

# Aggressive treatment of dyslipidemia: A review of supporting evidence

## ABSTRACT

Clinical trial data are now sufficient to support aggressive treatment of dyslipidemia. Cholesterol-lowering therapy is known to reduce the risk of clinical events across a wide range of lipid levels, even in patients with “normal” levels. Current data support lowering low-density lipoprotein cholesterol (LDL-C) levels at least to those recommended by the National Cholesterol Education Program, but perhaps even more aggressively in some patients. Of the available cholesterol-lowering agents, statins produce the greatest reductions in LDL-C levels and coronary events and are currently the best treatment option for most patients.

## KEY POINTS

Hypercholesterolemia’s effect on endothelial dysfunction is well established, as is the role of endothelial dysfunction in atherosclerosis and subsequent cardiovascular events.

Although the benefits of lipid lowering are well established in high-risk individuals, a number of trials show that the benefits extend also to lower-risk individuals.

Patients with diabetes and no previous myocardial infarction have the same risk for infarction as nondiabetic patients who have had a myocardial infarction. This suggests that all patients with diabetes should be treated as though they have prior coronary heart disease.

Statins are the most effective agents available for lowering LDL-C levels. Use of statins has led to greater reductions in coronary heart disease and total mortality than observed with other classes of drugs.

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**E**VIDENCE FROM CLINICAL TRIALS is now sufficient to support both the aggressive treatment of dyslipidemia and the use of HMG-CoA reductase inhibitors (statins) to do so.

Dyslipidemia’s effect on endothelial dysfunction and subsequent coronary artery atherosclerosis and coronary events is now well understood, and lowering levels of low-density lipoprotein cholesterol (LDL-C) has been shown to improve endothelial dysfunction not only in hypercholesterolemic patients with or without coronary heart disease (CHD), but also in people with lipid levels considered within the normal range.

## WHICH LIPIDS INCREASE CORONARY HEART DISEASE RISK?

A large body of epidemiologic evidence supports a direct relationship between CHD risk and the levels of LDL-C and total cholesterol.<sup>1,2</sup> In the Multiple Risk Factor Intervention Trial (MRFIT)<sup>1</sup> the relationship between serum cholesterol and CHD death was continuous, graded, and strong among men aged 35 to 57 years with no history of hospitalization for myocardial infarction (TABLE 1).

A strong inverse relationship also exists between the risk of CHD events and plasma high-density lipoprotein cholesterol (HDL-C) levels,<sup>3,4</sup> although clinical trials specifically designed to assess the benefits of trying to raise HDL-C levels have not been completed. Similarly, recent studies have provided clearer evidence of elevated triglycerides as a risk factor for cardiovascular disease.<sup>5,6</sup> However, the association between hypertriglyceridemia and CHD is not as strong as it is for LDL-C.





Triglyceride levels significantly predict the risk of CHD in univariate analyses, but the independent effect of plasma triglycerides is weaker or disappears when statistical adjustment is made for the effects of other risk factors (HDL-C in particular).<sup>5,6</sup>

### Consider total cholesterol when assessing coronary heart disease risk

Epidemiologic data emphasize the importance of considering the combined impact of different plasma lipids in assessing CHD risk. A combination of hypertriglyceridemia (plasma triglyceride > 200 mg/dL) with a low HDL-C level (< 39 mg/dL in men or < 43 mg/dL in women) or with a high total cholesterol/HDL-C ratio (> 5) predicts a particularly high CHD risk.<sup>4</sup>

Similarly, Framingham Heart Study data showed that men and women with triglyceride levels greater than 150 mg/dL combined with low HDL-C levels (< 40 mg/dL) have a very high rate of coronary artery disease.<sup>7</sup> Because of the strong interrelationships between elevated triglyceride levels, reduced HDL-C levels, and elevated LDL-C levels, it is difficult to determine the independent contributions of these traits to CHD risk. It is likely that all are involved in multiple steps of the disease process.

### Other coronary heart disease risk factors

These clusters of lipid alterations are also usually associated with other conditions that promote vascular disease. These include increases in coagulation factors such as fibrinogen, factor VII, and plasminogen activator inhibitors, lipid factors such as apolipoprotein B and lipoprotein (a), insulin resistance, and homocysteine.

Among these factors, lipoprotein (a) has recently been associated with the severity of coronary atheroma.<sup>8,9</sup> Atherosclerosis is also accompanied by biochemical markers of inflammation such as C-reactive protein and the intercellular adhesion molecule ICAM-1.<sup>5</sup> In addition, epidemiologic data emphasize the importance of considering the joint impact of the other major risk factors in patients with dyslipidemia, such as smoking, diabetes, and hypertension, which increase the risk of CHD synergistically.<sup>1</sup>

**TABLE 1**

### MRFIT: The higher the cholesterol level, the higher the CHD mortality rate

CHOLESTEROL DECILE	CHOLESTEROL RANGE, MG/DL	6-YEAR CHD* MORTALITY RATE, PER 1,000	RELATIVE RISK
1	≤ 167	3.16	1.00
2	168–181	3.32	1.05
3	182–192	4.15	1.31
4	193–202	4.21	1.33
5	203–212	5.43	1.72
6	213–220	5.81	1.84
7	221–231	6.94	2.20
8	232–244	7.35	2.33
9	245–263	9.10	2.88
10	≥ 264	13.05	4.13

\*CHD: coronary heart disease

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### VASCULAR ENDOTHELIAL DYSFUNCTION IN CORONARY HEART DISEASE

Injury to the vascular endothelium appears to be the key event in the origin, progression, and clinical manifestation of atherosclerotic plaques.<sup>10</sup> Endothelial dysfunction increases in the presence of traditional cardiovascular risk factors and therefore plays an important role in the pathogenesis of atherosclerosis. It is well established that elevated plasma lipid levels, smoking, diabetes, and hypertension increase the number of atherosclerotic plaques in the coronary arteries,<sup>11</sup> and therefore, the risk of CHD.

Myocardial infarction is most often not the result of high-grade stenoses,<sup>12,13</sup> but rather of the rupture of vulnerable lesions characterized by an eccentric lipid-rich core, a high macrophage density, and a weak fibrous cap.<sup>14</sup> Although lesions with these characteristics account for only 10% to 20% of all lesions, they are associated with 60% to 90% of clinical events.<sup>14</sup>



**TABLE 2**

## Effects of coronary heart disease risk factors on endothelial function

### Dyslipidemia

The amount of biologically active nitric oxide, an endothelium-derived vasodilator which also inhibits platelet aggregation, lipid oxidation, and monocyte migration, is reduced in hypercholesterolemia and further reduced in atherosclerosis, even in children and young adults<sup>15</sup>

Levels of endothelin, a potent vasoconstrictor, are increased and correlate positively with the degree of atherosclerotic lesion formation<sup>16</sup>

Endothelial cell production of endothelin is increased in hypercholesterolemia and atherosclerosis, and endothelin receptor expression is down-regulated<sup>16</sup>

Oxidized LDL cholesterol is a likely stimulus for increased endothelin production<sup>17</sup>

### Smoking

Flow-mediated dilation is impaired or absent in smokers, is slightly less impaired in former smokers, and is inversely related to lifetime dose smoked<sup>18</sup>

Passive smoking is associated with dose-related impairment of endothelium-dependent dilation, with flow-mediated dilation being significantly impaired in both active and passive smokers vs controls<sup>19</sup>

### Diabetes

Vascular reactivity to hyperemia (with increased flow causing endothelium-dependent dilation) was significantly impaired in young (15 to 40 years old) insulin-dependent diabetic people vs matched controls<sup>20</sup>

Flow-mediated dilation was inversely related to both the duration of diabetes and LDL cholesterol levels, even though these levels were only mildly elevated (< 160 mg/dL in the majority of patients)<sup>20</sup>

### Hypertension

Endothelium-dependent vascular relaxation in response to acetylcholine is significantly blunted in patients with hypertension, an effect independent of sympathetic activity<sup>21</sup>

Abnormal serum cholesterol levels predispose patients to rupture of vulnerable plaques.<sup>13</sup> A reanalysis of data from the Familial Atherosclerosis Treatment Study (FATS)<sup>14</sup> suggests that aggressive cholesterol-lowering therapy reduces the risk of acute coronary events by depleting lipids from these vulnerable plaques, thereby stabilizing them.

The effects of dyslipidemia and other major CHD risk factors on endothelial function are summarized in **TABLE 2**.<sup>15–22</sup>

## ■ LIPID-LOWERING THERAPY

### Effects on cardiovascular events

A number of important clinical trials have shown that the risk of CHD can be significantly lowered by reducing LDL-C levels.<sup>23–32</sup>

**TABLE 3** summarizes the reduction in cardiovascular events observed in recent primary and

secondary prevention studies as a result of LDL-C lowering.

### Benefits even in those at low risk

The benefits of lipid lowering on CHD risk are now well established in high-risk people, but a number of trials now provide evidence that the benefits extend also to lower-risk people. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),<sup>29</sup> aggressive lowering of average LDL-C levels in people with no evidence of CHD substantially reduced cardiovascular risk. Moreover, the degree of benefit was independent of the baseline LDL-C level.

Results from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID),<sup>30</sup> Atorvastatin vs Revascularization Treatment (AVERT),<sup>31</sup> and the Scandinavian Simvastatin Survival Study (4S)<sup>33</sup> also support the concept of no apparent threshold

**Aggressive lipid lowering stabilizes vulnerable atherosclerotic plaques**



TABLE 3

### Reduction in LDL-C and relative risk of coronary heart disease in large prevention studies

STUDY	REDUCTION IN LDL-C VS PLACEBO (%)	RISK REDUCTION (%)
Scandinavian Simvastatin Survival Study (4S) <sup>26</sup>	35	34
Coronary and Recurrent Events (CARE) <sup>27</sup>	28	24
West of Scotland Coronary Prevention Study <sup>28</sup>	26	33
Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) <sup>30</sup>	25	24
Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) <sup>29</sup>	25	37

**Vulnerable plaques are small, lipid-rich, and have a thin fibrous cap**

level below which further lipid lowering would not provide additional benefit. In LIPID and 4S the benefits of treatment extended to all patients independent of baseline LDL-C level.<sup>30,33</sup> In AVERT, aggressive LDL-C reductions (to a mean of 77 mg/dL) with atorvastatin 80 mg/day was associated with significantly fewer ischemic events compared with patients who underwent angioplasty.<sup>31</sup> In the Post Coronary Artery Bypass Graft Trial,<sup>34</sup> aggressive treatment to reduce LDL-C levels to less than 100 mg/dL slowed progression of atherosclerosis in bypass grafts to a greater extent than less aggressive lipid lowering. However, in contrast to these results, a post hoc analysis of the Cholesterol and Recurrent Events study (CARE)<sup>27</sup> found no improvement in major coronary events in individuals with baseline LDL-C levels of less than 125 mg/dL. In addition, all major end point trials to date have limited entry to those with baseline triglycerides less than 400 mg/dL or less, and little information is available for subjects with more severe elevations.

Reduction in the relative risk for CHD is related to the degree of LDL-C lowering. A recent meta-analysis estimated that CHD risk is reduced by 15% for each 10% reduction in plasma LDL-C level.<sup>35</sup> The relationship between LDL-C reduction and relative risk reduction is log-linear: a given absolute reduction in LDL-C level will produce the same reduction in relative risk across a wide range of LDL-C levels. The effect of lowering LDL-C on absolute risk reduction, however, depends on the baseline risk of cardiovascular events of the patient group.<sup>35</sup>

### Effects of lipid lowering on endothelial function

Angiographic studies generally show that the risk of cardiovascular events can be dramatically reduced by lipid-lowering therapy, even in the face of modest (1% to 2%) changes in the degree of stenosis of preexisting coronary lesions.<sup>36,37</sup> These results suggest that the propensity for development of CHD events is determined not only by the size of the atheroma and the degree of luminal encroachment, but also by the vulnerability of the atheroma.<sup>38</sup>

A number of recent studies<sup>38-42</sup> have shown that reducing LDL-C improves endothelial function and stabilizes existing atherosclerotic plaques. Cholesterol-lowering therapy for 6 months has been shown to reverse the impairment of acetylcholine-induced dilation of epicardial coronary arteries and to improve acetylcholine-induced increases in coronary blood flow<sup>39</sup> in patients with hypercholesterolemia. In contrast, no changes in response to acetylcholine were observed after 8 months of usual care without drug therapy.

In patients with coronary atherosclerosis and total cholesterol levels ranging from 159 to 302 mg/dL, treatment with lovastatin for 6 months significantly reduced total cholesterol levels and improved endothelial vasomotor function as assessed by quantitative angiography and Holter monitoring following intracoronary infusion of acetylcholine.<sup>40</sup> In patients with atherosclerosis and total serum cholesterol levels of 180 to 280 mg/dL, lovastatin plus probucol significantly reduced plasma LDL-C levels by 38% and improved endothelium-dependent vasomotion, as





assessed by reductions in coronary artery diameter.<sup>41</sup> These effects were also observed in patients with severe primary hypercholesterolemia (baseline total cholesterol range 358 to 485 mg/dL) who were treated with atorvastatin alone or with simvastatin plus cholestyramine.<sup>42</sup> Atorvastatin, the most efficacious statin,<sup>43</sup> reduced total cholesterol and LDL-C by 41% and 46%, respectively, and significantly improved endothelial function. Combination therapy with simvastatin plus cholestyramine produced similar results.<sup>42</sup>

In healthy adults without hypercholesterolemia who were treated with simvastatin 10 mg/day for 12 weeks, flow-mediated endothelium-dependent dilation increased from 5% at baseline to 10.5, 13.3, and 15.7% (all  $P < .05$ ) at 2, 4, and 12 weeks, respectively.<sup>44</sup> Over the same 12-week period, mean serum cholesterol levels decreased from 201 to 155 mg/dL.<sup>44</sup> Atorvastatin and simvastatin have also been shown to prevent the inhibitory effect of oxidized LDL-C on bovine aortic endothelial nitric oxide synthase.<sup>45</sup>

### Conclusions from clinical trial data

Overall, these results suggest the following:

- Improved endothelial function contributes significantly to the reduction in myocardial infarction and revascularization procedures
- Lipid-lowering therapy can rapidly improve endothelial function
- This improvement is observed even after lowering cholesterol levels to below the levels recommended by treatment guidelines.

### ■ BASE TREATMENT INTENSITY ON RISK

The most recent US<sup>46</sup> and European<sup>47</sup> guidelines for the treatment of hypercholesterolemia base the intensity of therapy on the patient's risk status. Patients with CHD or with multiple risk factors for CHD should be treated more aggressively than those at lower risk.<sup>46,47</sup>

The National Cholesterol Education Program (NCEP) guidelines recommend a target LDL-C level of less than 100 mg/dL for patients with established CHD, and a level of less than 130 mg/dL for those without CHD but with two risk factors.<sup>46</sup> According to the

National Health and Nutrition Examination Survey, the latter population represents the majority of patients at risk. The goal for patients without CHD and fewer than two risk factors is 160 mg/dL.<sup>46</sup>

Although current data show no apparent threshold level below which further lipid lowering would not provide additional benefit, there may be a point beyond which the absolute risk is so low that treatment is not worthwhile from a practical standpoint. This issue is contentious. The greatest reduction in absolute risk occurs in patients with the highest absolute risk—ie, those with existing CHD. For now, treatment decisions in patients without preexisting CHD should be based on an assessment of the patient's overall risk, according to current guidelines.

### Treat all diabetic patients

Some patient groups, however, may benefit from more aggressive therapy. For example, recent data<sup>48</sup> indicate that patients with diabetes and no previous myocardial infarction have the same risk for infarction as nondiabetic patients who have had a myocardial infarction. Thus, all patients with diabetes should be treated as though they have prior CHD.

### ■ SELECTING THE BEST DRUG THERAPY

In determining the most appropriate agent to use for a particular patient, the patient's lipoprotein profile and the drug's lipid-lowering characteristics need to be considered. TABLE 4 summarizes important characteristics of niacin, bile acid sequestrants (resins), fibrates, and statins.<sup>46,49–53</sup>

#### Niacin

Niacin lowers LDL-C and raises HDL-C and triglyceride levels substantially. Niacin causes immediate flushing, although this appears to be less a problem with a new timed-release formulation. It can cause hyperglycemia and therefore is not recommended in diabetic patients.<sup>54</sup> It can also raise uric acid levels and may precipitate or aggravate gout.

#### Bile acid sequestrants

Bile acid sequestrants (resins) lower LDL-C and raise HDL-C moderately. Because they

**Treat  
diabetic  
patients  
as if they  
have coronary  
heart disease**



TABLE 4

## Profiles of lipid-lowering agents

DRUG	EFFECT ON LDL CHOLESTEROL	EFFECT ON HDL CHOLESTEROL	EFFECT ON TRIGLYCERIDES	EFFECT ON LIPOPROTEIN (A)	COMMENTS
<b>Niacin</b> Controlled-release Crystalline	Lowered 10% to 25%	Raised 15% to 35%	Lowered 20% to 50%	Lowered 15% to 30%	Poor tolerability reduces compliance; not for use in diabetic patients; controlled-release form increases risk of liver damage
<b>Bile acid sequestrants</b> Cholestyramine Colesteslam Colestipol	Lowered 15% to 30%	Raised 3% to 5%	Unchanged	Unchanged	Triglyceride levels may rise dramatically in some patients
<b>Fibrates</b> Bezafibrate Ciprofibrate Clofibrate Fenofibrate Gemfibrozil	Lowered 10% to 15%	Raised 10% to 35%	Lowered 20% to 50%	Unchanged	Lower risk of coronary heart disease; primarily used to treat hypertriglyceridemia; may lower LDL levels 15% to 30% if baseline triglycerides are below 150 mg/dL; may raise LDL levels if triglycerides are elevated
<b>Statins</b> Atorvastatin Cerivastatin Fluvastatin Lovastatin Pravastatin Simvastatin	Lowered 20% to 60%	Raised 5% to 15%	Lowered as much as 40% or not at all	Unchanged	Well-tolerated; lower mortality rates in primary and secondary prevention of coronary heart disease; no precautions in patients with comorbidities; lowering of triglycerides proportional to baseline total lipid levels

ADAPTED FROM REFERENCES 46,49-53

raise triglycerides, they are not suitable for patients with combined dyslipidemia, unless given with a triglyceride-lowering agent.

Bile acid sequestrants are inconvenient to administer, unpalatable, and not well tolerated because of gastrointestinal symptoms (eg, constipation, reflux esophagitis, dyspepsia),<sup>46</sup> all of which reduce compliance.

### Fibrates

Fibrates lower LDL-C modestly, although newer fibrates (fenofibrate, bezafibrate) appear to be more effective. Fibrates raise HDL-C levels substantially and lower triglyceride levels substantially. Fibrates can cause gastrointestinal problems such as diarrhea, vomiting, dyspepsia, and flatulence.

### Statins

Statins are the most effective agents available for lowering LDL-C levels, and this lipid-lowering efficacy has led to greater reductions in CHD and total mortality than those observed with other classes of drugs used in earlier intervention studies.<sup>23,24,55</sup> Statins raise HDL-C moderately, and this effect appears greatest in patients with elevated baseline triglycerides.<sup>56</sup> There is also preliminary evidence that some statins may elevate HDL-C more than others, especially at higher doses.<sup>57,58</sup> Statins lower triglyceride levels only moderately, the effect apparently related to the degree of hypertriglyceridemia and the dose of the statin.<sup>56</sup>

Statins are particularly useful in patients with severe forms of hypercholesterolemia or in those with established CHD in whom substan-



tial reductions in LDL-C are required.<sup>49</sup> As a class, they are generally well tolerated, do not adversely affect glycemic control, and are useful in young and elderly patients with multiple risk factors.<sup>49</sup> They produce minor and reversible hepatic transaminase elevations in 0.1% to 2.5% of patients, depending on the type of statin and the dose. Nonspecific myalgias are probably the most commonly reported adverse effect. However, serious myocytitis with marked creatine kinase elevation is extremely rare.<sup>46</sup>

Statins are associated with a high rate of patient compliance,<sup>54</sup> although compliance is low with all therapies for chronic, asymptomatic conditions, demonstrating that we not only need to select the most effective agent, but also to follow up to see that patients refill their prescriptions and take their lipid-lowering medications regularly.

### Choose lipid-lowering agent based on triglyceride levels

Because plasma lipoproteins (especially those carrying large amounts of triglyceride) respond differently to different agents, the choice of lipid-lowering drug should take plasma triglyceride concentrations into account.

When triglyceride levels are greater than 180 mg/dL, do not give resins unless prescribing a triglyceride-lowering agent concomitantly. Statins should be the first choice in patients with triglycerides up to 450 mg/dL, and either statins or fibrates (or niacin in selected patients) should be given when

triglyceride levels are between 450 and 900 mg/dL.<sup>47</sup> However, effective lowering of triglycerides with statins may require the use of either higher doses or newer agents.

When triglyceride levels are very high ( $\geq 900$  mg/dL), lipid-lowering drugs are less effective and should generally be used only after diet, control of diabetes, and limitations in alcohol intake have been instituted.<sup>46,47</sup> In postmenopausal women, discontinuation of oral hormone replacement therapy is advised before starting lipid-lowering therapy. Fibrates and, to a lesser extent, niacin are most appropriate for this group of patients.

### ROLE OF STATINS IN AGGRESSIVE TREATMENT

Lipid-lowering improves endothelial dysfunction in hypercholesterolemic patients with or without CHD, even in individuals with lipid levels considered within the normal range. This knowledge and data from large prevention studies (including some in patients with average serum cholesterol levels)<sup>29–35</sup> support the aggressive lowering of LDL-C levels.

Since statins are the most effective agents available for lowering LDL-C levels, they are clearly the best option available for aggressive lipid lowering. The choice of statin should be based on the patient's dyslipidemia profile, the reduction in cholesterol required to get below goal levels, and the monetary cost of achieving the desired treatment goal.

**Statins are the best option when substantial lowering of LDL-C is required**

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ADDRESS: Evan A. Stein, MD, PhD, 2 Tesseneer Drive, Highland Heights, KY 41076; e-mail esteinmrl@aol.com.