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The Value of Lipid Lowering in Patients with Coronary Heart Disease

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Atherosclerosis is by far the most frequent cause of coronary heart disease (CHD). Five large studies have provided unequivocal evidence that lipid lowering by statins significantly reduce the incidence of CHD endpoints. New insights in pathophysiology show that statin therapy reduces progression of atherosclerosis and leads to plaque stabilization as well as a reduced plaque thrombogenicity. In CHD patients treatment with statins may prevent plaque rupture of atherosclerotic lesions and therefore reduce the occurrence of acute coronary syndromes. Patients with haemodynamically relevant stenosis and angina interfering with quality of life and patients who have less exercise tolerance may be regarded as candidates for coronary intervention. In these patients aggressive lipid-lowering may complement angioplasty by stabilizing untreated lesions.

According to the guidelines of the National Cholesterol Educational Program LDL-cholesterol of no more than 100 mg/dl is considered optimal in patients with CHD or other atherosclerotic diseases. The results of the Atorvastatin Comparative Cholesterol Efficacy and Safety Study demonstrate that in a majority of patients (76.3 %) these target levels of LDL-cholesterol can be reached by using an aggressive lipid-lowering therapy with statins. *J Clin Basic Cardiol 2001; 4: 31–34.*

Key words: coronary heart disease, lipid lowering, coronary intervention, statins

Atherosclerosis is by far the most frequent cause of coronary heart disease (CHD). Epidemiologic, clinical, genetic and experimental studies have clearly proven that high serum levels of cholesterol are causally related to atherosclerosis and increased risk of CHD. The Framingham Heart Study [1] provided early epidemiologic evidence that elevated serum cholesterol is a risk factor for CHD.

In the last years, new insights in plaque morphology have been obtained and since then we have entered a new area of the biology of the acute coronary syndrome.

Five randomized placebo-controlled megastudies – 4S (simvastatin), CARE, WOSCOP, LIPID (lovastatin), AFCAPS/TexCAPS (fluvastatin) [2–6] have provided unequivocal evidence that lipid lowering by statins significantly reduces the incidence of CHD endpoints. The AVERT (Atorvastatin versus Revascularization Treatment) study [7] compared aggressive lipid-lowering therapy with angioplasty in stable coronary artery disease. The conclusion of this study was that in low-risk patients with stable coronary artery disease, aggressive lipid-lowering therapy is at least as effective as angioplasty and usual care in reducing the incidence of ischaemic events.

How does Lipid-Lowering Improve Patients' Outcome?

Regression of fixed stenosis by lipid-lowering therapy

Until the late 1970s it was advocated that human atherosclerosis is irreversible. In the 1980s several large intervention trials with diet and various drug therapies were completed and clearly demonstrated regression of coronary lesions. Brown [8] reported the regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. In this 2½ year double-blind study arteriography was performed at baseline and after treatment. The patients were randomly assigned to lovastatin and colestipol, niacin and colestipol or placebo. The intervention groups showed a significant reduction of LDL-cholesterol of 46 % and 32 % respectively. LDL only slightly changed in the conventional-therapy group (–7 %). After 2½ years of conventional therapy a progression of the disease by 2.1 % with an increase in minimal lesion diameter of 0.05 ± 0.14 mm was seen. The two intervention groups showed a regression of stenoses by 0.7 and 0.9 % respectively with a decrease in minimal lesion diameter of 0.012 ± 0.16 mm and 0.035 ± 0.13 mm ($p < 0.005$). In 1993 Vos [9] pooled the data of 6 trials with interventions on diet, drug therapy, or ileal bypass surgery and trial periods of 2 to 5 years and found an overall relative risk for progression of 0.62 (95 % CI 0.54–0.72) and an odds ratio of regression of 2.13 (95 % CI 1.53–2.98) with intervention. In an editorial Loscalzo [10] commented on the importance of the study of Brown and of a surgical intervention study by Buchwald [11] examining the effect of partial ileal bypass for the treatment of hyperlipidaemia. He emphasized the important complementary information about the dynamic evolution of coronary atherosclerosis and its lipid determinants, but also stressed that the extent of change in luminal diameter measured in the study of Brown was small, and that statistical significance was achieved only by virtue of the power and precision of the computerized edge-detection techniques used to assess the coronary angiograms.

In summary major studies using coronary angiography have shown that intensive lipid modification by a variety of interventions retards the progression of atherosclerotic lesions and in a subset of patients lead to their regression. However, the clinical benefit of lipid lowering in terms of event reduction by far outweighs the angiographic improvement which is modest and rather disappointing. In order to solve this paradox we have to focus on plaque composition and vulnerability to rupture and plaque thrombogenicity, rather than on plaque size and stenosis severity.

Most acute coronary syndromes are caused by plaque rupture and superimposed thrombosis.

The vulnerable plaque concept and the role of inflammation

An unstable stable plaque is a lipid-rich, friable plaque, which is ready to rupture. The three major determinants for plaque1 rupture are shown in Table 1. Accumulation of lipids in the plaque with an inadequate fibrotic response and high

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Table 1. The vulnerable plaque

Determinants of vulnerability
• Size and consistency of the lipid-rich atheromatous core
• Thickness of fibrous cap covering the core
• Inflammation and repair within the fibrous cap

concentrations of leucocytes result in plaque vulnerability and instability. Monocytes and macrophages show a high biochemical activity by releasing metalloproteinases and tissue factor. These substances may contribute to the rupture of the plaque as well as to the formation of the final clot. There is increasing evidence that inflammation plays an important role in both the pathogenesis of atherosclerosis and subsequent plaque stability. Acute exacerbation of inflammation may be associated with acute coronary syndromes such as myocardial infarction and unstable angina. Acute phase proteins like C-reactive protein have been documented in a number of studies to correlate with the risk of development of coronary artery disease [12] as well as to predict the risk of acute events in patients with CHD [13].

According to experimental models lipid lowering has shown to affect many of the cellular processes that predispose to plaque rupture and thrombosis (Table 2) [14–17].

The improvement of endothelial function with lipid lowering may be one important mechanism of statin therapy. Endothelial dysfunction promotes atherosclerosis through vasoconstriction, monocyte and platelet adhesion, thrombogenesis, and cytokine and growth factor stimulation and release. Endothelium-mediated vasoconstrictors, adhesion molecules, cytokines, growth factors, and thrombogenic factors, such as endothelin, are increased by oxidized low-density lipoprotein. Endothelial leucocyte adhesion molecules are responsible for the specific binding of a number of circulating white blood cells to the vessel wall and have been implicated in atherosclerosis and inflammation. Niwa and colleagues [18] demonstrated that cellular interaction between monocytes and endothelial cells is inhibited by fluvastatin, mediated via reducing the expression of adhesion molecules, particularly in the side of monocyte. In an animal study Kimura [19] found that fluvastatin significantly attenuated the leucocyte adherence response to platelet-activating factor and leucotriene B_4 (LTB_4) and emigration response to LTB_4. Dunzendorfer [20] studied the transendothelial migration and chemotaxis of human peripheral blood neutrophils by pravastatin. The administration of pravastatin in concentrations within normal therapeutic ranges decreased chemotaxis of neutrophils and monocytes significantly.

Simvastatin and pravastatin [21] reduce the proliferation of macrophages induced by oxidized LDL *in vitro*. Macrophage-derived foam cells are the key cellular element in the early stage of atherosclerosis, a significant inhibition of oxidised LDL-induced macrophage growth by statins *in vitro*, may be an important factor of their anti-atherogenic action *in vivo*.

Table 2. Plaque stabilization by lipid lowering

Reduced vulnerability to rupture
• Lipid core ↓
• Macrophage density ↓
• Matrix synthesis ↑
Reduced plaque thrombogenicity
• Macrophage density ↓
• Tissue factor activity ↓
• Platelet deposition ↓
Improved endothelial function
• Vasoreactivity ↑

The German Atorvastatin Intravascular Ultrasound (GAIN) Study (unpublished data) demonstrated that lipid lowering by atorvastatin resulted in plaque stabilization and decreased plaque progression. In this 1 year randomized multicenter study atorvastatin was administered at a medium dosage of 32.5 ± 12.7 mg/day. Plaque composition and plaque volume were analysed by intravascular ultrasound. At baseline plaque composition in the atorvastatin group and in the control group were comparable with 83 % hypoechogenic, 12 % hyperechogenic, 2 % calcified and 3 % nonclassified material. After 1 year the atorvastatin group showed a significant increase of the hyperechogenic portion of the plaques compared to the control group (+39.7 % vs. +11.1 %, p = 0.03). In intravascular ultrasound examination hypoechogenity represents the lipid-rich fraction of a plaque and hyperechogenity connective tissue which is a stabilizing factor in the plaque. Therefore the significant increase of hyperechogenity by atorvastatin represents plaque stabilization, which was associated with a significant decrease in plaque progression compared to the control group (+2.2 % vs. +11.8 %).

These data show that statin therapy leads to plaque stabilization by reducing cellular infiltration and stimulating the fibrotic response. The vulnerable plaque becomes stable by developing connective tissue. Modifying hyperlipidaemia may further reduce progression of atherosclerosis by decreasing plaque progression.

In 1997 a study by Ridker et al. [22] provided evidence that among young normal men, baseline serum levels of C-reactive protein (CRP) are predictive of future myocardial infarction and ischaemic stroke. The risk increased with rising level of CRP, even when the value was within the normal range. The increased risk was independent of lipid-related and non-lipid-related cardiovascular risk factors and was reduced with aspirin in direct proportion to the baseline CRP value.

In an animal model [23] peripheral vascular disease was induced in the femoral artery of rabbits by mechanical damage followed by the administration of a high cholesterol diet over a 1-month period. In this model atorvastatin essentially eliminated arterial macrophage infiltration and reduced monocyte chemoattractant protein in both the neo-intima and the media and significantly decreased a cytokine activity modulating factor both within the atherosclerotic lesion and in the adjacent uninjured aorta. As a result of his study Bustos concludes that statin therapy may ameliorate the degree of neo-intimal inflammation and play a therapeutic role in the earliest stages of atherosclerosis.

Ridker [24] studied whether inflammation after myocardial infarction is a risk factor for recurrent coronary events and whether randomized treatment with pravastatin reduces that risk. In a nested case-control design CRP and serum amyloid A levels (SAA) in pre-randomization blood samples from 391 participants in the Cholesterol and Recurrent Events (CARE) trial who subsequently developed recurrent nonfatal myocardial infarction (MI) or a fatal coronary event and from an equal number of age- and sex-matched participants who remained free of these events during follow-up were compared. Overall, patients who suffered a recurrent event had significantly elevated levels of both of these highly sensitive but non-specific markers of inflammation. Patients with levels in the highest quintile had a relative risk of recurrent events 75 % higher than those with levels in the lowest quintile. The study group with the highest risk was that with consistent evidence of inflammation with elevation of both CRP and SAA who were randomly assigned to placebo. In stratified analyses, the association between inflammation and risk was significant among those randomized to placebo (p =

0.048) but was attenuated and nonsignificant among those randomized to pravastatin.

In a follow-up study [25] the authors demonstrated that statin therapy significantly reduced levels of CRP over the period of the trial. Subjects with elevated levels of CRP at baseline and randomized to placebo had an increase of CRP over time of about 4.2 %. Pravastatin therapy resulted in a significant decrease of CRP with a median reduction of 17 %. The evidence after MI of inflammation is associated with increased risk of recurrent coronary events. Statin therapy may decrease this risk, an observation consistent with a non-lipid effect of these agents.

Thrombogenicity of plaques

An unstable lipid-rich plaque contains a high density of monocytes and macrophages, which are chemically very active [26]. If the plaque ruptures substances such as tissue factor, a coagulant factor, are released, this may lead to clot formation [27]. However, in about 30 % of acute coronary syndromes thrombus formation occurs without plaque rupture. Stenotic plaques without endothelium may be in a hypercoagulative state activated by hyperlipidaemia, cigarette smoking and diabetes [28] Activation of monocytes and macrophages leads to the release of tissue factor, which produces thrombin and platelet activation. In this hypercoagulative state a simple fissure in the plaque or a deendothelialized plaque surface may trigger thrombus formation on the surface of the plaque [29].

Osamah [30] demonstrated a reduced platelet aggregation after a therapy with fluvastatin for 4 week. Furthermore, incubation of platelets with increasing concentrations of fluvastatin resulted in a dose-dependent decrease in platelet aggregation. Aviram [31] described similar effects administering lovastatin with alteration of the biochemical constituents of the platelet membrane, which results in decreased platelet aggregation. Atorvastatin [32] significantly reduced the deposition of platelets on a damaged wall that had been exposed to high shearing forces in a porcine model. In a number of experimental and clinical studies [33–35] statin therapy was associated with a significant reduction of tissue factor, an important membrane particle, which has been correlated to acute coronary syndromes.

The Role of Statin Therapy in Patients with CHD

Statins versus angioplasty

Since the publication of the AVERT study [7], its results showing that high-dose atorvastatin was at least as effective as angioplasty plus usual care in reducing coronary events in patients with stable angina are cited and commented in various lectures and reviews [36].

As described above, statins may reduce new ischaemic events due to plaque stabilization and reduction of thrombogenicity of vulnerable plaques. However, plaque regression only occurs in the dimension of a tenth of a millimetre and can therefore not be seen as an important factor in improving symptoms in patients with severely stenosed coronary arteries. Therefore coronary interventions are extremely appropriate in patients with haemodynamically relevant coronary artery stenoses with life-style limiting angina pectoris. But only patients with proven coronary artery disease and in whom signs of myocardial ischaemia are observed should be referred for coronary interventions. In the DEFER study [37] guide wire based coronary pressure measurements were used for the determination of coronary flow reserve. Patients were admitted to the study if they were referred for elective angioplasty of one coronary artery stenosis by visual assessment of at least 50 % and with no objective signs of reversible ischemia within the last 2 months. The preliminary results of this study indicate that in roughly 50 % of patients with stable angina scheduled for coronary angioplasty without objective proof of reversible myocardial ischaemia, the stenosis is found haemodynamically non-significant. Patients with a fractional flow reserve larger than 0.75 (ie, lesions which are haemodynamically non-significant) do not benefit from angioplasty as both their complaints and the occurrence of cardiac events are similar whether or not angioplasty has been performed. By analysing the study design of the AVERT study [7] it is shown that patients included in this study may be comparable to the study population of the DEFER study. The AVERT study group comprised of patients with stenosis of 50 percent or more in at least one coronary artery and had been recommended for angioplasty. The patients were asymptomatic or had Canadian Society Class (CSC) I or II angina and were able to complete at least 4 minutes of a treadmill test without marked ECG changes indicative for angina. Thus, it may be speculated that asymptomatic patients and subjects with mild angina (CSC I) and increased LDL-cholesterol are better off with an aggressive lipid-lowering therapy as with a coronary intervention without aggressive lipid-lowering.

For most patients lipid-lowering drug therapy and angioplasty are not alternative treatment regimens but complementary. In CHD patients treatment with statins may prevent plaque rupture of haemodynamically unimportant atherosclerotic lesions and therefore reduce the occurrence of acute coronary syndromes. Patients with haemodynamically relevant stenosis and angina interfering with quality of life and patients who have less exercise tolerance may be regarded as candidates for coronary intervention. In these patients aggressive lipid lowering may complement angioplasty by stabilizing untreated lesions.

Should all patients with CHD be treated with statins?

According to the guidelines of the National Cholesterol Educational Program (NCEP) [38] LDL-cholesterol of no more than 100 mg/dl is considered optimal in patients with CHD or other atherosclerotic diseases. The NCEP-algorithm for lipid lowering based on LDL-cholesterol levels is depicted in Table 3. Patients with established CHD are candidates for lipid-lowering drug therapy when LDL-cholesterol is 130 mg/dl or higher. In CHD patients with LDL-cholesterol levels 100–129 mg/dl, the physician should exercise clinical judgment in deciding whether to initiate drug treatment. The American College of Cardiology/AHA Task Force on Practice Guidelines [39] has recommended beginning lipid-lowering drug therapy as early as the time of discharge from the hospital in such patients. The ACCES Study (Atorvastatin Comparative Cholesterol Efficacy and Safety Study) [40] was designed to evaluate the efficacy and safety of atorvastatin versus other statins and to compare their ability to treat patients to NCEP goals. These goals were achieved in

Table 3. NCEP-guidelines for lipid-lowering therapy based on LDL-cholesterol

Patient population	Dietary therapy	Drug therapy	LDL goal
Pts without CHD and with fewer than 2 RF	> 160 mg/dl	> 190 mg/dl	< 160 mg/dl
Pts without CHD with 2 or more RF	> 130 mg/dl	> 160 mg/dl	< 130 mg/dl
Pts with CHD	> 100 mg/dl	> 130 mg/dl	< 100 mg/dl

RF = risk factor

76.3 % of atorvastatin-treated patients. This was a significantly greater proportion compared with patients treated with other statins tested. The results of this study demonstrate that in a majority of patients target levels of LDL-cholesterol can be reached with an aggressive lipid-lowering therapy with statins.

Future directions

There are still many unanswered questions concerning the benefit of aggressive lipid lowering in patients with acute coronary syndromes and stroke attacks. We have also to ask whether the present LDL-goals are sufficient or lower levels may provide additional benefits in CHD event reduction and whether the current guidelines for lipid-lowering need to be amended to incorporate lower levels of LDL-cholesterol. A number of ongoing studies address these questions and we may learn a few answers to these questions in the near future. The MIRACLE (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study investigated the effect of aggressive lipid lowering within 4 months after the onset of an acute coronary syndrome. The results of this study are expected to be presented within the next few months. In 1998 TNT (Treating New Targets), a 5-year study was started, which examines the clinical benefit of LDL-lowering to an average of 75 mg/dl compared to the present NCEP goal of 100 mg/dl in patients with CHD. The SPARCL (Stroke Prevention by Aggressive Reduction of Cholesterol Levels) study tests the hypothesis that robust lipid lowering will reduce cerebrovascular events in patients without CHD but who had a previous stroke or TIA.

However, the greatest and continuing challenge for all physicians and health care providers will consist in educational tasks. If we are able to provide a clear message concerning target levels of LDL-cholesterol to the general population and achieve a high acceptance rate, then changes in life style in combination with an aggressive lipid-lowering drug therapy may contribute to reduce morbidity and mortality of cardiovascular diseases.

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