



# Pushing down cholesterol ...

Lowering serum cholesterol has become one of our most powerful tools for controlling cardiovascular disease. Randomized trials in tens of thousands of patients have demonstrated the efficacy and safety of statins in reducing the risk of myocardial infarction, stroke, and cardiac death.

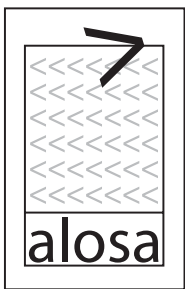
*But questions remain:*

**Who should be treated?**

**What is the right goal LDL level?**

**Which drugs should I use?**

**D**espite the nation's massive investment in managing cholesterol, we frequently miss the mark: diet and exercise messages go unheeded, medications are often underused, drug choices are sometimes arbitrary, and only a minority of patients reach their treatment goals. Better control of serum lipids presents an opportunity to improve care, reduce morbidity and mortality, and optimize therapeutic choices.



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*Balanced data about medications*



## In which patients should I check serum lipids, and how?

A fasting lipoprotein profile including total cholesterol, LDL, and HDL should be measured in all adults 20 years and older, at least once every 5 years.

## Who needs to be treated?<sup>1</sup>

**Identify patients** with coronary artery disease (CAD) or the following “risk equivalents”: symptomatic carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm, or diabetes. Any of these puts the patient at over 20% risk of having a coronary event in the next ten years.

### **Assess other risk factors:**

- Smoking;
- hypertension (BP  $\geq$ 140/90 mm/Hg, or taking an antihypertensive medication);
- low HDL-cholesterol ( $<$ 40 mg/dL); elevation of protective HDL-cholesterol  $\geq$ 60 mg/dL counts as a “negative” risk factor;
- family history of premature CAD (in a male first degree relative  $<$ 55 years, or in a female first degree relative  $<$ 65 years); and
- age (men  $\geq$ 45, women  $\geq$ 55).

**Calculate risk:** For patients without CAD or a CAD “risk equivalent,” but who have two or more of these other risk factors, estimate the 10-year CAD risk using the Framingham score (see accompanying evidence document, or online resources such as <http://hp2010.nhlbihin.net/atp/iii/calculator.asp>).



## For a given risk, how do I set a patient's LDL goal?

**Table 1. 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)

## How can I help my patients with therapeutic lifestyle changes (“TLC”)?

All patients with LDL levels greater than their goal should begin TLC by increasing physical activity, reducing weight when appropriate, stopping smoking, and improving diet. Clinicians should actively encourage these behavior changes and monitor follow-up cholesterol levels to determine whether medication therapy is necessary. Practical recommendations about diet and exercise are on the American Heart Association website: <http://www.americanheart.org/presenter.jhtml?identifier=4764>.



## If a drug is needed, which statin should I prescribe?

Statins are all members of the same therapeutic class, but no published head-to-head studies have compared statins at equipotent doses (e.g., atorvastatin 10 mg vs. simvastatin 40 mg) in achieving clinically important outcomes. Most statins reduce CAD events better than placebo, and seem to have about the same risk of side effects at comparable doses.<sup>2,3,4</sup> Therefore, at equivalent dose intensities, most statins will likely produce similar results.

**As a result, which statin to prescribe should be based primarily on:**

- (1) the extent of LDL lowering required to get to goal for a given patient, and
- (2) affordability.

**Table 2. 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%

■ 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

\*Adapted from Law et al *BMJ* 2003;326(7404):1423.

The following table shows the extent of LDL lowering required to achieve various target levels, based on the patient's starting LDL.

**Table 3. % LDL lowering required to achieve target LDL levels based on baseline LDL.**

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

■ Use atorvastatin 80 mg/d or rosuvastatin 40 mg/d   
 ■ Use any statin that lowers LDL by 40-50%   
 ■ Use any statin that lowers LDL by  $<40\%$    
 — Already at goal



Despite their clinical similarity, statins **do** differ substantially in price, as noted below, and affordability is a major factor in compliance. Therefore, when choosing among statins of equivalent potency, cost may be a relevant consideration.

**Table 4. Monthly cost of different statins at various doses and potencies.**

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 (generics)	\$18	\$20	\$28	\$28	—	\$33
pravastatin (Pravachol)	—	\$120	\$121	\$170	—	\$192
pravastatin (generic)	—	\$4	\$4	\$4	—	—
fluvastatin (Lescol)	—	—	\$94	\$92	—	\$116

■ 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

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

## What about high-intensity statin therapy?

A review of the current literature indicates that:

- high-intensity statins appear to be more effective than moderate-intensity therapy for prevention of cardiovascular (CV) events in patients with stable CAD or acute coronary syndromes (ACS) such as myocardial infarction or unstable angina.
- high-intensity therapy may cause a higher incidence of adverse effects, although this has not been demonstrated in all studies.
- the LDL levels achieved with more intensive therapy can help achieve the NCEP “optional” goal of 70 mg/dL for patients with CAD.



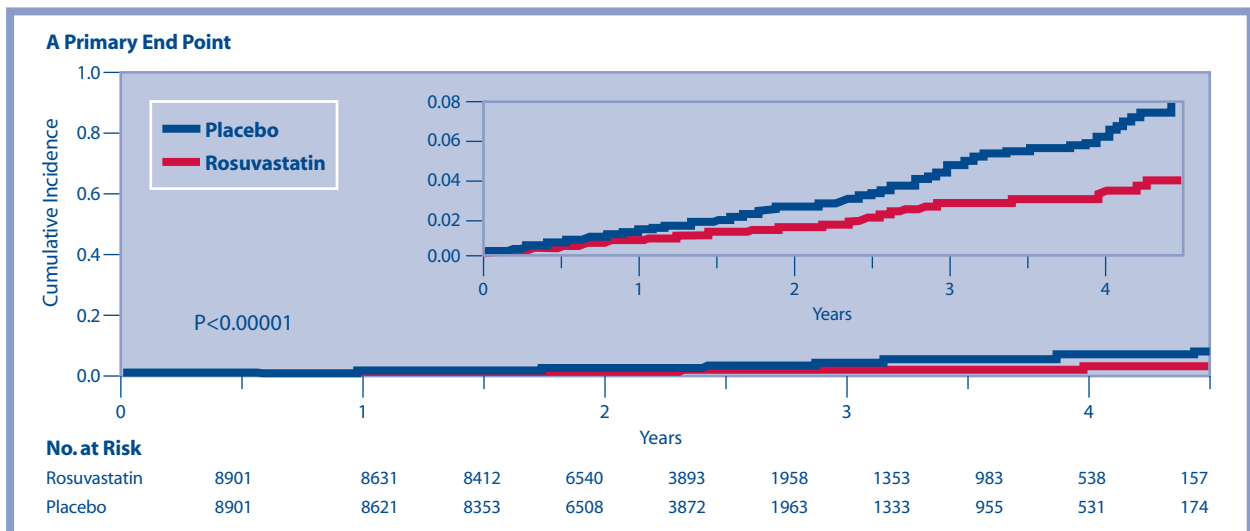
## What is the role, if any, of ezetimibe (Zetia, Vytorin)?

Ezetimibe is not a statin, and it lowers LDL by a completely different mechanism. Unlike the statins, it has never been shown to protect against real clinical outcomes such as MI or stroke; it was approved solely on the basis of its ability to influence the surrogate marker of LDL levels. As a result, there is little clinical trial evidence that a patient whose LDL is lowered with these products will have the same actual benefit that would be achieved by reaching that goal through better-established drugs (statins). Published results of clinical trials studying this question are still years away. Therefore, at present, clinical efforts should be directed at reducing a patient's LDL to target levels using a statin alone. If an additional agent is needed, add another drug that has been shown to have clinical benefits (e.g., nicotinic acid, bile acid sequestrants, or fibrates – monitoring closely for myopathy if fibrates are used).<sup>5</sup> Reserve ezetimibe for the rare patient who cannot tolerate statins or cannot get to LDL goal despite these steps.

## Is elevated C-reactive protein a new indication for statins?

The **JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin)** examined whether statins can benefit men aged  $\geq 50$  and women aged  $\geq 60$  years who have high-sensitivity C-reactive protein (hs-CRP)  $\geq 2.0$  mg/L but normal cholesterol levels (LDL  $< 130$  mg/dL).<sup>6</sup> It found that statin therapy substantially reduced the primary outcome (a composite of MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from CV causes) by 44% ( $p < 0.00001$ ).

**Figure 1. Primary outcome of the JUPITER trial.**

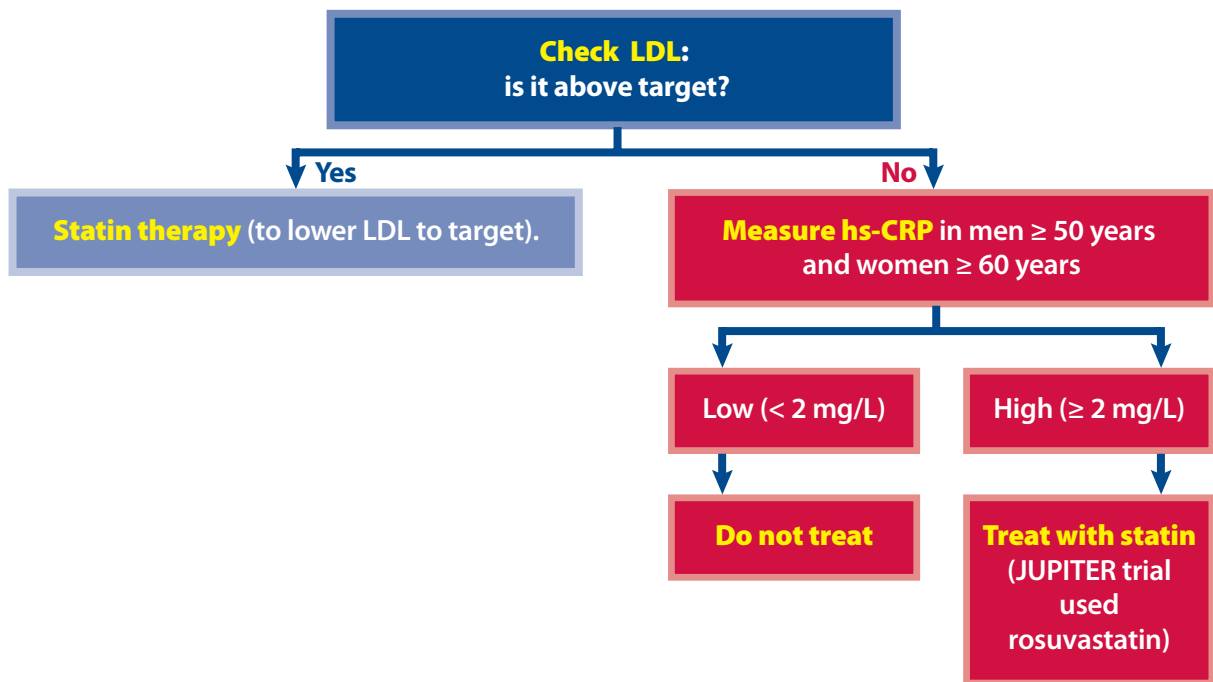


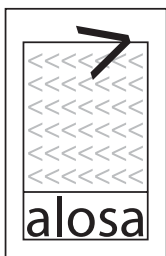
Reproduced with permission from Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* Nov 20 2008;359(21):2195-2207.



While JUPITER was conducted using rosuvastatin (Crestor), there is good evidence from previous clinical trials that other statins are also effective in lowering C-reactive protein.<sup>7</sup> Here is one plausible evidence-based approach to statin use in light of the findings of JUPITER:

**Figure 2. Use of statins for patients with elevated LDL or hs-CRP.**





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**References:** 1. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. Jul 13 2004;110(2):227-239. 2. Helfand M. Drug Class Review on HMG-CoA Reductase Inhibitors (Statins) 2006. Available at: <http://www.ncbi.nlm.nih.gov/books/bf/bkcg?book=statins>. 3. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol Mar* 1 1998;81(5):582-587. 4. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. Jun 28 2003;326(7404):1423. 5. Brown BG, Taylor AJ. Does ENHANCE diminish confidence in lowering LDL or in ezetimibe? *N Engl J Med*. Apr 3 2008;358(14):1504-1507. 6. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. Nov 20 2008;359(21):2195-2207. 7. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;344:1959-65.

**Additional references documenting these recommendations are provided in the evidence document accompanying this material and can be accessed at:**

[www.RxFacts.org](http://www.RxFacts.org)

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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.**