Review

LDL-cholesterol lowering and atherosclerosis – clinical benefit and possible mechanisms: an update

A.A. Kroon *, A.F.H. Stalenhoef

Department of Medicine, Division of General Internal Medicine, University Hospital Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, Netherlands

Received 21 March 1996; revised 21 February 1997; accepted 25 February 1997

Abstract

The results of several lipid-lowering randomized trials have been released during the past years and have confirmed the lipid hypothesis. Reduction of cholesterol by potent drugs in clinically symptomatic or asymptomatic patients with above-average cholesterol levels will substantially reduce the risk of coronary events. The present article gives a review of potent low-density lipoprotein cholesterol-lowering treatments and discusses developments in hypolipidaemic therapy in relation to recent primary and secondary prevention studies. In addition, possible mechanisms of cholesterol lowering in retardation of the atherosclerotic process are summarised. © 1997 Elsevier Science B.V.

Keywords: LDL-cholesterol; Atherosclerosis; Cholesterol lowering; Coronary artery disease; Peripheral vascular disease

1. Introduction

Cardiovascular diseases are the major cause of death in the Western societies. In the Netherlands 40% of all deaths in 1993 were caused by cardiovascular diseases, of which 40% were ischaemic heart disease and 23% cerebrovascular disease. The ability to prevent the development of atherosclerosis or, alternatively, to reduce the severity of established atherosclerotic plaques, often referred to as regression, has major implications for health care.

The validity of the lipid hypothesis has been debated for more than 40 years. The relation between total cholesterol and low-density lipoprotein (LDL) cholesterol levels and the incidence of coronary artery disease (CAD) and peripheral vascular disease (PVD) is now well established [1-3]. Epidemiological studies have shown parallel, age-related trends of atherosclerotic lesions in the abdominal aorta, carotid, and coronary arteries [4,5]. Since the beginning of the 1980s, many primary and secondary prevention trials, predominantly conducted in men with hypercholesterolaemia, have shown that lipid-lowering regimens result in reduction of angiographic lesions and are associated with a decreased incidence of atherosclerotic events [6-38]. Most of these trials have shown slowing or arrest of progression of coronary atherosclerosis. Reports concerning femoral atherosclerosis are more scarce [7,14-16,21,24,25]. In several recent clinical trials on plasma lipid regulation, measurements of carotid artery intima-media
thickness (IMT) have been included, because coronary and carotid atherosclerosis share coronary events as their major cause of morbidity and mortality [38–41]. Indeed, most of these studies have also shown a slowing of progression of IMT during lipid-lowering treatment.

The common denominator of most of these trials is reduction of LDL cholesterol [42]. However, the results of the recently published Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) may also indicate a role for lowering serum triglycerides and raising high-density lipoprotein (HDL) cholesterol in reversing the progression of atherosclerosis [35]. With the introduction of more potent cholesterol-lowering agents, the 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, the effects of lipid lowering on coronary and total mortality have been solidly confirmed, changing the lipid hypothesis into evidence [43]. In this article the background of LDL-cholesterol-lowering treatment will be discussed in relation to an update of the insights provided by atherosclerosis regression studies.

2. LDL-cholesterol-lowering treatments

We will focus on treatment with HMG-CoA reductase inhibitors because these drugs have made a major impact on the therapy of hypercholesterolaemic patients, in terms of both efficacy and tolerability. In addition, the value of treatment with LDL-apheresis will be discussed for more aggressive secondary prevention in drug-refractory cases.

2.1. HMG-CoA reductase inhibitors

HMG-CoA reductase is an enzyme that catalyses the rate-limiting step in cholesterol biosynthesis [44]. HMG-CoA reductase inhibitors reduce serum cholesterol levels by inhibiting the endogenous synthesis of cholesterol, thereby upregulating LDL receptors, especially in the liver [45,46]. This leads to increased removal from plasma of LDL as well as the precursors of LDL, intermediate density lipoproteins (IDL). This dual mechanism of decreased production and increased removal of LDL causes large reductions in serum cholesterol concentrations. Over the past few years numerous studies have shown the efficacy and safety of 4 HMG-CoA reductase inhibitors currently available: lovastatin, simvastatin, pravastatin, and fluvastatin. A reduction of total cholesterol ranging from 23–45% (mean 30%) can be achieved, due to a 26–42% (mean 35%) reduction of LDL-cholesterol. This effect is accompanied by a 11–32% (mean 20%) decrease in serum triglycerides and a 8–13% (mean 8%) increase of HDL-cholesterol [47,48]. Some reports have shown an increase in lipoprotein(a) [Lp(a)] levels during treatment with the statins, ranging from 8–12% [30,37,49]. On a milligram basis simvastatin is twice as potent as pravastatin and lovastatin, and 4 times as potent as fluvastatin [50,51]. The not yet approved drug, atorvastatin, has been reported to decrease LDL-cholesterol even more by up to 60% and reduce triglyceride levels by up to 40% [52,53], probably due to its long plasma half-life.

In general, HMG-CoA reductase inhibitors are well tolerated and side-effects are neither serious nor frequent [47]. Apart from increases in liver enzyme levels greater than 3-fold the upper normal limit, which occur in approximately 1% of statin-treated patients, the myopathy syndrome (elevation of creatine kinase activity above 10-fold the upper normal limit plus muscle pain or weakness) is the only side-effect worth mentioning. The incidence of myopathy during monotherapy with statins is approximately 1 in 1000, although the combination with fibrates, cyclosporin, nicotinic acid and erythromycin might amplify this risk [54].

In animal studies, treatment with HMG-CoA reductase inhibitors has been shown to retard the development of atherosclerosis [55,56]. Moreover, intensive lipid lowering using HMG-CoA reductase inhibitors is the most effective in terms of inducing plaque regression and reducing the number of clinical events in men with established CAD and PVD [18,19,25,28,30–41]. Recently, a meta-analysis that pooled data from four studies treating men and women with 10–40 mg per day pravastatin for 2–3 years showed that a decrease in LDL-cholesterol of 28% from baseline was associated with a 62% reduction in the combined incidence of non-fatal and fatal myocardial infarction [57]. More aggressive lipid lowering may even improve these benefits [58]. Therefore, if treatment goals in lowering LDL-
cholesterol are not reached, combination therapy with a reductase inhibitor and a bile-acid sequestrant should be considered. Since many patients with CAD show a combined elevation of total cholesterol and triglycerides, due to increases in the circulating masses of both LDL and very-low-density lipoproteins (VLDL), combination therapy of a reductase inhibitor and a fibric acid should be considered in these cases [59]. However, adverse reports linking myopathy to the use of this drug combination call for caution in the use of this regimen [60].

2.2. LDL-apheresis

In addition to drug treatment, alternative approaches to cholesterol-lowering have been performed by portocaval shunting, liver transplantation and plasmapheresis [61-63]. The latter has been shown to reduce mortality of CAD [64]. New techniques have been developed to replace plasmapheresis, which selectively remove apolipoprotein-B-containing lipoproteins from plasma [65–69]. The performance of regular LDL-apheresis permits the achievement of lower levels of LDL-cholesterol, which are usually not possible to attain with drug therapy alone [70–73]. Adverse events from LDL-apheresis are infrequent and similar to any extracorporeal treatment. They mainly include hypotension and chills, which have been reported with frequencies of 0.2–1.1% and 0.3–6.0%, respectively [70,73]. LDL-apheresis has been shown to change peripheral and cerebral haemodynamics favourably by short-term improvements in the rheological properties of whole blood and probably also by restoring endothelium-dependent vasodilation [74,75]. The application of this method may offer opportunities in the prevention of progression of atherosclerosis as has been shown in selected patients with a primary hyperlipidaemia and established CAD or PVD refractory to drug treatment [24,37,38,76–81].

3. Clinical trials

In 1994, convincing evidence for the value of lipid-lowering therapy in reducing clinical CAD events was published in a meta-analysis of 28 randomized controlled, primary and secondary prevention trials by Law et al. [82]. The analysis indicated that in men 55–64 years of age, a 10% decrease in total cholesterol produced a 7% reduction in ischaemic events during the first 2 years of the trial, a 22% reduction during years 2–5, and a 25% reduction after 5 years of the trial. These findings are consistent with a lag period between the initiation of lipid-lowering therapy and a reduction in clinical events.

3.1. Primary prevention trials

The early primary prevention trials were too small to demonstrate significant changes in mortality [82]. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPTT), a 7-year placebo-controlled study in 3806 men with elevated cholesterol [8,9], and the 5-year Helsinki Heart Study (HHS), in 4081 men with elevated LDL and/or very-low-density lipoprotein (VLDL) cholesterol [12], both showed a reduction in coronary events after long-term treatment with cholestyramine and gemfibrozil, respectively (Table 1). The investigators of the LRC-CPTT showed that each 1% reduction in serum cholesterol would result in an approximately 2% reduction in the risk of CAD [9]. After the disappointing results on mortality of the very large World Health Organization Clofibrate Trial [6], the LRC-CPTT and the HHS actually initiated the wide acceptance of the favourable effects of lipid-lowering treatment on cardiac mortality or CAD incidence, although much debate was raised by the increase in non-cardiac mortality (Table 1). This excess of deaths in the intervention groups has been explained by the use of fibrates, but also by an overestimation due to intention-to-treat analyses [84,85]. To overcome some of the limitations of the LRC-CPTT, in which the decrease in cholesterol was less than expected due to poor compliance to the study drug, or of the HHS, which used an agent less effective in lowering LDL-cholesterol, the West of Scotland Coronary Prevention Study (WOSCOPS) was designed using one of the HMG-CoA reductase inhibitors (Table 1) [34]. In this double-blind, randomized, placebo-controlled trial 6595 Scottish men between 45 and 64 years of age with a mean LDL-cholesterol of 5.0 mmol/l were treated with 40 mg per day pravastatin or placebo for a mean of 4.9 years. LDL-cholesterol...
### Table 1: Primary prevention studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Mean study duration (yr)</th>
<th>Total cholesterol (%)</th>
<th>Non-fatal MI (%)</th>
<th>All CAD events (%)</th>
<th>Non-CAD mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO-clofibrate [6]</td>
<td>10627</td>
<td>5.3</td>
<td>-9 *</td>
<td>-26 *</td>
<td>-20 *</td>
<td>+36 *</td>
</tr>
<tr>
<td>LRC-CPPT [8]</td>
<td>3806</td>
<td>7.4</td>
<td>-9 *</td>
<td>-19</td>
<td>-19 *</td>
<td>+33</td>
</tr>
<tr>
<td>HHS [12]</td>
<td>4081</td>
<td>5</td>
<td>-10 *</td>
<td>-36</td>
<td>-34 *</td>
<td>+25</td>
</tr>
<tr>
<td>WOSCOPS [34]</td>
<td>6595</td>
<td>4.9</td>
<td>-20 *</td>
<td>-31 *</td>
<td>-31 *</td>
<td>-11</td>
</tr>
</tbody>
</table>

Data represent percent changes in the intervention group versus the control group. MI = myocardial infarction; CAD = coronary artery disease; n.c. = not changed.

* Statistically significant change.

was lowered on average by 26% and the major end-point, death from CAD or non-fatal myocardial infarction, showed a significant reduction of 31%, whereas overall mortality was reduced by 22% without excess of non-cardiovascular deaths. This study unequivocally showed that primary prevention with a well-tolerated and potent drug, in a population at increased risk for CAD and no history of myocardial infarction, is effective and may also have a major impact for health care costs. The clinical benefits of lipid-regulating therapy in primary prevention trials preceding the WOSCOPS have been less dramatic and a matter of constant debate. However, hypercholesterolaemic individuals without established CAD represent an important population who will eventually die or become disabled by CAD events. Several studies are now in progress, which may provide more information about the benefits and risks of several treatment modalities in the primary prevention of CAD [86].

#### 3.2. Secondary prevention trials

The Scandinavian Simvastatin Survival Study (4S) and the Cholesterol and Recurrent Events (CARE) trial, both double-blind, randomized, placebo-controlled studies, provided definitive evidence of the benefit of lowering LDL-cholesterol in patients with established CAD [31,36]. In 4S, 4444 men and women with serum total cholesterol levels between 5.5 and 8.0 mmol/l were allocated to 20–40 mg per day simvastatin or placebo. After a median treatment period of 5.4 years, LDL-cholesterol was lowered on average by 35%, and total mortality was reduced by 30% because of a CAD mortality rate reduction of 42% in the simvastatin-treated patients. In the 5-year CARE study, 4159 men and women with a plasma total cholesterol level of less than 6.2 mmol/l and an LDL-cholesterol of 3.0–4.5 mmol/l were assigned to 40 mg per day pravastatin or placebo. LDL-cholesterol was lowered by 32% and maintained mean levels of 2.5 mmol/l throughout the follow-up. Fatal or non-fatal coronary events were significantly reduced by 24% due to an absolute risk reduction from 13.2 to 10.2% in the placebo- and pravastatin-treated group, respectively. Interestingly, no significant differences in non-cardiovascular mortality were observed in either study, and moreover, women seemed to benefit more from treatment than men in CARE.

Evidently, lipid lowering in a population with established CAD is more effective in reducing coronary and total mortality. However, since the separation of cholesterol-lowering trials into those studying primary and those studying secondary prevention has little foundation in coronary pathology, WOSCOPS, 4S, and the CARE study indicate that more aggressive lipid lowering further reduces the progression of CAD. Indeed, renewed meta-analysis of randomized cholesterol-lowering trials has shown a regression line between CAD and total mortality versus the percent of cholesterol reduction, indicating that further lowering of total cholesterol concentrations is associated with a decreased mortality [84]. As has been indicated by the meta-analysis of Law et al. [82], the greatest changes in atherosclerosis may be found after more than 2 years of intervention. Moreover, a recent analysis of 11 angiographic coronary
Atherosclerosis regression studies showed that reduction of LDL-cholesterol by 44% for the duration of 2.6 years in patients with CAD should completely arrest the progression of the disease [87].

4. Degree of cholesterol lowering

Current international guidelines for the secondary prevention of CAD in Europe and the USA stipulate that LDL-cholesterol levels should be reduced to 3–3.5 and to 2.6 mmol/l or below, respectively [88,89]. However, the recently published subgroup analysis of 4S showed that the percentage reduction in LDL-cholesterol (32–37%) and decrease in relative risk of CAD in patients on simvastatin (32–36%) was comparable and constant across all quartiles of baseline LDL-cholesterol, which ranged from below 4.39 mmol/l in the lowest quartile to more than 5.39 mmol/l in the highest quartile [90]. This indicates that, at least in subjects with baseline total cholesterol levels between 5.5 and 8.0 mmol/l, the percentage reduction in LDL-cholesterol rather than its absolute level on treatment may determine clinical benefit, since subjects in 4S with LDL-cholesterol levels well above the recommended value showed the same reduction in CAD risk as those below these levels. Indeed, it has been shown in a subgroup of 11 coronary atherosclerosis regression studies that the percent change in diameter stenosis of coronary arteries correlated with the percent change in LDL-cholesterol during the study and not with on-trial levels [87]. In the CARE trial, however, patients in the lowest tertile with baseline LDL-cholesterol levels below 3.2 mmol/l did not benefit from pravastatin treatment with regard to reduction in coronary events [36]. These results are consistent with epidemiological studies that show a stronger relation between LDL-cholesterol levels and coronary events at hypercholesterolaemic, as compared with average, levels [91], as well as some angiographic studies which showed that improvement in coronary artery stenosis in patients receiving lipid-lowering therapy is proportional to the baseline LDL-cholesterol level [26,92]. Although these data need confirmation, they suggest limits to the clinically important influence of the LDL-cholesterol level on CAD. Consequently, the issue of cholesterol-lowering to recommended, fixed target values versus guidelines in percent reduction of baseline cholesterol levels is not yet completely solved.

5. Mechanisms of cholesterol lowering in retardation of atherosclerosis

Several mechanisms have been suggested by which lowering of LDL-cholesterol may confer clinical benefit, including stabilization of rupture-prone atherosclerotic lesions, decreased LDL-oxidizability, improvement of vascular endothelial function, and reduction of an inflammatory or immunological response associated with atherosclerosis [93].

5.1. Plaque stabilization

Statins may have stabilizing and protective effects on atherosclerotic lesions, by making them less vulnerable to fissure and rupture. The culprit lesion causing thrombosis of the coronary arteries is thought to be 30–70% stenoses in the majority of cases. These lesions, characterised by a lipid-rich core, a thin fibrous caps, few smooth muscle cells and fibroblasts, and a large number of foam cells particularly at the shoulders of the caps, are prone to rupture and lead to thrombotic occlusions and consequent clinical events [94,95]. Moreover, enhanced vasoconstriction potentially promotes plaque fissuring and ulceration, which may lead to thrombosis [96,97]. Evidently, there seems to be a dissociation between the results of angiographic studies and clinical outcome: lipid-lowering therapy has been shown to reduce the incidence of cardiovascular events with only small changes in coronary anatomy [98,99]. Therefore, it is most likely that treatment of hypercholesterolaemia depletes the lipid core of early atheromatous plaques, and consequently stabilizes these lipid-rich lesions and prevents further complications such as intramural haemorrhage and intraluminal thrombosis, an assumption that has been demonstrated in the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) and the Stanford Coronary Risk Intervention Project (SCRIP) [28,100].
5.2. LDL-oxidizability

Oxidative modification of LDL plays a key event in the development of atherosclerosis. It has been shown that LDL must undergo oxidative modification before it can be taken up by macrophages [93,101]. Oxidative modification of LDL, maybe mediated by cell-surface receptors [102], converts it to a form recognised by the macrophage scavenger receptor [103], leading to its unlimited uptake and the formation of foam cells, an early hallmark of atherosclerotic plaques. In addition to promoting excess lipid accumulation, oxidised LDL may facilitate the progression of atherosclerotic lesion by disrupting normal endothelial cell function [104]. The finding of oxidised LDL and lipid peroxides in areas of atherosclerotic plaques and the observation that antioxidant treatment with probucol and vitamin E slows the progression of atherosclerosis in the animal model strongly support the role of LDL modification in atherogenesis [105-109]. Recently the results of a randomized, controlled trial of vitamin E in normocholesterolaemic subjects with CAD, the Cambridge Heart Antioxidant Study (CHAOS), were published [110]. The authors showed that treatment with 400–800 IU of α-tocopherol per day significantly reduced the number of non-fatal coronary events after 1 year of treatment, although total mortality was increased in this group. It is too early to advocate secondary prevention with pharmacological doses of vitamin E, since in the animal model a decrease in oxidative susceptibility alone has been shown not to be sufficient to attenuate atherogenesis when cholesterol levels remain markedly elevated [111,112]. Recent evidence indicates that oxidized LDL inhibits endothelium-dependent arterial relaxation by diminishing the release of vasoactive compounds such as endothelium-derived relaxing factor (EDRF), identified as nitric oxide (NO), and also substances with contracting properties, such as endothelin [115,116]. Early in the process of development of atherosclerosis increased reactions to contractile agonists and attenuated vasodilating responses have been observed [117]. It has been shown in animal models that the release of protective, anti-aggregating and vasodilating substances is diminished due to atherosclerosis of the vessels and also as a consequence of hypercholesterolaemia per se [118-122]. In humans, coronary atherosclerosis and hypercholesterolaemia have also been associated with dysfunction of endothelium-mediated vasomotion, which impairs coronary or myocardial blood flow and forearm blood flow [123-126]. Lipid-lowering therapy has shown to improve the endothelium mediated vasomotion after relative short periods of time [127–129]. For example, Egashira et al. [127] demonstrated a significant improvement in coronary blood flow in response to acetylcholine infusion in patients with hypercholesterolaemia and pravastatin therapy. Anderson et al. [130] showed recently that the addition of antioxidant therapy with probucol to cholesterol-lowering treatment with lovastatin improved acetylcholine-induced, endothelium-dependent vasodilation significantly more than cholesterol lowering alone. Moreover, in this process of reversal it has been found that functional improvements of the coronary circulation precede the structural, anatomical improvements [131].

5.3. Endothelial cell dysfunction

Lowering of LDL-cholesterol is also of importance for the restoration of the hypercholesterolaemia-induced endothelial dysfunction [114]. The normal endothelium participates in the regulation of the vascular tone by releasing substances with both anti-aggregating and vasodilating properties, such as prostacyclin and endothelium-derived relaxing factor (EDRF), identified as nitric oxide (NO), and also substances with contracting properties, such as endothelin [115,116]. Early in the process of development of atherosclerosis increased reactions to contractile agonists and attenuated vasodilating responses have been observed [117]. It has been shown in animal models that the release of protective, anti-aggregating and vasodilating substances is diminished due to atherosclerosis of the vessels and also as a consequence of hypercholesterolaemia per se [118-122]. In humans, coronary atherosclerosis and hypercholesterolaemia have also been associated with dysfunction of endothelium-mediated vasomotion, which impairs coronary or myocardial blood flow and forearm blood flow [123-126]. Lipid-lowering therapy has shown to improve the endothelium mediated vasomotion after relative short periods of time [127–129]. For example, Egashira et al. [127] demonstrated a significant improvement in coronary blood flow in response to acetylcholine infusion in patients with hypercholesterolaemia and pravastatin therapy. Anderson et al. [130] showed recently that the addition of antioxidant therapy with probucol to cholesterol-lowering treatment with lovastatin improved acetylcholine-induced, endothelium-dependent vasodilation significantly more than cholesterol lowering alone. Moreover, in this process of reversal it has been found that functional improvements of the coronary circulation precede the structural, anatomical improvements [131].

5.4. Reduction of inflammatory or immunological response

The data are consistent with a pathogenetic role of endothelial-cell injury, impaired fibrinolysis, and inflammatory activities in the progression of CAD [132]. The initial inciting event in atherosclerosis is intimal lipid deposition, which is followed by recruitment of inflammatory cells (monocytes and T-lymphocytes) into the intima, smooth muscle cell accumulation, and elaboration of collagen and matrix proteins by smooth muscle cells. These processes have been shown to be mediated by minimally modified LDL, and induces the expression of and interplay between adhesion molecules (selectins, ICAM-1, and VCAM-1), monocyte chemotactic proteins (e.g., MCP-1), growth factors (e.g., PDGF), and cytokines
(IL-1, IL-4, IL-6, TNFα, and INFγ) [103,133,134]. It has been shown that systemic administration of oxidised LDL stimulates leucocyte adhesion and platelet aggregation to the vascular endothelium [135]. In both man and rabbits, autoantibodies are found which recognize and selectively bind oxidised LDL [105]. Moreover, the titre of autoantibodies binding malondialdehyde-LDL was found to be an independent predictor of the progression of carotid atherosclerosis in man [136]. The proliferation of smooth muscle cells is promoted by a number of growth factors, including IL-1β and IL-1α, which are secreted by activated monocytes, macrophages, and endothelial cells [137]. Oxidised LDL has been shown to activate T-cells, which modulate the release of IL-1β and TNFα [138], whereas IL-4 has been found to induce 15-lipoxygenase activity of human monocytes, initiating lipid peroxidation [134].

6. Conclusion

The benefits of reducing cholesterol are now established beyond any reasonable doubt. The data indicate that several potential atherosclerosis reversal mechanisms exist, of which the reduction of the number of LDL particles is a central one. Treatment should be aimed primarily at reducing LDL-cholesterol, and secondarily at reducing triglycerides and raising HDL [139]. However, the prevention of CAD is too large an issue to be accomplished by drugs alone. A population-based strategy to decrease the incidence of CAD further must continue to focus on reducing the dietary content of saturated fat and cholesterol [140].

References


Ma PT, Gill G, Sudhoff TC, Bilheimer DW, Goldstein JL, Brown MS. Mevinolin, an inhibitor of cholesterol synthesis,
induces mRNA for low density lipoprotein receptors in livers of hamsters and rabbits. Proc Natl Acad Sci USA 1986;83:8370–8374.


[106] Rosenfeld ME, Khoo JC, Miller E, Parthasarathy S, Palinski


[135] Lehr HA, Frei B, Olofsson AM, Carew TE, Arfors KE. Protection from oxidized LDL-induced leukocyte adhesion to microvascular and macrovascular endothelium in vivo by...
vitamin C but not vitamin E. Circulation 1995;91:1525–1532.


