks.	27%	11% (p <0.001)	Safety profiles, tolerability, and incidence of liver and muscle adverse effects were similar between groups.
Conard <i>AJC</i> 2008	196 patients with hypercholesterolemia and at moderately high risk for coronary heart disease who had LDL levels >100 mg/dL with atorvastatin 20 mg. Median LDL at baseline was 120 mg/dL.	Atorvastatin 20 mg + ezetimibe 10 mg daily vs. atorvastatin 40 mg daily for 6 weeks.	31%	11% (p <0.001)	No serious adverse effects were reported, and there were no statistically significant or clinically meaningful differences in adverse effects between the groups.
Ballantyne <i>AJC</i> 2007	469 patients with hypercholesterolemia and at high risk of CHD, with an LDL of \geq 160 mg/dL and <250 mg/dL. Median LDL level at baseline was approx 190 mg/dL.	Rosuvastatin 40 mg + ezetimibe 10 mg daily vs. rosuvastatin 40 mg daily for 6 weeks.	70% (significantly more patients receiving combination therapy achieved LDL goals of <100 mg/dL and <70 mg/dL).	57% (p <0.001)	Both treatments were well tolerated. Frequency and type of adverse events were similar between treatment groups.

While adding ezetimibe to a statin reduces LDL levels more than a statin alone, CV morbidity or mortality were not assessed in these short-term (6-week) trials.

A recent systematic review compared combination therapy with high-dose statin monotherapy in high-risk patients. Statin–ezetimibe (2 trials; $n = 439$) did not reduce mortality more than high-dose statin monotherapy. No trials compared the effect of combination therapy versus high-dose statin monotherapy on the incidence of myocardial infarction, stroke, or revascularization procedures.⁴⁹

The **IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial)** study aims to determine whether the addition of ezetimibe to simvastatin improves CV outcomes compared with simvastatin monotherapy in patients after ACS. The trial will enroll approximately 18,000 moderate- to high-risk patients stabilized after ACS. Patients will be randomized to receive either ezetimibe 10 mg/simvastatin 40 mg combination therapy or simvastatin 40 mg. If consecutive measures of LDL are ≥ 79 mg/dL at follow-up, the simvastatin dose will be increased to 80 mg. The primary end-point is the first occurrence of CV death, non-fatal MI, rehospitalization for UA, coronary revascularization (occurring at least 30 days after randomization), or stroke. Patients will be followed for a minimum of 2.5 years and until at least 5,250 patients experience a primary end-point event.⁵⁰ Its results are not expected until 2012.

Bottom line: While waiting for data on CV outcomes with ezetimibe, focus on getting the patients' LDL down to target levels using a statin. If an additional agent is needed, add another drug that has been shown to have clinical benefits when added to statin therapy (e.g., nicotinic acid, fibrates, and bile acid sequestrants).⁵¹ Reserve ezetimibe for the rare patient who cannot tolerate statins or cannot get to the LDL goal despite these steps.

Are all statins the same?

Although all statins are members of the same therapeutic class, there is very little high-quality data comparing the relative efficacy and safety of different statins.⁵²

Statins differ in their ability to lower LDL. Table 9 presents data on the reductions in LDL that would be expected with different doses of statins. These figures are based largely on a meta-analysis of 164 placebo controlled trials;⁵³ short-term head-to-head trials have observed very similar results.⁵⁴

Table 9. Expected LDL lowering for different statins.

Drug	Daily dose of statin (mg)					
	5	10	20	40	60	80
rosuvastatin (Crestor)	38%	43%	48%	53%	-	-
atorvastatin (Lipitor)	-	37%	43%	49%	-	55%
lovastatin (Mevacor, generics)	-	21%	29%	37%	-	-
lovastatin (Altoprev)	-	21%	29%	-	42%	-
simvastatin (Zocor, generics)	23%	27%	32%	37%	-	42%
pravastatin (Pravachol, generics)	-	20%	24%	29%	-	33%
fluvastatin (Lescol)	-	-	21%	27%	-	33%
ezetimibe (10 mg) + simvastatin (Vytorin)	-	40%	45%	50%	-	55%

- Expected to lower LDL by \geq 50%
- Expected to lower LDL by 40-50%
- Expected to lower LDL by < 40%
- Not available at this dose

Unfortunately, no head-to-head studies have been published to date comparing statins of equivalent lipid lowering potency (e.g., atorvastatin 10 mg/d and simvastatin 40 mg/d) in terms of clinically important outcomes. The trials described in Table 6 do not provide head-to-head comparisons of statins at doses that have similar LDL-lowering effects. Most statins reduce CAD-events compared to placebo.⁵² Therefore, at equivalent dose intensities, there is reason to expect that they will result in equivalent outcomes.

Similarly, there are limited data to compare the safety of different statins. Elevations of creatinine kinase (CK) were observed in only 0.1% to 0.5% of patients in clinical trials, and there appear to be no major differences between any of the currently available products. The rate of liver toxicity is dose-dependent and low overall, with elevations of liver enzymes occurring in 0.5 to 2.0% of patients. Rates of liver toxicity for different statins appear comparable.⁵² One exception was a trial in which liver enzyme abnormalities were substantially more common with atorvastatin 80 mg daily than simvastatin 80 mg daily (23% vs. 12%), although atorvastatin also achieved greater reductions in LDL.⁵⁵

Bottom line: While statins differ in their ability to lower LDL, statin regimens that achieve the same LDL levels likely produce similar clinical outcomes and are likely to be equally safe.

Which statin should I prescribe?

Table 10 outlines the amount of LDL lowering required to achieve various target levels.

Table 10. Percentage LDL lowering required to achieve target LDL levels.

		Baseline LDL (mg/dL)				
		100	130	160	190	220
Target LDL (mg/dL)	70	30%	46%	56%	63%	68%
	100	-	23%	38%	47%	55%
	130	-	-	19%	32%	41%
	160	-	-	-	16%	27%

- Use atorvastatin 80 mg/day or rosuvastatin 40 mg/day
- Use any statin that lowers LDL by 40-50%
- Use any statin that lowers LDL by <40%
- Already at goal

Statin costs can differ substantially with respect to cost. Therefore, when choosing among statins of equivalent potency, cost may be a relevant consideration (see Table 11).

Table 11. Monthly costs of statins at various daily doses.

Drug	Daily dose of statin (mg)					
	5	10	20	40	60	80
rosuvastatin (Crestor)	\$124	\$124	\$124	\$124	-	-
atorvastatin (Lipitor)	-	\$90	\$125	\$125	-	\$123
lovastatin (Mevacor)	-	\$46	\$80	\$135	-	-
lovastatin (Altoprev)	-	\$78	\$179	-	\$202	-
lovastatin (generic)	-	\$4	\$4	\$4	-	-
simvastatin (Zocor)	\$72	\$80	\$150	\$142	-	\$147
simvastatin (generic)	\$18	\$20	\$28	\$28	-	\$33
pravastatin (Pravachol)	-	\$120	\$121	\$170	-	\$192
pravastatin (generic)	-	\$4	\$4	\$4	-	-
fluvastatin (Lescol)	-	-	\$94	\$92	-	\$116
ezetimibe (10 mg) + simvastatin (Vytorin)	-	\$118	\$116	\$115	-	\$116

The cost of each medication is based on the lowest price available from the following websites: www.drugstore.com, www.walmart.com, and www.walgreens.com. Prices obtained September 2009.

- Expected to lower LDL by ≥50%
- Expected to lower LDL by 40-50%
- Expected to lower LDL by <40%
- Not available at this dose

Bottom line: Because equipotent doses of statins appear equally effective and equally safe, which statin to prescribe should be based primarily on the amount of LDL lowering required to achieve the desired NCEP goal, and on affordability.

Adherence to statins

Several studies have documented that many patients adhere poorly to lipid-lowering therapy. One study of long-term statin therapy use found that 21% of patients discontinued treatment in the first 3 months of treatment, increasing to 44% after 6 months. After 10 years, only 42% of patients were still taking their statins; only 1 patient in 4 filled at least 80% of prescribed statins after 5 years.⁵⁶ A transnational evaluation of adherence to lipid-lowering drugs found that adherence was substantially better for statins than other lipid-lowering medications, yet adherence to statins in the year after initiation was only 64%.⁵⁷ A more recent evaluation of statin adherence in the first year of treatment in a well insured population found that patients on average went without therapy for over a third of the year.⁵⁸ It is important to monitor patients' adherence to ensure that they are deriving the expected benefit from their medications.

Appendix 1. Framingham Point Scores, NIH Publication No. 01-3305

Men

Estimate of 10-Year Risk for Men

(Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	< 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥ 30

10-Year risk _____%

Women

Estimate of 10-Year Risk for Women

(Framingham Point Scores)

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Year Risk %
< 9	< 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥ 30

10-Year risk _____%

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