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Current aspects of statins

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Clinical trials have demonstrated that inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) significantly reduce cardiovascular-related morbidity and mortality in patients with and without coronary artery disease. Furthermore, statins are currently the most potent cholesterol-lowering drugs available. Subanalyses of the LIPID study have shown that patients suffering from unstable angina pectoris had at least the same benefit from statin therapy as did patients after myocardial infarction. Studies recently published (AVERT) or not published yet (MIRACL) provide more information on the topic of therapy with statins in the early phase of acute coronary syndromes. *J Clin Basic Cardiol 1999; 2: 203–8.*

Key words: statins, coronary artery disease, atherosclerosis, HMG-CoA-reductase inhibition, cholesterol lowering

Epidemiological data show a strong correlation of plasma cholesterol concentration and occlusive coronary diseases [1, 2]. Statins [3] significantly reduce mortality and cardiovascular related morbidity in patients with and without previous coronary artery disease [4–7]. The mechanism of action of these drugs is the inhibition of rate-limiting HMG-CoA reductase-dependent hepatic cholesterol synthesis [8], thereby decreasing hepatic production of low density lipoprotein (LDL) (Table 1) and upregulating expression of hepatic LDL-receptors leads to lower concentrations of circulating LDL. With decreasing LDL concentrations, development of atherosclerotic plaques is retarded. Lipid loss could render the plaques less occlusive and less likely to disrupt and cause acute vascular events.

Statin therapy in patients with and without coronary artery disease

Clinical trials investigating statin therapy in primary prevention (WOSCOPS, AFCAPS/TexCAPS [9]) and in secondary prevention (4S, CARE [10], LIPID [11]) supported the hypothesis that drugs that lower plasma cholesterol concentration are of benefit to patients with and at risk of developing coronary artery disease (Table 2). The clinical benefit of statin therapy used in these trials is manifest early in the course of lipid-lowering therapy and before regression of atherosclerotic plaques could occur. Improvement in arterial topographical morphology as a result of statin therapy assessed by quantitative angiography occurs slowly and only to a small extent. For example, the Multicentre Anti-Atheroma Study (MAAS) [12] revealed that statistically significant but only small improvement in arterial morphology occurred with statin therapy after four years with no evidence of regression at two years. It is difficult to attribute the early appearance of clinical benefit in the 4S and WOSCOPS trials solely to LDL-lowering effects. In contrast, about nine years elapsed before any real clinical

benefit was found in the Program on the Surgical Control of the Hyperlipidaemias (POSCH) trial [13]. The decrease in plasma cholesterol concentration by partial ileal bypass was similar to that achieved in the statin trials and it may be that the clinical effects in the POSCH trial are attributable purely to changes in circulating lipoproteins. HMG-CoA reductase is an important enzyme not only for cholesterol synthesis, but also for the synthesis of proteins involved in cell metabolism and cell to cell interaction. Statins, as inhibitors of this enzyme, could modify constituents of the vascular milieu, which may contribute to their clinical effects. There seems to be a few different mechanisms of action of statins other than LDL cholesterol lowering with direct effects on thrombosis, atherosclerosis and inflammation.

Mechanisms of action of statins beyond LDL cholesterol lowering

The reduction in clinical events secondary to lipid lowering has been conventionally attributed to the selective depletion of both the lipid and foam-cell contents of vulnerable plaques by altering the balance between LDL accumulation and efflux in the plaques. This effect makes the plaque less likely to fissure and cause acute vascular effects, which is likely to contribute significantly to the reduction in clinical endpoints.

It has been shown that pravastatin influences cholesterol metabolism in macrophages directly in a manner analogous to its effect in hepatocytes [14]. Inhibition of endogenous cholesterol synthesis by macrophages has the potential to reduce macrophage activation, foam-cell formation and the thrombogenicity of plaques. Furthermore, consecutive alteration of the lipid to cell ratio of the atherosclerotic lesion makes the plaque less prone to rupture. Statins also modulate immune function [15–17]. Statins can inhibit platelet derived growth factor (PDGF)-induced DNA synthesis, which contributes to migration and proliferation of macrophages [18], platelets,

Table 1. Characteristics of statins

Drug	Lovastatin	Pravastatin	Simvastatin	Fluvastatin	Atorvastatin
Bioavailability (%)	30	34	60–85	90	90
Plasma-half-life (h)	2	3	2	1.2	14
Protein-binding (%)	95	50	98	> 99	98
Cytochrome-P-450 3A4-substrate	yes	no	yes	no	yes
Renal elimination (%)	10	20	13	6	< 5
Dosage (mg; range)	20–80	10–40	10–40	20–80	10–80
LDL-lowering potency (at maximum dosage) (%)	40	30	40	25	55

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Table 2. Clinical studies on statin therapy

	4 S	CARE	AFCAPS/TeXCAPS LIPID		AVERT	MIRACL
Design	CHD	CHD	no CHD	CHD	Comparative study of statin and angioplasty	Early intervention
Year of publication	1994	1996	1998	1998	–	–
Patients	4444	4159	6605	9014	341	2100
Inclusion criteria	Stable angina AMI > 6 month	AMI 3–20 months	no CHD	AMI or unstable angina 3–36 months	Luminal narrowing > 50%; CCS stage 0–II	Unstable angina; non-Q-wave MI
Exclusion Criteria	Unstable angina, ur- gent revascularisation	Diabetes mellitus	Insulin dependent diabetes mellitus		Unstable angina and AMI < 2 weeks, PTCA < 6 month	Urgent interventions or interventions recently performed
Baseline lipid profile	TC 219–309 (261) TG < 221	TC < 240 (209) LDL-C 115–174 TG < 350	TC 180–264(221) LDL-C 130–190 HDL-C 45/47 (female) TG < 400	TC 155–271(218) TG < 445	TC > 115(154) TG < 500	TC < 270
Study duration	5.4 y	5 y	5.2 y	6.1 y	1.5 y	16 weeks
Drug dosage (mg/day)	Simvastatin 20–40	Pravastatin 40	Lovastatin 20–40	Pravastatin 40	Atorvastatin 80	Atorvastatin 80
LDL-lowering(%)	35	32	25	25	46	?
Primary Endpoint	Total mortality	CHD-death + non- fatal AMI	AMI, unstable angina, sudden cardiac death	CHD-death	Ischaemic event	Ischaemic event
Results (risk reduction)	Mortality 30 % CHD-mortality 42 %	CHD-death or non-fatal AMI 24 %	AMI, unstable angina, sudden cardiac death (37 %)	Mortality 22 % CHD-mortality 24 %	Ischaemic events 36 %	?
Unstable angina	Tertiary endpoint	Tertiary endpoint	Secondary endpoint	Secondary endpoint	Secondary endpoint	Secondary endpoint
Risk reduction	Non significant	Non significant	32 %	12 %	47.5 %	?

smooth muscle cells and fibroblasts in blood vessels and in atherosclerotic lesions [19]. Cholesterol lowering measures with statins have been shown to improve endothelial function and vasomotion in hypercholesterolaemic patients [20, 21]. The endothelial dysfunction that accompanies hypercholesterolaemia may be because of an abnormality in the nitric oxide L-arginine pathway which is corrected when LDL concentrations are decreased by statins. Improvements in myocardial perfusion as demonstrated by thallium-201 single-photon emission computed tomography have been documented in patients with coronary artery disease after short term statin therapy [22]. Short-term cholesterol reduction with statins attenuates cardiovascular reactivity assessed by measurement of blood pressure responses to angiotensin II, noradrenaline, by cold pressure testing and isometric exercise. This effect would be expected to lower the haemodynamic stress on plaques and lessen the probability of acute disruption and thrombosis [23].

A significant reduction in serum fibrinogen levels and in adenosine-diphosphate-induced platelet aggregation have been demonstrated with statin therapy in type-IIa hypercholesterolaemic patients [24]. In conjunction with alterations in platelet reactivity, humoral thrombogenic and hyperfibrinolytic factors have also been found in hypercholesterolaemia. Statins have been shown to reduce elevated plasma levels of thrombin-antithrombin III complex, fibrinopeptide A, thrombomodulin, and plasminogen activator inhibitor 1 (PAI-1) in patients with hypercholesterolaemia. These effects point to the possibility that statins may in part act as anti-thrombotic agents [25, 26].

Statins in early and long-term treatment of unstable angina

The LIPID trial was the first large-scale multicentre study including patients with unstable angina as a qualifying event. In 36 % of the entire study-population at least one episode of unstable angina occurred 3–36 months before starting therapy with the study medication. Analysis of this subgroup revealed a 26 % non-significant risk-reduction in cardiovascular mortality.

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL [27]) study compares early aggressive cholesterol lowering therapy with atorvastatin in patients with unstable angina or non-Q-wave myocardial infarction with usual care in reduction of recurrent ischaemia. 2100 patients should be included one to four days after hospitalisation for unstable angina or non-Q-wave myocardial infarction with no early revascularisation. Exclusion criteria are total cholesterol of more than 270 mg per deciliter, ongoing treatment with statins at study entry, or prior coronary artery bypass grafting, percutaneous coronary intervention or Q-wave myocardial infarction within the last four weeks and severe cardiac arrhythmias or severe heart failure (NYHA III–IV). Follow-up period will be 16 weeks with time of recurrent ischaemic events (death, non-fatal myocardial infarction, resuscitation after cardiac arrest, and worsening angina with objective evidence of myocardial ischaemia resulting in hospitalisation) as a primary endpoint. If this study shows clinical benefits, these could be attributed to a few different mechanisms of action of statins other than LDL cholesterol lowering with direct effects on thrombosis, atherosclerosis and inflammation.

Lipid lowering with statins and angioplasty in patients with stable coronary artery disease

Coronary revascularisation by percutaneous techniques is widely used in the treatment of patients with stable angina pectoris, inducible myocardial ischaemia, or both. Studies comparing percutaneous revascularisation and conservative strategies with medical treatment suggested that patients who underwent revascularisation had an improvement in their quality of life, exercise tolerance, or both [28–30]. However, there are uncertainties about the effect of conservative strategies with medical treatment, as compared with percutaneous interventions, on the incidence of ischaemic events and the need of subsequent revascularisation [31, 32]. As already mentioned, statin therapy has been shown to reduce significantly the incidence of cardiovascular events, overall mortality and

the need for revascularisation [4–7, 9–11]. In patients with mostly one- or two-vessel coronary artery disease, relatively normal left ventricular systolic function, and no severe symptoms of angina pectoris [33], aggressive lipid-lowering therapy with statins [34] has been shown to be almost as effective as angioplasty and usual care in reducing the incidence of ischaemic events [35, 36]. The aggressive lipid-lowering strategy resulted in a more pronounced reduction in the mean serum LDL cholesterol level compared with patients randomized to angioplasty allowed by usual care, which could include (in 71 % of the total group) lipid lowering treatment (46 % versus 18 % LDL reduction). Within the follow-up period of 18 months the incidence of ischaemic events, defined as death from cardiac cause, resuscitation after cardiac arrest, non-fatal myocardial infarction, cerebrovascular accident, coronary artery bypass grafting, angioplasty as an event, worsening angina with objective evidence of myocardial ischaemia resulting in hospitalization, was 36 % (13.4 % versus 20.9 %, not statistically significant; $p=0.048$) lower in the atorvastatin group. This reduction in events was due to a smaller number of angioplasty procedures, coronary artery bypass operations, and hospitalizations for worsening angina in the aggressive lipid-lowering treatment group. As compared with the patients who were treated with angioplasty and usual care, the patients who received high-dose statin therapy had a significantly longer time to the first ischaemic event. The design of the study has been open-label, so that bias with more likely interventional treatment of patients with more severe angina seems to be possible. Aggressive lipid-lowering treatment appears to be as safe and as effective as angioplasty and usual care in reducing the incidence of ischaemic events. Because these data are based on a very small number of patients treated within clinical trials and a relatively short follow-up period, additional long-term studies on a large number of patients are required to give definitive recommendations.

How much to lower serum cholesterol?

The three major secondary prevention trials [6, 10, 11] have resulted in a pattern of approximately one percent decrease in events for each one percent decline in LDL-cholesterol (Table 3). Emphasis has now focused on “how low should we go with LDL cholesterol?” [37]. There are distinct relationships between serum cholesterol concentration and coronary mortality in individuals with no history of coronary artery disease and in patients with documented coronary artery disease [38]. The observations from the placebo arms of several large trials [39–41] and observational studies [42] relating to coronary atherosclerosis have since confirmed this disparate relationship between serum cholesterol and mortality in symptomatic compared with asymptomatic individuals (Figure 1). The slope of this relationship is considerably lower in the three major lipid lowering trials in secondary prevention involving statins [6, 10, 11]. The curve described in the placebo arms of several large trials and observational studies defines the interplay of multiple coronary risk factors, of which serum lipid level is but one. Modification of one factor, such as serum cholesterol, would permit the remaining risk factors to continue their interaction and does not guarantee that mortality would traverse down the trajectory defined by the original relationships [38]. This could explain why the treatment groups in

Table 3. Relationship between LDL-cholesterol reduction and total and cardiovascular mortality in randomized clinical trials with statins

Trial	Drug	Dose (mg/d)	LDL-C reduction	CV Mortality	Total Mortality
4S	Simvastatin	20–40	35 %	42 %	30 %
LIPID	Pravastatin	40	18 %	22 %	24 %
CARE	Pravastatin	40	28 %	20 %	–
WOSCOPS	Pravastatin	40	26 %	33 %	22 %
AF/TexCAPS	Lovastatin	40	25 %	Acute events 37 %	

the major lipid lowering trials in secondary prevention involving statins form a curve with a flatter slope. The current debate on lipid lowering therapy focuses on the degree of the response to treatment. If one were to stay within the limits imposed by the data, it is clear that it would not be possible to extrapolate to serum cholesterol values significantly lower than 170 mg/dl. Even at a total cholesterol level of 160 mg/dl, a value not achieved in any of the trials reported thus far, it is evident that these patients would still remain a risk of six-fold compared with that anticipated from the Lipid Research Clinics Program Prevalence Study [38]. The current controversy with respect to treatment for serum total-cholesterol or LDL-cholesterol relates to matters that could influence the relationship between lipid levels and death rates within the confidence intervals of regression lines [43]. In addition to the current preoccupation with statins, the issue that requires attention is whether one should look beyond these drugs at other secondary preventive measures and “lifestyle modification” programs and their potential effects on the prognosis of patients with coronary atherosclerosis [44].

Cost effectiveness of statin treatment in patients with and without coronary heart disease

Before the widespread use of cholesterol lowering drugs is recommended, it is important to demonstrate that their use is cost effective. This is especially important because interventions to lower cholesterol levels with drugs involve large populations of patients and potentially high costs. Analyses including costs of the intervention and direct and indirect costs associated with morbidity from coronary causes demonstrated statin therapy to be cost effective among men and women at a wide range of age (35–70 years) and cholesterol levels (> 213 mg of cholesterol per deciliter). When direct and indirect costs per year of life gained were studied, treatment with statins led to a saving among young men and women about 35 years old. In the older groups of patients, the direct and indirect costs per year of life gained ranged from 1125 to 12,469 Euro [45–

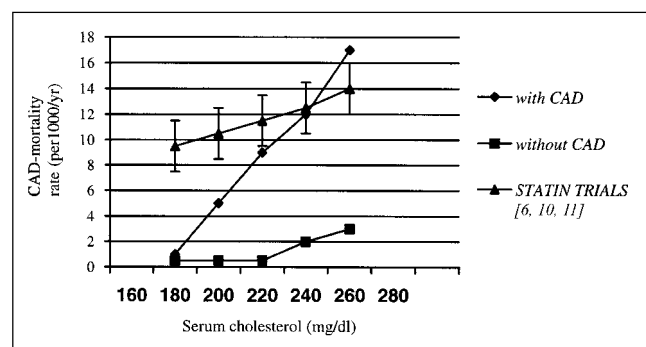


Figure 1. Relationship between serum cholesterol and coronary artery disease mortality rate. Data from the Lipid Research Clinics Program Prevalence Study [49] and in the three major lipid lowering trials in secondary prevention involving statins (▲) [6, 10, 11].

47]. In primary prevention of myocardial infarction the number of persons to treat to prevent one non-fatal infarction per year range from 263 (WOSCOPS [5]) to 311 (AFCAPS/ TexCAPS [9]). The costs to prevent one non-fatal myocardial infarction per year range from 200,690 to 237,318 Euro. In healthy men the degree of protection that statins provide against non-fatal myocardial infarction is similar to that of inhibition of platelet aggregation with aspirin [48] (Table 4). This similarity has been shown for men at high risk of myocardial infarction (Thrombosis Prevention Study [49]), as well as for low risk men, such as participants in the Physicians' Health Study [50]. Thus, the risk reduction of myocardial infarction was 37 % in the AFCAPS/TexCAPS [9] trial, 31 % in the WOSCOPS [5] trial, 41 % in the Physicians' Health Study [50] and 32 % in the Thrombosis Prevention Trial [49]. In primary prevention of myocardial infarction with aspirin, the number of patients needed to be treated to prevent one non fatal infarction per year ranges from 347 (Thrombosis Prevention Trial [49]) and 643 (Physicians' Health Study [50]), hence the costs to prevent one non-fatal myocardial infarction are 15,887 (Thrombosis Prevention Study [49]) and 29,440 (Physicians' Health Study [50]) Euro respectively. Despite their similarity in ability to prevent myocardial infarction, aspirin and the statins differ in their mode of action. However, what is known is that aspirin is far cheaper than the statins and hence much more cost effective in primary prevention of acute coronary events. In contrast to statin therapy, most countries can afford aspirin for the primary prevention of acute coronary events. On top of making changes in lifestyle [51], such as giving up smoking, making dietary changes, increasing physical activity, and, in patients with hypertension, lowering blood pressure, aspirin is much cheaper and therefore probably more appropriate than statins for primary prevention of patients at high risk for a first myocardial infarction [52].

Recommendations on lipid lowering therapy with statins in patients with and without coronary artery disease

The second report of the expert panel detection, evaluation, and treatment of high blood cholesterol in adults and the second joint task force of the joint European and other societies on coronary prevention [53] has summarized the current recommendations for the management of high cholesterol [54–56]. These guidelines on cholesterol lowering are based upon epidemiological observations that showed a graded relationship between the cholesterol concentration and the coronary risk. The guidelines are influenced by absence (primary prevention) and presence (secondary prevention) of preexisting coronary artery disease [38] (Table 5). A recent meta-analysis of 38 primary and secondary prevention trials found that for every 10 percent reduction in serum cholesterol, coronary heart disease mortality would be reduced by 15 % and total mortality risk would be reduced by 11 % [57]. No increase in non-coronary heart disease was seen.

A serum LDL-cholesterol level above 160 mg/dl is classified as high risk, 130–150 as intermediate risk and a level below 130 mg/dl is considered to be desirable. Therapeutic decisions are also based upon the presence or absence of other major risk factors for coronary heart disease, like age, sex, fam-

Table 4. Projected events prevented per 1000 patients treated for approximately five years in statin randomized clinical trials

Event	4S 5.4 years	LIPID 6.1 years	CARE 5.0 years	WOSCOPS 4.9 years	AF/TexCAPS 5.2 years
Death	338	31	8	9	1
CHD-death	35	19	11	6	2
CV-death	32	23	–	7	3
Major coronary event	90	36	30	24	16
AMI	67	29	24	20	12
CVA/TIA	16	8	12	0	–
CABG/PTCA	59	27	47	8	16

CVA = cerebrovascular accident; TIA = transient ischaemic attack; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; Death = death regardless of cause; CHD death = death from coronary heart disease; CV death = death from any cardiovascular cause; AMI = total fatal or non-fatal myocardial infarction

ily history of premature coronary artery disease, current cigarette smoking, hypertension, diabetes mellitus, and low HDL cholesterol level.

In primary prevention, drug therapy with a statin upon the findings of the WOSCOPS trial should be considered if, after an adequate trial of dietary modification, serum LDL cholesterol remains above 190 mg/dl in any patients or above 160 mg/dl in a patient with two or more coronary heart disease risk factors. The goal of serum LDL cholesterol concentration should be below 160 mg/dl in patients with less than two risk factors and below 130 mg/dl in patients with two or more coronary heart disease risk factors.

Because of the knowledge that men and women with coronary heart disease have a risk of myocardial infarction 20 times higher than those without coronary heart disease [38], current guidelines for LDL lowering in secondary prevention are much more aggressive than previously. The risk of fatal or non fatal myocardial infarction is significantly reduced in patients treated with lipid lowering drugs, particularly in those with a left ventricular systolic function of at least 50 % [13, 58]. Patients who already have coronary artery disease benefit from more aggressive lipid management. A serum LDL cholesterol level from 90 to 100 mg/dl is optimal. Thus, dietary modification should be employed in any patient with an LDL cholesterol level exceeding 100 mg/dl. Drug therapy should be considered if the LDL cholesterol level remains above 130 mg/dl.

Recent large-scale clinical trials suggest that cholesterol lowering with statins is not associated with an increased incidence of non-cardiovascular death due to accidents, suicide or violence [59, 60].

Table 5. Blood LDL-cholesterol in management of CHD- and non CHD-patients

Serum LDL-cholesterol levels	
< 100 mg/dl (< 115 mg/dl)*	Aim in secondary prevention
< 130 mg/dl	Ideal if no clinical coronary artery disease
130–160 mg/dl	Borderline; risk factor and lifestyle management; then drugs if coronary heart disease
> 160 mg/dl	High risk; drugs if more than 2 risk factors**
> 190 mg/dl	Very high risk; drugs even if less than two risk factors

* The Second Joint Task Force of the Joint European and other Societies on Coronary Prevention [53]

** Overall risk factors for coronary heart disease (CHD) defined by NCEP [45, 46] as family history of CHD, smoking, hypertension, diabetes mellitus, male gender over 45, women over 55 without estrogen replacement, and HDL cholesterol < 35 mg/dl

Conclusion

Attention has been almost entirely focused on the extent to which therapy with statins lowers plasma LDL concentrations and the established clinical benefits of statin therapy have been directly, and virtually exclusively, attributed to this effect. However, it is increasingly likely that we cannot attribute the relatively early reduction in mortality seen in clinical trials of statin therapy solely to LDL-dependent reduction in plaque volume, plaque lipid and regression on coronary atherosclerosis. There is evidence that statins have effects on immune function, macrophage metabolism, cell proliferation, endothelial function, vasomotion, platelet reactivity and humoral thrombogenic factors independent of changes in plasma LDL concentrations. The modulation of the pathophysiological determinants of acute coronary syndromes account for the early clinical benefit observed. In conclusion, statins improve haemorrhological characteristics involved in coagulation, endothelial dysfunction and vasomotion early in the course of therapy. Alterations in plaque geometry, lipid content, and thrombogenicity are likely to require therapy for a longer time before clinical benefits become evident.

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