OPEN ACCESS

Review Article

# Atherosclerosis, cholesterol, nutrition, and statins – a critical review

## Atherosklerose, Cholesterin, Ernährung und Statine – eine kritische Übersicht

## Abstract

Atherosclerosis, which causes approximately half of all deaths of adults over age 60 in industrialized nations, is a pandemic among inappropriately nourished and/or physically hypoactive children, adolescents, and adults world wide. Although nowadays statins are widely prescribed to middle age and elderly adults with high blood lipid levels as pharmacological prevention for the late complications of atherosclerosis, from a critical point of view statins seem not to solve the problem, especially when compared with certain natural ingredients of our nutrition like micronutrients as alternative strategy. Statin ingestion is associated with lowering of serum cholesterol and low-density lipoprotein concentrations; some prospective studies have shown statistical associations with subsequent modest reduction of mortality from cardiovascular disease. However, specific biochemical pathways and pharmacological roles of statins in prevention of atherosclerosis, if any, are unknown. Moreover, there have been no systematic cost-benefit analyses of life-style prophylaxis versus statin prophylaxis versus combined life-style plus statin prophylaxis versus neither life-style nor statin prophylaxis for clinically significant complications of cardiovascular diseases in the elderly. Further, in the trials of effectiveness statins were not compared with management of nutrition, which is the most appropriate alternative intervention. Such studies seem to be important, as the ever increasing world population, especially in developing countries, now demand expensive statins, which may be unaffordable for mitigating the pandemic. Studies of this kind are necessary to identify more precisely those patients for whom cardiovascular benefits will outweigh the risks and costs of the statin treatment in comparison with nutritional interventions.
Against the background of the current pathogenetic concept of atherogenesis some of its possible risk factors, particularly the roles of cholesterol and homocysteine, and the effects of statins versus nutritional (micronutrients) interventions in prevention and treatment of the disease are discussed. The prevailing opinion that serum cholesterol as a mediator of the disease is increased by eating saturated fats and decreased by eating polyunsaturated fats is being challenged. Evidently, the beneficial effects of statins in atherosclerosis are not mainly due to its cholesterol lowering effect, rather than to its “pleiotropic effects”. Other pathogenetic factors in atherosclerosis are involved, like inflammatory and immunologic processes, that can be modulated by statins as well as by other drugs or by the Mediterranean-style nutrition and by micronutrients (folate, B-vitamins).

**Keywords:** atherosclerosis, nutrition, micronutrients, statins, homocysteine, lipid-hypothesis, cholesterol, Mediterranean-style nutrition, B-vitamins, folate, Atorvastatin, Simvastatin

**Jan-Olaf Gebbers**[1]

1 Institute of Environmental Medicine, Kantonsspital, Luzern, Switzerland

## Zusammenfassung

Die Atherosklerose, etwa für die Hälfte aller Todesursachen der über 60jährigen in den Industrienationen verantwortlich, ist eine Pandemie unter fehlernährten und/oder körperlich hypoaktiven Kindern, Jugendlichen und Erwachsenen. Obwohl heutzutage Statine großzügig für Erwachsene im mittleren und hohen Alter mit hohen Blutfettspiegeln als pharmakologische Prävention der atherosklerotischen Spätfolgen verschrieben werden, erscheinen, kritisch betrachtet, Statine nicht die Lösung des Problems zu sein, speziell wenn ihre Wirkungen mit denen natürlicher Nahrungskomponenten, wie Mikro-Nahrungsbestandteile, als alternative Strategie verglichen werden. Die Einnahme von Statinen geht mit einer Senkung des Serumspiegels des Cholesterins und der Low-density-Lipoproteine (LDL) einher. Hierbei haben einige prospektive Studien statistische Zusammenhänge mit einer nachfolgenden bescheidenen Reduktion der Mortalität kardiovaskulärer Krankheiten gezeigt. Jedoch sind die spezifischen biochemischen Einflüsse und die pharmakologische Rolle der Statine für die Prävention der Atherosklerose unbekannt. Im weiteren sind bislang keine systematischen Kosten-Nutzen-Analysen der Lifestyle-Prophylaxe versus Statin-Prophylaxe versus kombinierter Lifestyle- und Statin-Prophylaxe versus weder Lifestyle- noch Statin-Prophylaxe für klinisch bedeutende Komplikationen kardiovaskulärer Krankheiten bei Älteren durchgeführt worden. Zudem wurden die klinischen Studien zur Statinwirkung nicht mit entsprechenden Ernährungsmaßnahmen als angemessenster Alternativintervention verglichen. Derlei Studien erscheinen deshalb wichtig zu sein, da die wachsende Weltbevölkerung, gerade auch in den wirtschaftlichen Entwicklungsländern, jetzt die teuren Statine verlangt, welche aber zur Eindämmung der Pandemie unerschwinglich sein können. Studien dieser Art sind für die genauere Definition derjenigen Personen notwendig, für die der kardiovaskuläre Nutzen die Risiken und Kosten der Statin-Therapie vergleichsweise zu Ernährungsinterventionen überwiegt. Vor dem Hintergrund des heutigen Konzepts der Atherogenese werden einige ihrer möglichen Risikofaktoren, vor allem die Rolle des Cholesterins und Homozysteins, und die Wirkungen der Statine gegenüber von Ernährungsinterventionen (Mikro-Nahrungsbestandteile) für die Prävention und Therapie der Krankheit diskutiert. Die vorherrschende Meinung, dass Serum-Cholesterin als Krankheitsmediator mit der Aufnahme von gesättigten Fettsäuren erhöht und von ungesättigten Fettsäuren erniedrigt wird, wird kritisiert. Offensichtlich sind die günstigen Effekte der Statine auf die Entwicklung der Atherosklerose hauptsächlich nicht ihren cholesterinsenkenden, sondern eher ihren 'pleiotropen' Wirkungen zuzuschreiben. Andere pathogenetische Faktoren sind bei der Atherosklerose wichtig, wie entzündliche und immunologische Prozesse, die mit Statinen und anderen Medikamenten oder aber mit mediterraner Ernährungsweise und Mikro-Nahrungsbestandteilen (z.B. Folsäure, B-Vitaminen) moduliert werden können.


**Schlüsselwörter:** Atherosklerose, Ernährung, Mikro-Nahrungsbestandteile, Statine, Homozystein, Lipid-Hypothese, Cholesterin, Mediterrane Ernährung, B-Vitamine, Folsäure, Atorvastatin, Simvastatin

## Introduction

Strategies to treat atherosclerosis only pharmacologically should take its multifactorial etiology into account (Figure 1). It may be inadvisable to dwell inordinately upon lowering serum cholesterol through prophylaxis, especially since high serum levels of cholesterol may not be the most important factor in most individuals with the disease [1], [2].

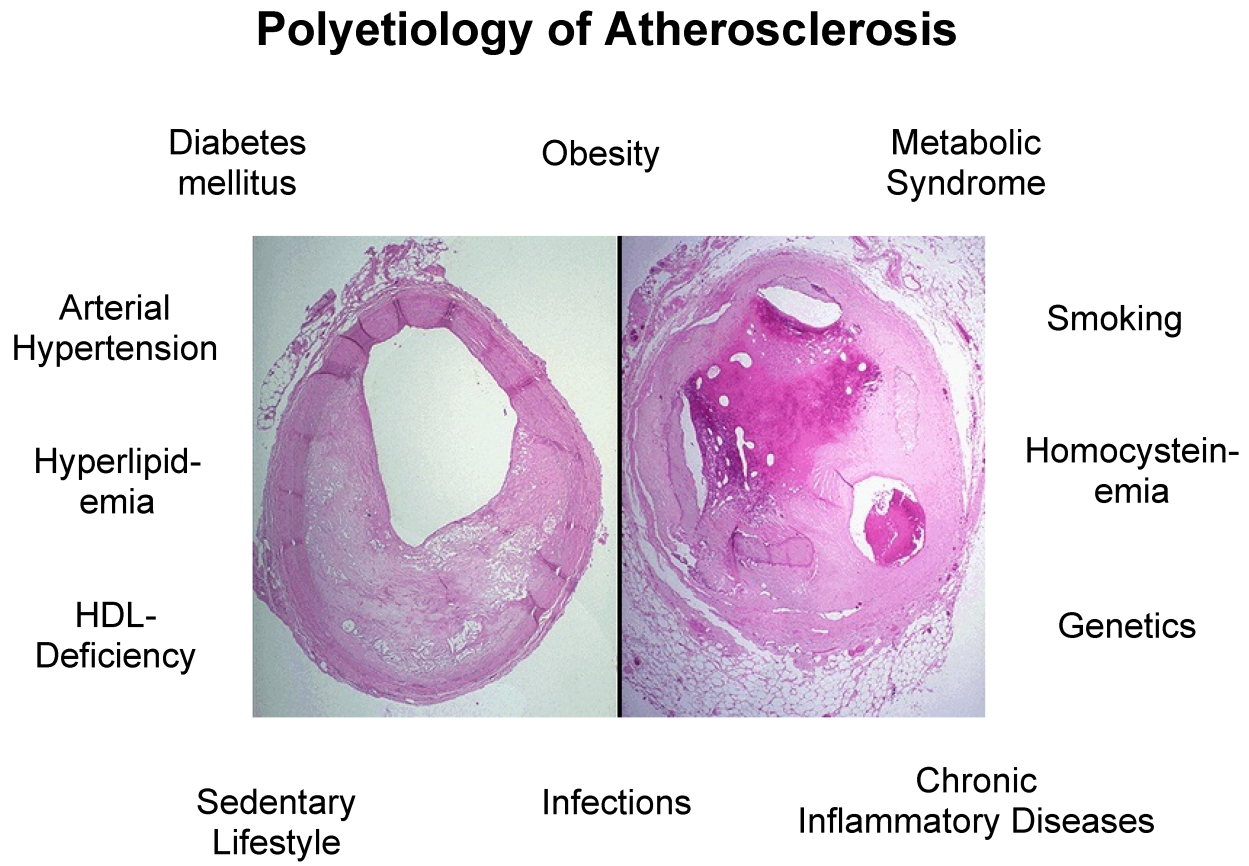


**Figure 1: Polyetiology of atherosclerosis: Histology of different states of obstructing atherogenesis surrounded by the known risk factors**

Statins are a recent development; they have become the stars of the drug industry's response to coronary artery atherosclerosis. Worldwide, their annual sales are now about 30 billion dollars, increasing every year [3]. This is not only profitable for drug manufacturers but also for those whose careers depend on financing and marketing the sales of statins. But does this necessarily translate into improvement in the overall health of the population? Questioning statin-euphoria has opened another question; for whom should statins be used? Paradoxically, as knowledge of the actions of statins has increased, rational answers to the latter question have become increasingly difficult to find.

## The multifactorial pathogenesis of atherosclerosis

Great progress has been made in identifying risk factors and pathogenetical processes leading to atherosclerosis. A variety of different risk factors, such as smoking, hypertension and shear stress, hypercholesterolemia, diabetes mellitus, obesity, sedentary life style and aging have been described, although the impact of each one of those factors is unknown. All these factors lead to *endothelial activation and/or dysfunction*, which can elicit a series of cellular interactions that culminate in the lesions of atherosclerosis.

The involvement of vascular endothelium in disease processes such as atherosclerosis has been recognized since the time of Virchow [4], but mechanistic insights into the pathophysiology of this tissue have developed only recently, largely as a result of application of modern cellular and molecular biologic techniques [5]. We now appreciate that the single-cell thick lining of the circulatory system is, in fact, a vital organ whose health is essential to normal vascular physiology and whose dysfunction can be a critical factor in the pathogenesis of vascular tissue. The vascular endothelium is a dynamic mutable interface, whose structural and functional properties are responsive to a variety of stimuli, both local and systemic, and further more its phenotypic modulation to a dysfunctional state can constitute a pathogenetic risk factor for vascular diseases.

In the vascular wall, certain consequences of endothelial dysfunction are directly related to the pathogenesis of atherosclerosis and its complications. These consequences include altered vascular reactivity and vasospasms; altered intimal permeability to plasma constituents, enhanced mononuclear leukocyte recruitment and intimal accumulation of mononuclear cells; altered vascular cell growth regulation and survival (e.g. decreased endothelial regeneration, increased smooth muscle proliferation, enhanced susceptibility to apop-

tosis); and altered hemostatic/fibrolytic balances (favoring thrombin generation, and platelet and fibrin deposition). Pathophysiological stimuli of arterial endothelial dysfunction, that are especially relevant to atherosclerosis, include activation by cytokines and bacterial products; infection by bacteria, viruses, and other pathogens; stimulation by advanced glycation endproducts generated in diabetes and with aging; chronic exposure to homocysteinemia and accumulation of oxidized lipoproteins and their components (e.g. lysophosphatidylcholine) within the vessel wall – all these different factors lead to a chronic inflammatory process [6].

In addition to these biochemical stimuli, it is now clear that various biomechanical forces, generated by the pulsatile flow of blood through the branched arterial vascular system, can also influence the structure and function of endothelial cells and even modulate their expression of pathophysiologically relevant genes [7].

The possibility that hemodynamic forces can act directly as pathophysiological stimuli for endothelial dysfunction provides a conceptual rationale for the longstanding observation that earliest lesions of atherosclerosis characteristically develop in a non-random pattern, the geometry of which correlates with branch-points and other regions of altered blood flow [2], [7], [8].

Of major significance is the fact, that the accumulation of substantial numbers of monocytes/macrophages and activated T and B lymphocytes in focal areas of the arterial intima appears to be a hall mark of atherosclerosis – atherosclerosis is an inflammatory disease induced at sites of hemodynamic strain in the vascular system [6]. Studies both in humans and in experimental animal models show an involvement of innate and adaptive immune mechanisms in the disease process manifesting itself as infiltration and activation of mononuclear cells, activation of humoral cascade systems, cytokine secretion, cell death, and induction of fibromyoproliferative processes [6], [9].

A large number of experimental and clinical studies have established that the immune system plays an important pathogenetic role in atherosclerosis. Current data imply innate immunity as necessary for lesion formation and this has led investigators to conclude that atherosclerosis is an inflammatory disease. The role of adaptive immunity is more complex – it is present throughout disease development and general immune defects reduce the extent of disease in experimental models. However, specific defects may have entirely different effects and it is likely that certain effector mechanisms of adaptive immunity are proatherogenetic while others may be atheroprotective.

Attempts to treat or prevent atherosclerosis by modulating immune activity have been successful in experimental models. Current interest focuses on specific antigens, such as infectious agents, heat shock protein 60, and macromolecular components of *Chlamydia pneumoniae*. In addition, it is possible that modulation of immunologically nonspecific inflammatory reactions may be useful for treating atherosclerosis. Finally, inflammatory markers have already proven to be useful for the diagnosis of active plaques and acute coronary syndromes. All these data imply that the immune system plays an active role in atherosclerosis, which can therefore be viewed as an inflammatory vascular response to a metabolic disturbance [10].

## Serum cholesterol and atherosclerosis

Atherosclerosis, being ubiquitous, develops at all serum cholesterol levels [1], [2]. Some investigators claimed that a significant relationship exists between serum cholesterol levels and atherosclerosis severity at autopsy in the general population, but they failed whether this has statistical or biological significance [2]. A review of these publications concluded that no significant biological relationship existed [11]. It has called attention to the International Atherosclerosis Project [12] in which correlations varied among the population. The overall correlation was 0.75, but the cholesterol analyses were not from the subjects autopsied [11]. Correlation between atherosclerosis severity and animal fat intake was almost zero and likewise for blood cholesterol and animal fat intake. The stronger positive correlation with nutritonal animal protein was ignored because of the preconceived etiological importance of nutritonal fat. A study by Strong et al. [13] reported correlations of 0.26 and 0.36 between postmortem cholesterol levels and raised lesions in the aorta and coronary arteries of whites and an explanatory power of only 6.8% and 13%, respectively. In blacks, the correlation coefficients were feeble to zero – hardly the substantive correlation alleged and certainly not suggestive of causality [1], [2].

Despite the strong suspected relationship and current literature for cholesterol and low-density lipoproteins, neither the PDAY study (Pathobiological Determinants of Atherosclerosis in Youth research group) [13], [14] nor the Framingham Study provided correlation of these variables with atherosclerosis severity. The PDAY study [14] measured total cholesterol levels but gave no correlation coefficients for total cholesterol or low-density lipoproteins, presumably because they were biologically so weak. They reported only the combined very-low-density and low-density lipoprotein values, but their contributions were unimpressive and weaker than in a previous report with fewer subjects [14]. Furthermore, the results are subject to confounding effects of age, drug abusage, arteriitis, and failure to exclude subjects with recognized disorders (metabolic lipid disorders, diabetes mellitus, hypertension), which should be treated separately. The pathological and experimental evidence fails to support a causal relationship between cholesterol, particularly nutritional cholesterol and atherosclerosis [1], [2], [11].

## Low fat nutrition

The low-fat nutrition, propagated since years, may even cause metabolic disturbances. Pursuing good health may mean including enough fat in the nutrition. Fat that is either consumed or synthesized *de novo* in cells is considered new, whereas old fat is stored in adipose tissue, waiting to be used. According to Chakravarthy et al. [15], the liver discriminates between these sources as it coordinates nutrient and energy homeostasis.

Fatty acids serve as the natural ligand for PPARα, a hepatocyte nuclear receptor that regulates genes involved in the metabolism of glucose, fatty acids, and cholesterol. When fed a nutrition with no fat, mice lacking fatty acid synthase developed hypoglycemia due to a failure in activating target genes of PPARα that control gluconeogenesis. Paradoxically, the liver in these mice became fat-laden because of the mobilization of peripheral fat and the inability of the liver to express PPARα target genes involved in fatty acid oxidation. Adding nutritional fat or an agonist of PPARα reversed these symptoms. Mice lacking fatty acid synthase also had low serum and liver cholesterol levels due to decreased hepatic cholesterol synthesis. The authors propose that new fat may activate a distinct pool of PPARα in the liver to maintain normal levels of glucose, fat and cholesterol. Metabolic abnormalities associated with obesity and diabetes mellitus might be treated by pharmacologically activating these distinct receptor pools [15].

Concerning the lipid-atherosclerosis relation, not the quantity but the quality of serum lipoproteins may be of particular importance. Recent evidence indicates the potential preventive pleiotropic effects of high-density-cholesterol of atherosclerosis [16], [17].

In a short-term study, Mediterranean nutritions were tested against a low-fat nutrition in randomized 772 asymptomatic adults (age range 55-80 years) with diabetes or at least three cardiovascular risk factors to follow one of three nutritions: a low-fat nutrition, a Mediterranean nutrition that included >30g of virgin olive oil daily, or Mediterranean nutrition that included >30g of walnuts, hazelnuts, and almonds daily. Those on the Mediterranean nutritions received free oil or nuts and were told to increase their consumption of vegetable fats and oils. After 3 months, compared with the low-fat nutrition, each of the Mediterranean nutritions were associated with significantly lower mean blood pressure (systolic 6-7 mmHg; diastolic 2-3 mmHg), fasting glucose level (5-7 mg/dL), and total-to-HDL cholesterol ratio (HDL: high-density lipoprotein). Weight-loss was similar among the three groups. Researches could not address clinical outcomes because of the short term of the study. However, in terms of effects on cardiovascular risk factors, the Mediterranean nutritions appeared to be better than a widely recommended low-fat nutrition [18].

## Are statins mainly cholesterol inhibitors?

Statins are regarded as effective inhibitors of cardiovascular disease because they act directly on inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes HMG-CoA to mevalonate, a rate-limiting step in the biosynthesis of cholesterol. It was assumed that statin-mediated reductions of blood cholesterol levels would be associated with corresponding reductions in the risks of atherosclerosis-mediated diseases.

However, other mechanisms are at work too, as was shown by the West of Scotland Coronary Prevention Study, in which cardiovascular complications began to decrease within six months after the start of the study, before significant lowering of blood cholesterol was observed [19]. A subsequent study of statins in subjects without high blood cholesterol levels showed that the clinical benefit of statins was independent of the initial levels of low-density lipoprotein (LDL) and total cholesterol [20]. One should also recall that non-statin reducers of blood cholesterol do not reduce the risk of myocardial infarction as much as do statins with equivalent reductions of blood cholesterol [21]. Despite that, new statins continue to be advertised as superior blood lipid reducers that yield clinical benefit through their inhibition of cholesterol synthesis.

With the realization that statins have other actions, attention has been drawn to endothelial integrity and function. These depend on various factors including nitrous oxide (NO) synthesis, vessel wall relaxivity, inhibition of vascular smooth muscle proliferation, leukocyte adherence, and platelet aggregation. Oxidized LDLs are not only atherogenic *per se*, but also inhibit NO-synthetase. Statins act by lowering LDL and improving endothelial function via increased NO and work also via increasing NO synthetase without inhibiting LDL [22]. Simvastatin enhances the regeneration of endothelial cells via VEGF secretion in injured arteries [23]. These findings lead to plausible explanations of the lipid-independence of beneficial statin effects.

This is particularly relevant because statins do much more than decrease LDL cholesterol levels. Strong basic science evidence also suggests that the effects of statins on inflammation, thrombosis, and oxidation are plausible mechanisms for mediating the benefits of statin therapy often referred to as “pleiotropic effects” [24]. However, they have not yet led to an adequate appreciation for whom statins may or may not benefit clinically.

Other substances than statins have been described for the experimental treatment of atherosclerosis, e.g., the amine-carboxyborane derivates [25]. In rodents, the amine carboxyboranes were potent hypolipidemic agents, lowering both serum cholesterol and triglyceride concentrations, in addition to lowering cholesterol content of very low-density lipoprotein (VLDL) and low-density lipo-

protein (LDL) and elevating high-density lipoprotein (HDL) cholesterol concentrations. *De novo* regulatory enzymes involved in lipid synthesis were also inhibited (e.g., hypocholesterolemic 3-hydroxy-3-methyl-Coenzyme A reductase, acyl-Coenzyme A cholesterol acyltransferase, and sn-glycerol-3-phosphatacyltransferase). Concurrently, the agents modulated LDL and HDL receptor binding, internalization, and degradation, so that less cholesterol was delivered to the plaques and more broken down from esters and conducted to the liver for biliary excretion. Tissue lipids in the aorta wall of the rat were reduced and fewer atherosclerotic morphologic lesions were present in quail aortas after treatment with the agents. Cholesterol absorption from the rat intestine was reduced in the presence of the drug. Genetic hyperlipidemic mice demonstrated the same types of reduction after treatment with the agents. The agents would effectively lower lipids in tissue based on the inhibition of regulatory enzymes in pigs [25].

Like statins, amine-carboxyboranes were shown to be effective anti-inflammatory agents, e.g., against septic shock, induced edema, pleurisy, and chronic arthritis at 2.5 to 8 mg/kg. Lysosomal and proteolytic enzyme activities were also inhibited. More significantly, the agents were dual inhibitors of prostaglandin-cyclo-oxygenase and 5'-lipoxygenase activities. These compounds also affected cytokine release and white cell migration [25].

## Statins as immunomodulators

As mentioned above, atherosclerosis is recognized to have notable inflammatory and immunologic components [4], [6], [9], [10], and in parallel, statins appear to have the ability to inhibit inflammatory processes directly. The action of statins turns out to be more complex and broader than was originally expected, and recent studies have revealed their multiple immunologic actions. The fact that statins inhibit recruitment and activation of immune-competent cells, such as macrophages, raises the question whether they may also be beneficial in other chronic inflammatory conditions and (auto-)immune diseases.

Increasing evidence indicates that some beneficial effects of statins may result from their ability to modulate arterial cell gene expression by mechanisms independent of cholesterol reduction [26]. Among the first reports of the immunologic effects of statins was the finding that this class of drug actually inhibits the interferon-γ (INF-γ)-induced expression of class II major histocompatibility complex (MHC II) on antigen-presenting cells (APC), and thus identify a new mechanism by which statins may modulate immune responses [27]. This inhibitory effect was induced by nano- and micromolecular concentrations of statins, particularly of Atorvastatin, in primary cultures of human macrophages and endothelial cells stimulated with INF-γ. Expression of class I MHC, which activates cytolytic CD8+ T-lymphocytes, was not affected by statins [27].

Selective modulation of the immune response may affect the progression of atherosclerosis [28]. Two reports confirm that reducing the inflammatory component of cardiovascular disease through the use of statin therapy improves the clinical outcome independently of the reduction of serum cholesterol levels [29], [30]. The main finding of both articles is that a decrease in C-reactive protein, a marker of inflammation, is independent of the reductions achieved in LDL-cholesterol levels.

Even in the area of infection, there are findings that statin therapy has a favourable effect on sepsis and can reduce the replication of HIV [31].

The notion that the anti-inflammatory effects of statins ameliorate cardiovascular disease suggests that it should be possible to create other anti-inflammatory agents, perhaps tailored to the specific immunologic abnormalities in atheroma. Determining the mechanisms of action of statins and their relative importance will help to rationalize the design of such therapies and nutritions.

## Homocysteine, folate, and atherosclerosis

More than 30 years ago, McCully made the initial clinical observation linking elevated plasma homocysteine levels with atherosclerotic vascular disease in a post-mortem review [32]. We now realize that NO synthetase, and through the latter, endothelial function, are influenced by a series of factors, among which are micronutrients such as homocysteine, a methionine-derived component of the nutrition.

Homocysteine is metabolized either reversibly by methylation, a process that requires folic acid and vitamin B12 – or irreversibly by loss of cystein, a process that requires vitamin B6 [33]. Increased plasma concentrations of homocysteine are associated with increased risk of cardiovascular disease [32], [34], [35]. However, 5-methyltetrahydro-folate, the most important circulating metabolite of folic acid, acts to increase NO synthesis as one of additional positive effects caused by the reduction of homocysteine. A high intake of folic acid in the nutrition (5 mg/d) improves endothelial function [36].

Nowadays, hyperhomocysteinemia is a well established, independent risk factor for the development of atherosclerosis. Elevated homocysteine adversely affects arterial endothelial function [36], increases oxidative damage and promotes inflammation and thrombosis [35]. There is a dose-response relationship across a wide range of homocysteine levels (including so-called normal range) [36]. A recent study exemplifies this. Amongst >3000 patients with chronic heart disease, a subsequent coronary event was 2.5 times more likely in patients with elevated compared to normal serum homocysteine, and each 5 µmol/L of homocysteine predicted a 25% increase in risk [37].

Homocysteine levels are directly related to the status of the nutrients involved in its metabolism, particularly folate and vitamins B12 and B6, although other nutrients such as riboflavin and carnitine also affect it. It has been estimated that approximately 2/3 of the prevalence of high homocysteine is due to low vitamin status [38].

This provides a convincing basis for conducting randomised clinical trials using those vitamins to lower homocysteine in order to prevent complications of atherosclerosis like coronary artery disease. It has been quite satisfactorily demonstrated that homocysteine levels can be lowered by increasing vitamin intake – in a great many trials (see recent review [39]), even though some subtleties are not yet fully resolved, such as how much of which vitamins is the ideal way to reduce homocysteine levels, the role of genetic variation (MTHFR polymorphism), and the extent to which the homocysteine reduction depends on the initial vitamin status.

The lowering of elevated homocysteine plasma levels on endothelial function has been studied and positive results were reported in 50% of those 21 trials, 41% failed to detect any improvement, and in 9% the outcome was borderline significant or independent of homocysteine reduction [38], [39].

Other trials have found benefits in reduced arterial stiffness, fewer abnormal exercise ECGs, and a non-significant decrease in cerebrovascular atherosclerosis (measured by MRI imaging) [39].

A recent study also showed improved intermediary outcome, i.e. carotid arterial intima-media thickening, something previously reported in renaltransplant patients [38]. A related measure, even closer to the ultimate clinical end-points, is the rate of restenosis after angioplasty. A homocysteine-lowering supplement decreased such relapses in over 500 Swiss patients, although in a German trial of over 600 patients (but which used much less B12) it failed to do so [39].

The Swiss trial mentioned above found a reduced rate of 1 year composite cardiovascular disease end points, and a recent, small, open prospective Italian trial in hemodialysis patients reported lowered cardiovascular disease death and mortality from homocysteine reduction [39]. A reanalysis of the VISP trial data identified a sub-set of 2155 patients (without renal disease and with initial B12 levels likely to respond to supplements) in whom there was a significant 21% reduction in clinical end points [39].

One could wonder whether the average pre-treatment homocysteine levels in some of these trials were high enough, or the amount of homocysteine reduction obtained was sufficient, or whether the issue is actually the vitamin levels themselves with homocysteine being only an indicator. But, as mentioned above, the earlier evidence suggested the homocysteine-cardiovascular disease link is biological and applies across a broad homocysteine range. It is possible that some combination of initial vitamin status and treatment mix could explain the positive trial results (for example some authors have focused specifically on B12 and its absorption in the elderly); but this currently remains speculation.

For the moment we cannot say that the data supports the use of homocysteine-lowering vitamin supplements. Still, the reduced stroke incidence found in the new HOPE 2 Study and the positive clinical outcomes from the VISP sub-set and Swiss trial all need follow-ups. The new SEARCH (Study for the Evaluation of Additional Reductions in Cholesterol and Homocysteine) trial may provide some of those answers [40].

It is further recommended the monitoring of B12 and folate status in the elderly and the consumption of foods rich in those nutrients. Whether anything is gained from also monitoring homocysteine levels remains yet unclear.

Apart from homocysteine there can be another genetically induced factor, which, however, is not well manipulated pharmacologically like homocysteine: Lipoprotein a is an isolated cardiovascular risk factor which can only rarely be treated pharmacologically by nicotinic acid preparations. Additional lipid fractions such as apolipoprotein A and B, who constitute risk factors, can be diminished by nutrition as well as by statins.

## Nutrition and atherosclerosis

The topic is further complicated when we realize that NO synthetase, and through the latter, endothelial function, are influenced by a series of factors, as the above mentioned homocysteine, a methionine-derived component of the nutrition [41], [42].

Not only statins, but also a variety of food ingredients can influence endothelial function via cellular NO production. Other components of the nutrition exert anti-atherogenic effects by different mechanisms. For example, the glitazones, components of certain vegetables, inhibit adhesion of leukocytes on damaged endothelium [43].

A further layer of complexity was uncovered during studies of diabetes mellitus. In particular, studying the effect of the statin Simvastatin showed a reduction of risk for vascular accidents that was independent of the initial LDL blood cholesterol level [44]. On the other hand, patients with Type II diabetes mellitus showed no influence on the reactivity of their vessels to NO when treated intensively with a LDL-lowering drug, Atorvastatin [45] or Simvastatin [46], both in contrast to folic acid, which regained NO-dependent vascular reactivity [47]. A 6-month study of Atorvastatin for patients with type II diabetes showed improvement of vascular reactivity unrelated to any reduction in LDL [48]. This improvement did correlate, however, with reductions in C-reactive protein, an observation that led to the postulate that this particular beneficial effect of statin in these patients might be related to some anti-inflammatory activity of Atorvastatin. Finally, further studies showed that Vitamin C supplements improved endothelial-dependent vasodilation in patients with type I diabetes, but not in healthy control subjects [49]. Vitamin C inhibits endothelial dysfunction in diabetics in which it improves NO production: it stabilizes and

increases intraendothelial concentrations of the essential NO synthase cofactor tetrahydrobiopterin [50].

## Nutrition versus statins

Although they might perturb the research programs of some established investigators, results like those of the Lyon Heart Study [51], which showed that improvements in nutrition led to far better clinical outcomes than did statin therapy per se, justify a need for better understanding of the anti-atherogenic synergy of nutritional factors with statins.

Along these lines, a recent study showed that the additional administration of folic acid was of no additional benefit for the patients under statin treatment [52]. However, an alternative interpretation of this finding could be that statins did not result in additional benefit of those who were already taking folic acid nutritional supplements. These matters are currently under scrutiny in studies that investigate the efficacy of statins and folic acid in combination or alone, e.g., the SEARCH [40].

Some recent published studies indicate again the marked clinical benefit of the 'Mediterranean nutrition' on cardiovascular function, including that of the elderly [53], which is associated with improved endothelial function in persons with metabolic syndrome [54].

To determine the extent to which primary and secondary prevention has contributed to decreased coronary heart disease mortality in England and Wales since the 1980s, researchers used the IMPACT coronary heart disease mortality model to synthesize data from national surveys, official statistics, clinical audits, controlled trials, and meta-analysis [55]. From 1981 through 2000, age-specific coronary heart disease mortality fell by 62% in men and 45% in women, and resulted in about 30,000 fewer deaths (5000 in people with known coronary heart disease and 25,000 in people without this disease). Population cholesterol levels fell by 4.2%, resulting in about 7900 fewer deaths. Of the *5770 fewer deaths attributed to nutritional changes*, about 1200 were in coronary heart disease patients and about 4500 were in people without this disease. In contrast, statin treatment was estimated to have prevented only 1990 deaths in people with coronary heart disease and 145 deaths in people without. Mean population diastolic blood pressure fell by 7.7%, resulting in 7700 fewer deaths (about 500 in coronary heart disease patients, 5300 in healthy people, and 1900 in hypertensive people). Overall, 81% of averted deaths were in people without coronary heart disease and 19% were in those with known disease. The value of these results is that they integrate several data sources and indicate that primary prevention contributed more to the decline in coronary heart disease mortality than did secondary prevention. The results do not address questions about cost-effectiveness [55].

In summary, if we want to make the best of what common micronutrients and statins may offer in the prophylaxis of atherosclerosis, we should try to learn more about how to assess the positive effects of statins against their potential toxic risks (neuro- and myopathies, rhabdomyolysis, renal tubular necrosis and acute kidney failure) in individual patients [56], [57], [58], [59], [60]. Additionally, titrating lipid-lowering therapy to reduce LDL cholesterol to very low levels (e.g. <70 mg/dL) by statins can be difficult, costly, is not without risk and no solid evidence appears to support this recommendation of the National Cholesterol Education Program [61].

In a recent study, the potential effect of reducing the intake of industrially produced trans fatty acids on the incidence of coronary heart disease in the United states was calculated [62]. The authors estimated on the basis of reported relations between trans fat intake and coronary heart disease events in prospective studies 10% to 19% of coronary heart disease events could be averted by reducing the intake of trans fat. Thus, given the 1.2 million annual myocardial infarctions and deaths from coronary heart disease in the United States, near-elimination of industrially produced trans fats might avert between 72,000 (6%) and 228,000 (19%) coronary heart diseases each year [62], [63].

The unequivocal beneficial effects of long term caloric restriction on the blood pressure, the ratio of cholesterol/HDL-cholesterol, and the body mass index (BMI), which have been demonstrated recently [64], [65], must carry some especially important lessons for public health and educational policies in our obesity-ridden, low exertion, industrialized societies, which should surely be at least as useful to us in the long run as is the ongoing education of our affluent population about the availability and cost of prophylactic statins. A recently published hypothesis indicates the possible fact that *statins are analogues of vitamin D*, since several effects of statins match well with those of that vitamin particularly the anomalous results, such as unexpected benefits of statins like the modulation of inflammations and immune states [66].

## Conclusions

Nowadays, we have to face our dependence on results of studies sponsored by the industry, particularly we have become too dependent on manufacturers as the predominant source of our scientific knowledge about the effects of medications [67].

With pharmaceutical costs increasing faster than most other health care expenditures, we require studies that will meet the needs of evidence-based presriptions and treatments and not just the needs of the pharmaceutical industry. These trials must not only be conducted involving combination therapies of the company's own products or the test drug against a placebo but rather against nutritional regimens [68]. The conduct of such equivalence or non-inferiority studies imposes markedly higher methodological demands compared with traditional studies to prove the superiority of a treatment vs. placebo or standard therapy. It is not a question of whether we can afford to pay for our own drug and nutritional trials; *it is*

*increasingly evident that we cannot afford not to do so* [67].

# Notes

## Acknowledgement

The author thanks Doctor Daniel N. Slatkin, M.D., Essex, CT, USA for valuable suggestions and critical discussions.

## Conflicts of interest

I declare to have no conflicts of interest.

# References

1. Gebbers JO. Cholesterin ist für die Atherosklerose ohne Bedeutung. Die Ergebnisse von Autopsien stützen die Lipidhypothese nicht. Ars Medici. 1998;88:564-9.
2. Giannini O, Gebbers JO. Fragwürdige KHK-Epidemiologie. Ars Medici. 1999;89(5):320-5.
3. Get ready for statin price wars. Marketplace 2006 June 23. Available from: http://marketplace.publicradio.org/shows/2006/06/23/PM200606234.html.
4. Virchow R. Der atheromatöse Prozess der Arterien. Wien Med Wochenschr. 1856;6:825-41.
5. Gimbrone MA, Topper JN. Biology of the Vessel Wall: Endothelium. In: Chien KR, editor. Molecular Basis of Heart Diseases. Troy, MO: Hartcourt Brace; 1998. p. 331-48
6. Ross R. Atherosclerosis - an inflammatory disease. N Engl J Med. 1999;340(2):115-26.
7. Resnick N, Gimbrone MA Jr. Hemodynamic forces are complex regulators of endothelial gene expression. FASEB J. 1995;9(10):874-82.
8. Cornhill JF, Roach MR. A quantitative study of the localization of atherosclerotic lesions in the rabbit aorta. Atherosclerosis. 1976;23(3):489-501.
9. Hansson GK. Cell-mediated immunity in atherosclerosis. Curr Opin Lipidol. 1997;8(5):301-11.
10. Hansson GK, Zhou X, Tornquist E, Paulsson G. The role of adaptive immunity in atherosclerosis. Ann N Y Acad Sci. 2000;902:53-64.
11. Stehbens WE, Smith RL. Serum cholesterol correlations with atherosclerosis at autopsy. Am Clin Lab. 1997;16(3):14-5.
12. Scrimshaw NS, Guzman MA. Diet and atherosclerosis. Lab Invest. 1968;18(5):623-8.
13. Strong JP, Johnson WD, Oalmann MC, Wissler RW. Community pathology of atherosclerosis and coronary heart disease in New Orleans: Relationship of risk factors to atherosclerotic lesions. In: Gotto AM, Smith LC, Allen B, editors. Atherosclerosis V. New York, NY: Springer; 1980. p. 719-30.
14. Strong JP, Malcom GT, McMahan CA, Tracy RE, Newman WP 3rd, Herderick EE, Cornhill JF. Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. JAMA. 1999;281(8):727-35.
15. Chakravarthy MV, Pan Z, Zhu Y, Tordjman K, Schneider JG, Coleman T, Turk J, Semenkovich CF. "New" hepatic fat activates PPARalpha to maintain glucose, lipid, and cholesterol homeostasis. Cell Metab. 2005;1(5):309-22.
16. Spieker LE, Sudano I, Hurlimann D, Lerch PG, Lang MG, Binggeli C, Corti R, Ruschitzka F, Lüscher TF, Noll G. High-density lipoprotein restores endothelial function in hypercholesterolemic men. Circulation. 2002;105(12):1399-402.
17. Spieker L, Ruschitzka F, Lüscher TF, Noll G. HDL-Cholesterin bei Atherosklerose - zu wenig des Guten. Swiss Med Forum. 2003;3(39):920-6.
18. Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ruiz-Gutierrez V, Covas MI, Fiol M, Gomez-Gracia E, Lopez-Sabater MC, Vinyoles E, Aros F, Conde M, Lahoz C, Lapetra J, Saez G, Ros E; PREDIMED Study Investigators. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med. 2006;145(1):1-11.
19. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333(20):1301-7.
20. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360(9326):7-22.
21. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996;335(14):1001-9.
22. Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation. 1998;97(12):1129-35.
23. Matsuno H, Takei M, Hayashi H, Nakajima K, Ishisaki A, Kozawa O. Simvastatin enhances the regeneration of endothelial cells via VEGF secretion in injured arteries. J Cardiovasc Pharmacol. 2004;43(3):333-40.
24. Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol. 2005;45:89-118.
25. Hall IH, Chen SY, Rajendran KG, Sood A, Spielvogel BF, Shih J. Hypolipidemic, anti-obesity, anti-inflammatory, anti-osteoporotic, and anti-neoplastic properties of amine carboxyboranes. Environ Health Perspect. 1994;102 Suppl 7:21-30.
26. Faggiotto A, Paoletti R. State-of-the-Art lecture. Statins and blockers of the renin-angiotensin system: vascular protection beyond their primary mode of action. Hypertension. 1999;34(4 Pt 2):987-96.
27. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. Nat Med. 2000;6(12):1399-402.
28. Palinski W, Witztum JL. Immune responses to oxidative neoepitopes on LDL and phospholipids modulate the development of atherosclerosis. J Intern Med. 2000;247(3):371-80.
29. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. N Engl J Med. 2005;352(1):20-8.

30. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, Orazem J, Magorien RD, O'Shaughnessy C, Ganz P; Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005;352(1):29-38.

31. del Real G, Jimenez-Baranda S, Mira E, Lacalle RA, Lucas P, Gomez-Mouton C, Alegret M, Pena JM, Rodriguez-Zapata M, Alvarez-Mon M, Martinez-A C, Manes S. Statins inhibit HIV-1 infection by down-regulating Rho activity. J Exp Med. 2004;200(4):541-7.

32. McCully KS. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. Am J Pathol. 1969;56(1):111-28.

33. Moat SJ, Lang D, McDowell IF, Clarke ZL, Madhavan AK, Lewis MJ, Goodfellow J. Folate, homocysteine, endothelial function and cardiovascular disease. J Nutr Biochem. 2004;15(2):64-79.

34. Stamler JS, Osborne JA, Jaraki O, Rabbani LE, Mullins M, Singel D, Loscalzo J. Adverse vascular effects of homocysteine are modulated by endothelium-derived relaxing factor and related oxides of nitrogen. J Clin Invest. 1993;91(1):308-18.

35. Rodgers GM, Conn MT. Homocysteine, an atherogenic stimulus, reduces protein C activation by arterial and venous endothelial cells. Blood. 1990;75(4):895-901.

36. Ueland PM, Refsum H, Brattstrom L. Plasma homocysteine and cardiovascular disease. In: RB Francis, editor. Atherosclerotic cardiovascular disease, hemostasis, and endothelial function. New York: Marcel Dekker; 1992. p. 183-236.

37. McNulty H, Dowey le RC, Strain JJ, Dunne A, Ward M, Molloy AM, McAnena LB, Hughes JP, Hannon-Fletcher M, Scott JM. Riboflavin lowers homocysteine in individuals homozygous for the MTHFR 677C->T polymorphism. Circulation. 2006;113(1):74-80.

38. Refsum H, Nurk E, Smith AD, Ueland PM, Gjesdal CG, Bjelland I, Tverdal A, Tell GS, Nygard O, Vollset SE. The Hordaland Homocysteine Study: a community-based study of homocysteine, its determinants, and associations with disease. J Nutr. 2006;136(6 Suppl):1731S-1740S.

39. Arbor Clinical Nutrition Update. Homocysteine and heart disease in 2006. 2006;258. Available from: http://www.nutritionupdates.org/sub?sub03.php ?item=2

40. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH). Oxford: Clinical Trial Service Unit; 2006 [updated 2006 May 16; cited 2007 Aug 08]. Available from: http://www.ctsu.ox.ac.uk/projects/search /index_html

41. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. JAMA. 1995;274(13):1049-57.

42. Moat SJ, Doshi SN, Lang D, McDowell IF, Lewis MJ, Goodfellow J. Treatment of coronary heart disease with folic acid: is there a future? Am J Physiol Heart Circ Physiol. 2004;287(1):H1-7.

43. Li AC, Brown KK, Silvestre MJ, Willson TM, Palinski W, Glass CK. Peroxisome proliferator-activated receptor gamma ligands inhibit development of atherosclerosis in LDL receptor-deficient mice. J Clin Invest. 2000;106(4):523-31.

44. Collins R, Armitage J, Parish S, Sleigh P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003;361(9374):2005-16.

45. van Etten RW, de Koning EJ, Honing ML, Stroes ES, Gaillard CA, Rabelink TJ. Intensive lipid lowering by statin therapy does not improve vasoreactivity in patients with type 2 diabetes. Arterioscler Thromb Vasc Biol. 2002;22(5):799-804.

46. van de Ree MA, Huisman MV, de Man FH, van der Vijver JC, Meinders AE, Blauw GJ. Impaired endothelium-dependent vasodilation in type 2 diabetes mellitus and the lack of effect of simvastatin. Cardiovasc Res. 2001;52(2):299-305.

47. van Etten RW, de Koning EJ, Verhaar MC, Gaillard CA, Rabelink TJ. Impaired NO-dependent vasodilation in patients with Type II (non-insulin-dependent) diabetes mellitus is restored by acute administration of folate. Diabetologia. 2002;45(7):1004-10.

48. Tan KC, Chow WS, Tam SC, Ai VH, Lam CH, Lam KS. Atorvastatin lowers C-reactive protein and improves endothelium-dependent vasodilation in type 2 diabetes mellitus. J Clin Endocrinol Metab. 2002;87(2):563-8.

49. Timimi FK, Ting HH, Haley EA, Roddy MA, Ganz P, Creager MA. Vitamin C improves endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. J Am Coll Cardiol. 1998;31(3):552-7.

50. Heller R, Unbehaun A, Schellenberg B, Mayer B, Werner-Felmayer G, Werner ER. L-ascorbic acid potentiates endothelial nitric oxide synthesis via a chemical stabilization of tetrahydrobiopterin. J Biol Chem. 2001;276(1):40-7.

51. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation. 1999;99(6):779-85.

52. Liem AH, van Boven AJ, Veeger NJ, Withagen AJ, Robles de Medina RM, Tijssen JG, van Veldhuisen DJ; Folic Acid on Risk Diminishment After Acute Myocarial Infarction Study Group. Efficacy of folic acid when added to statin therapy in patients with hypercholesterolemia following acute myocardial infarction: a randomised pilot trial. Int J Cardiol. 2004;93(2-3):175-9.

53. Knoops KT, de Groot LC, Kromhout D, Perrin AE, Moreiras-Varela O, Menotti A, van Staveren WA. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. JAMA. 2004;292(12):1433-9.

54. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F, Giugliano D. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA. 2004;292(12):1440-6.

55. Unal B, Critchley JA, Capewell S. Modelling the decline in coronary heart disease deaths in England and Wales, 1981-2000: comparing contributions from primary prevention and secondary prevention. BMJ. 2005;331(7517):614.

56. Gaist D, Jeppesen U, Andersen M, Garcia Rodriguez LA, Hallas J, Sindrup SH. Statins and risk of polyneuropathy: a case-control study. Neurology. 2002;58(9):1333-7.

57. Silverberg C. Atorvastatin-induced polyneuropathy. Ann Intern Med. 2003;139(9):792-3.

58. Finsterer J. Fibrat und Statin-Myopathie [Fibrate and statine myopathy]. Nervenarzt. 2003;74(2):115-22.

59. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, Gurwitz JH, Chan KA, Goodman MJ, Platt R. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004;292(21):2585-90.

60. Wolfe SM. Dangers of rosuvastatin identified before and after FDA approval. Lancet. 2004;363(9427):2189-90.

61. Hayward RA, Hofer TP, Vijan S. Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. Ann Intern Med. 2006;145(7):520-30.

62. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Trans fatty acids and cardiovascular disease. N Engl J Med. 2006;354(15):1601-13.

63. Heart disease and stroke statistics - 2004 update. Dallas: American Heart Association, 2003.

64. Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proc Natl Acad Sci U S A. 2004;101(17):6659-63.

65. Krapf R. BMI oder: Wer ist überhaupt noch normalgewichtig? Swiss Med Forum. 2004;4(50):1265.

66. Grimes DS. Are statins analogues of vitamin D? Lancet. 2006;368(9529):83-6.

67. Avorn J. Torcetrapib and atorvastatin--should marketing drive the research agenda? N Engl J Med. 2005;352(25):2573-6.

68. Kleist P. Zehn Anforderungen an therapeutische Äquivalenzstudien. Oder warum der fehlende Nachweis von Unterschieden und Äquivalenz nicht dasselbe bedeuten. Swiss Med Forum. 2006;6(37):814-9.

**Corresponding author:**
Prof. Dr. med. Jan-Olaf Gebbers
Institute of Environmental Medicine, Kantonsspital, CH-6000 Luzern 16, Switzerland, Tel.: 0041-41-2054270
janolaf.gebbers@ksl.ch

***Please cite as***
*Gebbers JO. Atherosclerosis, cholesterol, nutrition, and statins – a critical review. GMS Ger Med Sci. 2007;5:Doc04.*

***This article is freely available from***
*http://www.egms.de/en/gms/2007-5/000040.shtml*

***Received:*** *2006-12-07*
***Revised:*** *2007-06-28*