The value of lipid lowering in patients with coronary heart disease

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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 Intervention. In these patients aggressive lipid-lowering may complement angioplasty by stabilizing untreated lesions.

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

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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 vasconstrictors, adhesion molecules, cytokines, growth factors, and thrombogenic factors, such as endothelin, are increased by oxidized low-density lipoprotein. Endothelial leucocyte adherence 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 leukotriene B4 (LTB4) and emigration response to LTB4. In an animal model [20] 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 and matrix synthesis 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.

Reduced vulnerability to rupture
- Lipid core ↓
- Macrophage density ↓
- Matrix synthesis ↑

Reduced plaque thrombogenicity
- Macrophage density ↓
- Tissue factor activity ↓
- Platelet deposition ↓

Improved endothelial function
- Vasoreactivity ↑
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].

As described above, statins may reduce new ischaemic events and improve symptoms. However, in the DEFER study [37] guide wire based coronary interventions are extremely appropriate 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 significan-tly greater proportion compared with patients treated with placebo. The results of this study demonstrate that in a majority of patients targets level 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 lifestyle may lead to incorporate lower levels of LDL-cholesterol.

Lipid Lowering in CHD Patients

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