

EXPERT  
REVIEWS

# Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms

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Harumi Okuyama\*<sup>1</sup>,  
Peter H Langsjoen<sup>2</sup>,  
Tomohito Hamazaki<sup>3</sup>,  
Yoichi Ogushi<sup>4</sup>,  
Rokuro Hama<sup>5</sup>,  
Tetsuyuki Kobayashi<sup>6</sup>  
and Hajime Uchino<sup>7</sup>

<sup>1</sup>Nagoya City University and Institute for Consumer Science and Human Life, Kinjo Gakuin University, 2-1723 Omori, Moriyama, Nagoya 463-8521, Japan

<sup>2</sup>Clinical Cardiology Practice, 1107 Doctors Drive, Tyler, TX 75701, USA

<sup>3</sup>Toiyama Onsen Daini Hospital, 1-13-6 Taromaru-Nishimachi, Toyama-city, Toyama 939-8271, Japan

<sup>4</sup>Ogushi Institute of Medical Informatics, 12-43-2, Daikancho, Hiratsuka, Kanagawa 254-0807, Japan

<sup>5</sup>Non-Profit Organization Japan Institute of Pharmacovigilance (Kusuri-no-Check), Ueshio 5-1-20, Tennouji-ku, Osaka 543-0002, Japan

<sup>6</sup>Graduate School of Humanities and Sciences, Ochanomizu University, 2-1-1 Ohtsuka, Bunkyo-ku, Tokyo 112-8610, Japan

<sup>7</sup>Medical Corp. Uchino-kai, 5-10-12 Yahata, Minami-ku, Kumamoto 861-4113, Japan

\*Author for correspondence:

Tel.: +81 528 763 840

Fax: +81 528 763 840

okuyamah@kinjo-u.ac.jp

In contrast to the current belief that cholesterol reduction with statins decreases atherosclerosis, we present a perspective that statins may be causative in coronary artery calcification and can function as mitochondrial toxins that impair muscle function in the heart and blood vessels through the depletion of coenzyme Q<sub>10</sub> and 'heme A', and thereby ATP generation. Statins inhibit the synthesis of vitamin K<sub>2</sub>, the cofactor for matrix Gla-protein activation, which in turn protects arteries from calcification. Statins inhibit the biosynthesis of selenium containing proteins, one of which is glutathione peroxidase serving to suppress peroxidative stress. An impairment of selenoprotein biosynthesis may be a factor in congestive heart failure, reminiscent of the dilated cardiomyopathies seen with selenium deficiency. Thus, the epidemic of heart failure and atherosclerosis that plagues the modern world may paradoxically be aggravated by the pervasive use of statin drugs. We propose that current statin treatment guidelines be critically reevaluated.

**KEYWORDS:** atherosclerosis • ATP generation • coenzyme Q<sub>10</sub> • heart failure • mitochondrial toxin • selenoprotein • statin • statin cardiomyopathy • vitamin K<sub>2</sub>

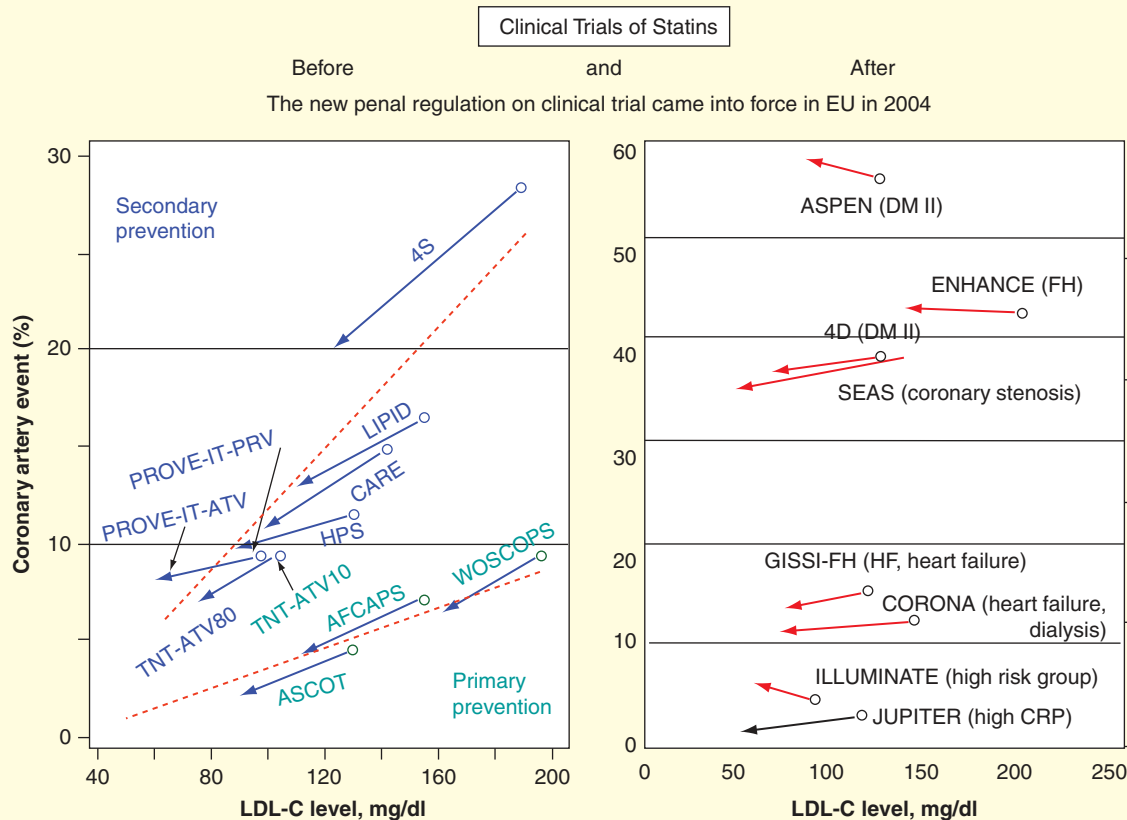
The relationship between plasma total cholesterol (TC) and coronary heart disease (CHD) is not simple. Around 1990, the 'bad low-density lipoprotein cholesterol (LDL-C), good high-density lipoprotein cholesterol (HDL-C) hypothesis' was introduced in clinical trials. Because the direct assay method to determine LDL-C was found to be unreliable, LDL-C values are presently calculated by the Friedewald's equation,  $LDL-C = TC - HDL-C - 0.2 \times \text{triglyceride (TG)}$  (in units of mg/dl), but the equation is not accurate when the HDL-C and TG values are extremely high. There are cases when the formula 'LDL-C = TC - 80' mg/dl is used. We will use TC and LDL-C without any further comments, and the latter comprises roughly two-thirds of the former.

## The 'bad & good cholesterol hypothesis' lost its foundation

The 'good and bad cholesterol hypothesis' is based on simplified interpretations that LDL carries TGs and cholesterol to peripheral tissues, whereas HDL reverse-transport cholesterol to

the liver to excrete excess cholesterol to feces, mostly as bile acids. However, HDL contains lecithin cholesterol acyltransferase enzyme to form cholesterol ester, which is transported to LDL by cholesterol ester transport protein in plasma. Roughly 1.5 g of cholesterol is required daily in adults for a variety of essential functions, and 0.3 g (about half of ingested cholesterol) can be obtained from 2 eggs plus 100 g meat and the rest (~1.2 g), the majority of daily required amount, is biosynthesized in adult tissues. The cholesterol taken-up by HDL is transferred to LDL, which is redistributed to and reused by peripheral tissues.

Recently, cholesterol ester transport protein inhibitors were developed and they were effective in lowering LDL-C/HDL-C ratios but they were essentially ineffective in preventing CHD [1]. Moreover, statins or statins plus other cholesterol-lowering drugs were effective in lowering LDL-C but were essentially ineffective in preventing CHD [2,3] as will be summarized below. All these observations go against the 'good cholesterol/bad cholesterol hypothesis',



**Figure 1. Clinical trials of statins for the prevention of CHD-comparison of the effectiveness reported before and after the year 2004 when new penal regulations on clinical trials came into effect in the EU.** The arrow tail and head represent the LDL-C level and CHD event of the control and intervention groups, respectively. The major types of the participants are shown in parentheses. Each clinical trial with statin is shown in abbreviated name.

CHD: Coronary heart disease; CRP: C-reactive protein; DM: Diabetes mellitus; FH: Familial hypercholesterolemia; LDL-C: Low-density lipoprotein cholesterol.

Modified with permission from Lipid Technology [7].

and we should not try to explain the correlation between plasma cholesterol levels and CHD events based on this hypothesis.

Since the introduction of statins to clinical medicine in 1987, several kinds of statins were reported to be effective in lowering LDL-C and also preventing CHD events (mostly in 1990s). However, unfair and unethical problems were associated with clinical trials reported by industry-supported scientists, and new penal regulations on clinical trials came into effect in 2004 [4,5]. After 2004–2005, all clinical trials, performed by scientists relatively free of conflict of interest with pharmaceutical industries, reported that statins were effective in lowering LDL-C but no significant beneficial effects were observed for the prevention of CHD (FIGURE 1). Currently, the majority of scientists continue to claim that statins are effective in preventing CHD, but these claims are based on meta-analyses of reports, including those published before the EU regulation (mostly in 1990s). However, our group did not adopt the results of industry-supported publications as reliable in our cholesterol guidelines [6,7]. Thus, we are in a position not to accept the effectiveness of statins to prevent CHD (FIGURE 1, left), but rather we support the pharmacological

interpretations that statins stimulate the development of atherosclerosis and heart failure. The lines of evidence described below led us to propose that current statin therapy should be critically and urgently reevaluated.

### Statins are mitochondrion toxic

In mitochondria, subcellular organelles, electron transport chain and ATP synthesizing enzymes are localized in the inner membranes (FIGURE 2). Fatty acids and sugars are burned (hydrogen is pulled out) to store energy as ATP. In the electron transport chain, each hydrogen (H) atom forms an electron ( $e^-$ ) and a proton ( $H^+$ ), and the electron is transported through complex I or complex II to coenzyme  $Q_{10}$  ( $CoQ_{10}$ ) and then to complex III and finally to complex IV. Protons are concentrated in the mitochondrial membrane space between the outer and the inner membranes and they form a gradient that drives the ATP-synthesizing enzyme ATPase, and the molecular motor is turned on to generate ATP [8,9].

$CoQ_{10}$  (both in its oxidized ubiquinone and reduced ubiquinol forms) and 'heme A' are essential components of the electron transport chain and are synthesized from prenyl-intermediates in

the cholesterol biosynthetic pathway. Statins inhibit CoQ<sub>10</sub> and 'heme A' biosynthesis, and thereby ATP generation. ATP is essential for normal heart muscle function, metabolism of cellular components and other activities in cell life. Cholesterol is a major component of cell membranes, functioning to maintain their integrity, which is likely to be affected by statins. Thus, statins are mitochondrial toxins making all cells ATP depleted. Because most mammalian cells depend on mitochondria for their energy metabolism, statins are general cell toxins.

CoQ<sub>10</sub> is an essential cofactor in electron and proton transport in mitochondrial energy production [8-10], as well as in several other aspects of cellular metabolism [11]. The bioenergetic effect of CoQ<sub>10</sub> is believed to be of fundamental importance in its clinical application, particularly as it relates to cells with exceedingly high metabolic demands such as cardiac myocytes. The reduced form of CoQ<sub>10</sub> (ubiquinol) is recognized to be a clinically relevant antioxidant in different cellular compartments, especially the mitochondrial membranes [12,13], where it protects mitochondrial DNA from damage. It is well known that mitochondrial DNA is much more vulnerable to oxidative damage than nuclear DNA.

### Decreased ATP generation & resulting cell damage contribute to the development of CHD in familial hypercholesterolemia cases & in statin-treated people

The initial pathophysiology of the onset of atherosclerosis has not been well defined (FIGURE 3). However, any tissue damage, whether derived from a pathogen or noninfectious damage, may induce inflammation to repair damaged tissues leading to many diseases, including atherosclerosis. These inflammatory repair mechanisms are mediated through Toll-like receptors in response to activators produced by infections, hypoxic-ischemic damage, overwork and/or stress and elevated advanced glycation end products [14]. The associated coronary artery stenosis leads to decreased blood flow and reduced supply of nutrients and oxygen, leading to decreased ATP generation in blood vessels and heart muscle cells.

In the case of familial hypercholesterolemia, the supply of nutrients, particularly fats, to peripheral tissues is restricted from early age, due to defective or deficient LDL receptors. This leads to

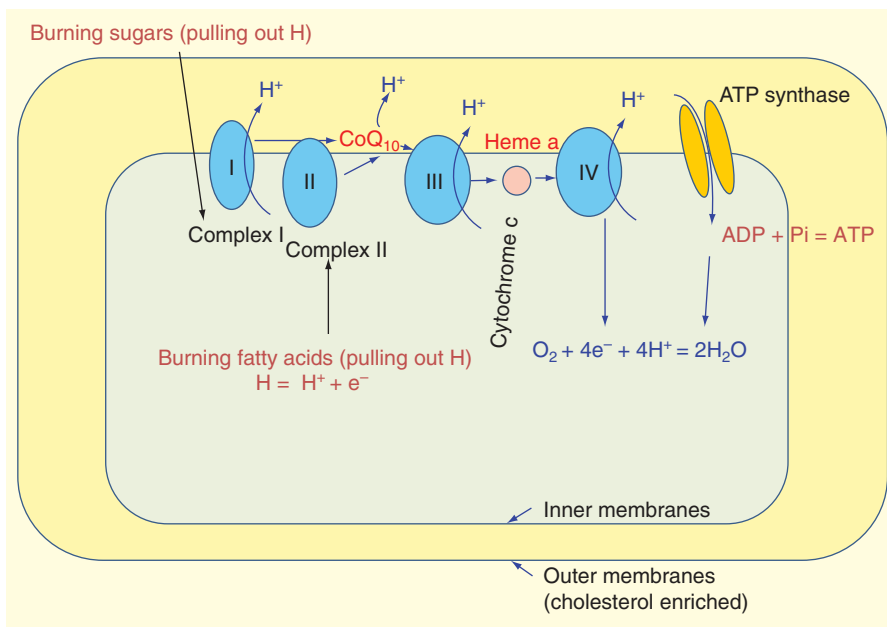


Figure 2. Statins are mitochondrion toxic. See text for detailed explanations.

decreased ATP generation and cellular damage (FIGURE 3). Walter Hartenbach, former professor of pathology at München University, observed cellular damage in the artery wall before fatty plaques (cholesterol accumulation) were formed [15].

In the case of statins, ATP generation is impaired by their inhibition of CoQ<sub>10</sub> and of 'heme A' biosynthesis. Similar to the case of CHD and familial hypercholesterolemia (FIGURE 3), limited supply of ATP could be a major cause for heart muscle and coronary artery damage. The impact of statins on heart muscle will be

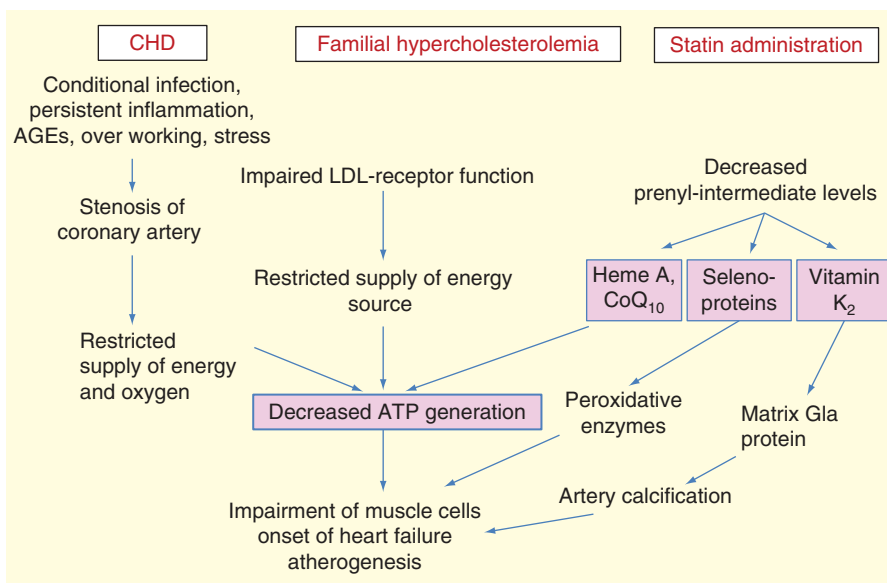
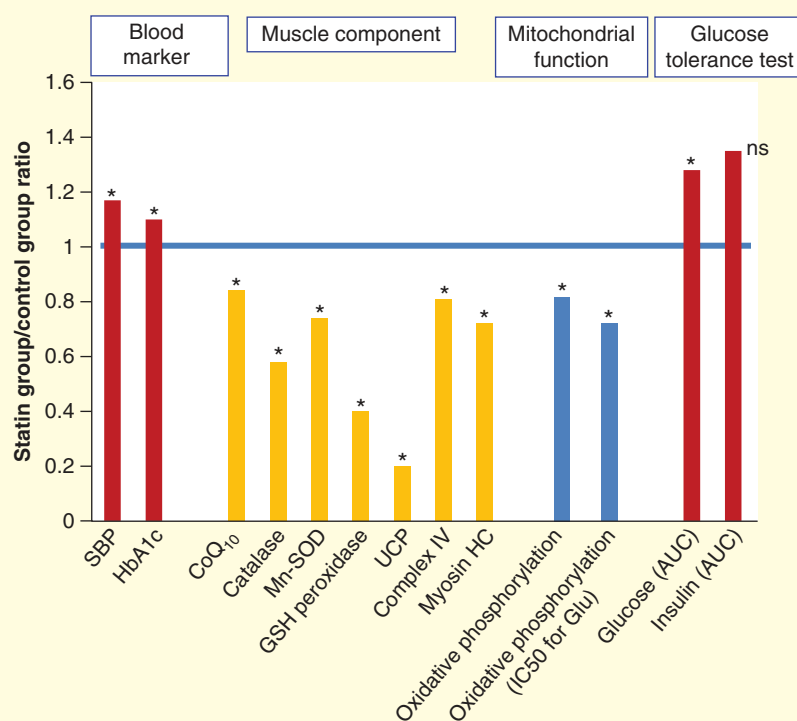


Figure 3. Presumed factors leading to atherosclerosis and heart failure. See text for detailed explanations. AGE: Advanced glycation end-products; CHD: Coronary heart disease; LDL: Low-density lipoprotein.



**Figure 4. Comparison of skeletal muscle properties in the leg between statin users and statin non-users.** As compared with non-users, statin users exhibited higher systolic blood pressure and elevated glycated hemoglobin (HbA1c) level. Levels of CoQ<sub>10</sub>, anti-peroxidative enzymes, uncoupling protein (UCP), Complex IV, and myosin were lower, oxidative phosphorylation ability was lower and glucose level in glucose tolerance test was higher [16].  
\*p < 0.05.  
AUC: Area under the curve; GSH: Glutathione; HC: Heavy chain; SBP: Systolic blood pressure; SOD: Superoxide dismutase.

discussed later in this study. A recent example of the effect of statins on skeletal muscle has been evaluated (FIGURE 4) [16].

### Statin administration & selenium deficiency cause heart failure through a common mechanism

Selenium is an essential trace element, and is incorporated into selenoproteins using tRNA<sup>sc</sup> that is specific for selenocysteinyl-tRNA<sup>sc</sup>. A minor base of the tRNA<sup>sc</sup>, isopentenyl adenine, is synthesized from a prenyl-intermediate, and its synthesis is inhibited by statins (FIGURE 5). In the Keshan province of China, dilated cardiomyopathy was common, which was later revealed to be due to selenium deficiency.

Selenoproteins include glutathione peroxidase, iodothyronine deiodinase, thioredoxin reductases and more than 10 other kinds of selenoproteins. When glutathione peroxidase synthesis is inhibited by statins, peroxidative stress is elevated, which is generally accepted as causative for atherogenesis, carcinogenesis and aging. Statins also lower the levels of anti-peroxidative enzymes, such as superoxide dismutase and catalase, by unknown mechanisms (FIGURE 4).

In accordance with the mechanisms described above, glutathione peroxidase activity in erythrocytes was shown clinically

to be inversely associated with CHD events and positively with event-free survival when patients with CHD were followed up for 5.4 years (FIGURE 6) [17].

Although not directly related to the topic of this article, selenoproteins are involved in several steps of glucose metabolism and insulin actions, providing a potential etiologic basis for statin-induced diabetes mellitus [18]. We presented an urgent proposal that statins are contraindicated in patients with diabetes mellitus [19].

### Statin inhibit vitamin K<sub>2</sub> synthesis & accelerate artery calcification

Vitamin K<sub>1</sub> (VK<sub>1</sub>), rich in vegetable oils and vegetables, has one double bond at the phytyl side chain. When ingested, its side chain is cleaved to form VK<sub>3</sub>, after which an isoprenyl residue with four double bonds is inserted into VK<sub>3</sub> to form VK<sub>2</sub> (menaquinone-4) (FIGURE 7). The enzymes synthesizing VK<sub>2</sub> from VK<sub>1</sub> are present in many tissues, including the brain, and statins inhibit the conversion of VK<sub>3</sub> to VK<sub>2</sub> by restricting the supply of the isoprenyl intermediate. VKs serve as cofactors for an enzyme catalyzing γ-carboxylation of glutamyl residues in proteins such as coagulation factors, osteocalcin and matrix Gla protein. VK<sub>2</sub> serves as the cofactor in the carboxylation of matrix Gla protein present in bone, blood vessel, lung, heart and kidney soft tissues. In

γ-carboxylated form, the matrix Gla protein retains capacity to bind calcium and protect blood vessels from calcification. Statins inhibit VK<sub>2</sub> formation, and thereby accelerate coronary artery calcification, an important marker of the progress of atherosclerosis.

When VKs are used as cofactors, they are reactivated in tissues. Therefore, VK deficiency is generally considered uncommon, except for the cases of long-term administration of warfarin as an anticoagulant. Chronic administration of warfarin is known to accelerate artery calcification [20]. Although not directly related to statins, dihydro-VK<sub>1</sub> produced during partial hydrogenation of vegetable oils is not converted to VK<sub>2</sub>, and its administration leads to tissue VK<sub>2</sub> deficiency [21], which might be associated with atherogenesis.

In a clinical study of diabetics, high-frequency statin users were shown to exhibit accelerated coronary artery calcification compared with low-frequency statin users [22]. Incredibly, the lead author chose to interpret this increase in coronary calcification in a positive light by speculating that: “statins may lower the lipid-rich core of atherosclerotic plaques, and may enhance the density of calcification as part of the healing process, potentially contributing to plaque stabilization and decreased cardiovascular disease events” [23].

Nakazato *et al.* evaluated coronary computed tomography angiography in 2413 patients on statins and 4260 patients not on statins. None of the subjects had any known coronary artery disease. **Statin use was associated with a significant increase in the prevalence and extent of coronary plaques containing calcium** [24].

In the case of end-stage kidney disease, the level of proteins induced via VK-absence (PIVKA-II) was elevated, the degree of carotid artery calcification was elevated, and coronary artery mortality and all-cause mortality were higher in those with lower matrix Gla protein levels [25]. Besides  $\gamma$ -carboxylation, VK<sub>2</sub> is known to regulate gene expressions through the SXR receptor, and statins adverse effects through this pathway are expected to be revealed more extensively in the near future.

Thus, statins can stimulate atherogenesis and heart failure through the suppression of prenyl-intermediates.

### Clinical trials showing or suggesting that statins increased atherosclerotic disease & heart failure

#### Japan Lipid Intervention Trial

This was the first large-scale intervention trial with a statin performed in Japan, and those with TC levels of  $\geq 220$  mg/dl were treated with a low-dose simvastatin for 6 years with no control group [26]. The horizontal axis in FIGURE 8 is plotted with TC levels after treatment. The mortality rates for cardiovascular disease, cerebrovascular disease, cancer and all causes were elevated along with decreasing TC levels from 220 mg/dl. The higher mortality rates in higher TC groups after treatment (FIGURE 8) could be due to the fact that this population included 12-fold greater proportion of familial hypercholesterolemia compared with that of general populations (0.2%). Although the authors of this report proposed to maintain TC levels below 240 mg/dl for the prevention of coronary events, we emphasized the risk of lowering TC levels below 220 mg/dl with statin [27].

#### A follow-up study on US veterans with statins

US veterans diagnosed with heart failure were treated with statins for 5 years and compared with those without statin

treatment (FIGURE 9) [28]. The authors of this report concluded that 'veterans who were not exposed to statin therapy at any time during the study period were 1.6-times more likely to suffer all-cause mortality'. However, a critical problem is

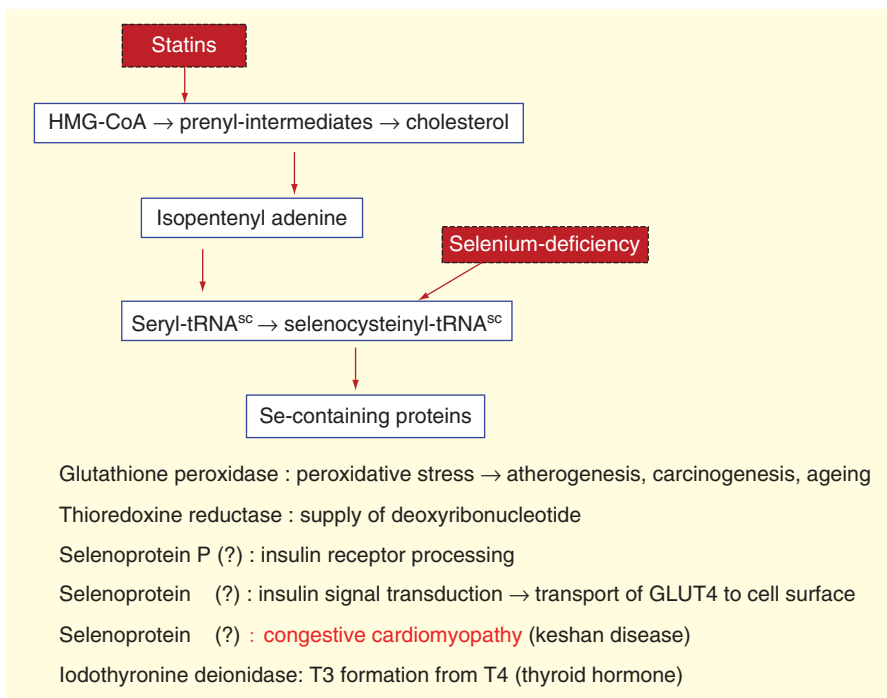


Figure 5. Statin administration and Selenium-deficiency cause heart failure through a common mechanism. See text for detailed explanations.

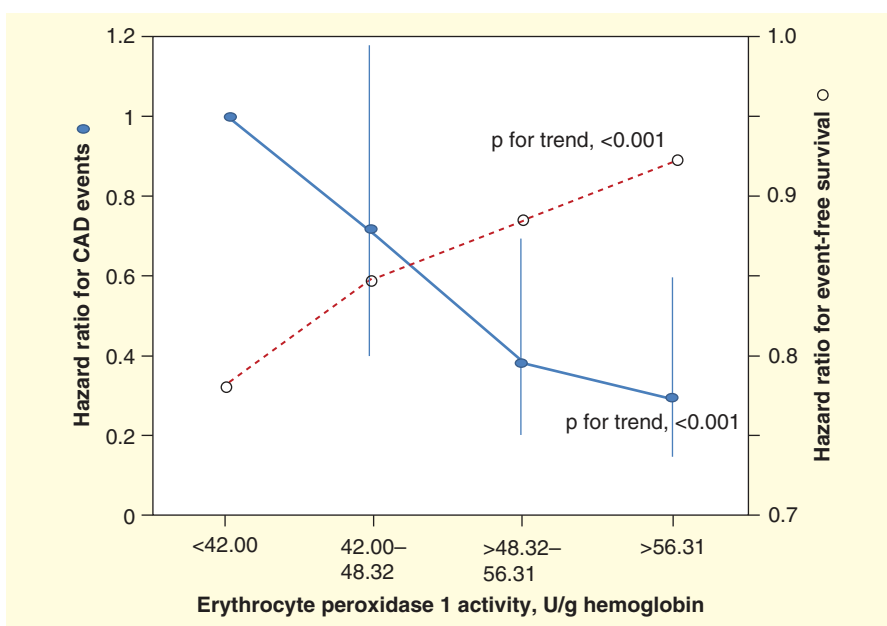
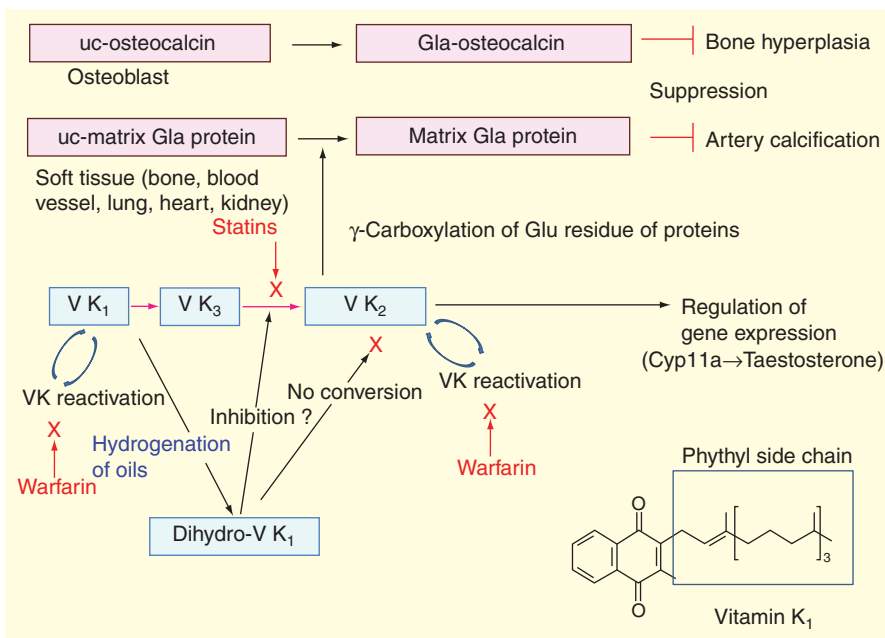


Figure 6. Relationship between red cell glutathione (GSH) peroxidase activity and coronary artery disease (CAD) events. Patients with CAD (n = 636) were grouped by erythrocyte GSH peroxidase activity, and coronary artery (CAD) events were followed up for 5.4 years [17]. Event-free survival was determined at 5.4 years of follow-up. Note the scale difference in the left and right ordinates.



**Figure 7. Statins accelerate artery calcification.** UC forms of osteocalcin and matrix Gla protein are carboxylated at their glutamyl residues by a vitamin K-dependent enzyme, and the carboxylated, activated form, for example, Matrix Gla protein binds calcium to prevent artery calcification. See text for detailed explanations. Gla: Carboxylated glutamyl residue (active form); Uc: Undercarboxylated (inactive form); VK: Vitamin K.

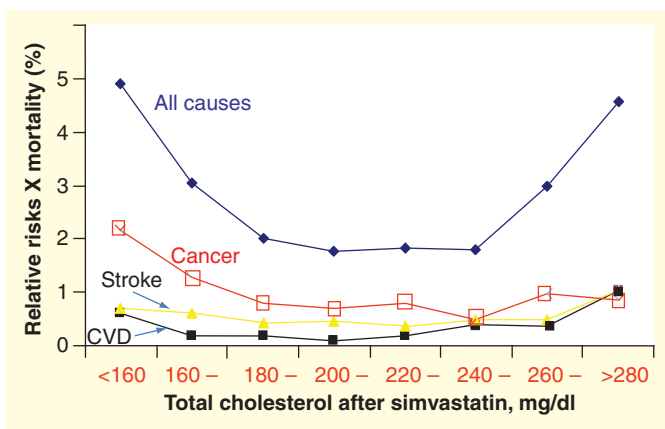
associated with the statistics comparing statin users and statin nonusers. When statin users and nonusers were grouped, the former group should have TC (or LDL-C) levels higher than those in statin nonuser group. Particularly in aged group,

inverse associations are often observed between TC levels and all-cause mortality [2]. Therefore, the statin user group should have characteristics leading to lower mortality at the start of the grouping, which is very likely to be reflected in the all-cause mortality shown in FIGURE 9. It is essential in this kind of cohort study to adjust background distribution of TC levels.

Incidence of diabetes mellitus was greater in the statin user group and appears to have increased along with the period of statin use (FIGURE 9), which is consistent with the observations that statins increase diabetes mellitus [18]. The pharmacological mechanisms of statins causing diabetes mellitus have been discussed in detail elsewhere [7].

More importantly, CHD mortality in the statin-user group was higher and appears to have increased along with the length of statin use when compared with the statin nonuser group (FIGURE 9). Among 72 years of age in average, no positive or even inverse association of CHD mortality with TC is expected [29], and the pro-

portion of familial hypercholesterolemia is expected to be much less than in general population. Hence, we interpret the results (FIGURE 9) that statins increased CHD mortality through mechanisms as described in previous sections of this article. At least, we can point out that these results are not consistent with those of clinical trials performed in 1990s, in which a relative risk reduction of approximately 30% in CHD events is claimed (FIGURE 1, left).



**Figure 8. Japan Lipid Intervention Trial with a low dose of simvastatin.** Those with total cholesterol (TC) levels of  $\geq 220$  mg/dl were treated with simvastatin for 6 years ( $n = 41,801$ , 35–70 years of age) [26]. The abscissa is plotted with TC values after treatment. In the ordinate plot, the risk values relative to that at 200 mg/dl were multiplied by the mortality rate for each cause of death at this basal point simply to visualize the weight of each cause of death. This population included 12-fold greater proportion of familial hypercholesterolemic subjects (see text for details). CVD: Cardiovascular disease.

**A large-scale follow-up study in Danes who were diagnosed with cancer**

Danes at  $\geq 40$  years of age and diagnosed with cancer were followed up for 15 years, and statin users and statin nonusers were compared [30]. In this large-scale, cohort study, the authors concluded that the cancer mortality and all-cause mortality were lower in the statin user group (FIGURE 10). However, the same criticism as described in the follow-up study on US veterans (FIGURE 9) applies to this conclusion, that is, background cholesterol levels need to be adjusted for between the groups of statin users and nonusers before making any conclusions.

Similar to the case in US veterans (FIGURE 9), the mortality from cardiovascular disease was higher in the statin user group and tended to increase dose dependently. We interpret the results to indicate that statins increased cardiovascular disease mortality in this population by the mechanisms described earlier in this article, or at least we can point out that these results are not consistent with those of clinical trials showing about a 30% decrease in CHD events (FIGURE 1, left).

## Clinical impact of statin-induced depletion & supplementation of CoQ<sub>10</sub>

### Statin induced CoQ<sub>10</sub> depletion & muscle damage

Statin adverse effects on skeletal muscle are the most commonly reported statin side effects.

Skeletal muscle weakness, muscle pain and skeletal muscle cell death with elevated creatinine kinase levels are a well-recognized phenomenon among prescribing physicians and patients alike. Statins have been demonstrated to decrease the concentration of mitochondria in muscle, oxidative phosphorylation capacity and skeletal muscle mitochondrial DNA levels [16,31,32]. In view of this obvious skeletal muscle toxicity, it would be naïve to assume that statins would not likewise negatively impact the much harder working heart muscle cells, which have exceedingly high ATP requirements. Indeed, in animal data, statins have been shown to increase mortality in cardiomyopathic hamsters [33] and to increase ischemia/reperfusion heart muscle damage in dogs [34–36].

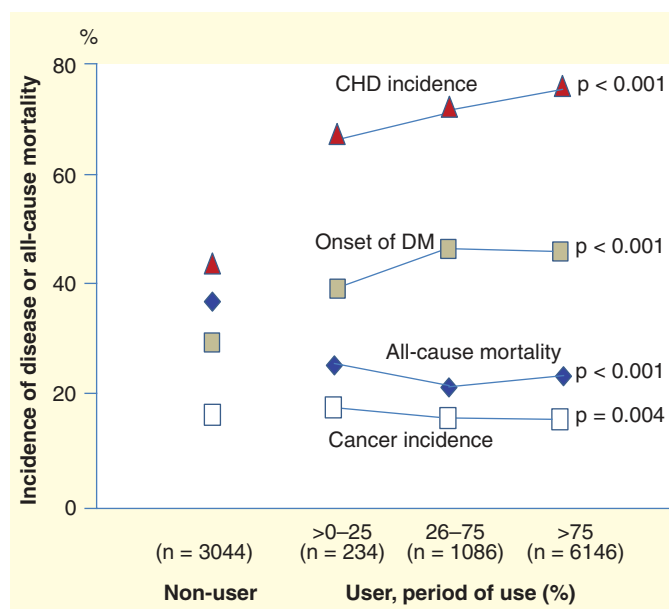
### Evidence for a causative role for statins in human heart failure

The first reported cases of statin-related heart failure were published in 1990 [37]. Five previously stable cardiomyopathic patients had a dramatic deterioration in myocardial function measurements and in clinical status shortly after beginning lovastatin. These patients returned to prestatin condition after stopping their statin therapy and doubling their supplemental CoQ<sub>10</sub> from 100 to 200 mg/day.

In 2004, it was demonstrated that diastolic dysfunction developed in 10 of 14 healthy hyperlipidemic subjects after 3–6 months of atorvastatin at 20 mg/day [38]. Impairment in the ATP-dependent process of diastole is an early finding in congestive heart failure. In this study, the early diastolic dysfunction was asymptomatic and reversed to normal after 3 months of supplemental CoQ<sub>10</sub> at 300 mg/day, while the patients continued to take their statin therapy. In contrast to this mild asymptomatic impairment in heart muscle function, in an ongoing study, patients who have been on statin treatment for an average of 6 years presented with overt and often permanent congestive heart failure.

In 2005, 50 consecutive patients presenting with severe statin side effects were followed up for a mean of 28 months [39]. In addition to symptoms of muscle pain and weakness, fatigue, dyspnea, peripheral neuropathy and memory loss, roughly one-fourth of these patients had evidence of congestive heart failure at the time of presentation. All 50 patients had their statin drug discontinued due to side effects and all were supplemented with an average of 240 mg of CoQ<sub>10</sub> per day and followed up for 2 years. The patients' chief complaints improved dramatically and 50% of those with heart failure showed significant improvement in heart muscle function. There were no adverse effects from statin drug discontinuation with no myocardial infarctions or strokes and no side effects from CoQ<sub>10</sub> supplementation.

In 2008, a study in 29 patients with coronary artery disease found a significant increase in brain natriuretic peptide secondary to atorvastatin-induced plasma CoQ<sub>10</sub> depletion [40] after a



**Figure 9. Effect of statins on the incidence of disease and all-cause mortality in US veterans.**

Those diagnosed with heart failure (n = 10,510, average age of 72 years, mainly male) were treated with statins for 5 years, and were compared with those without statin treatment (n = 3044) [28]. See text for our critical interpretations.

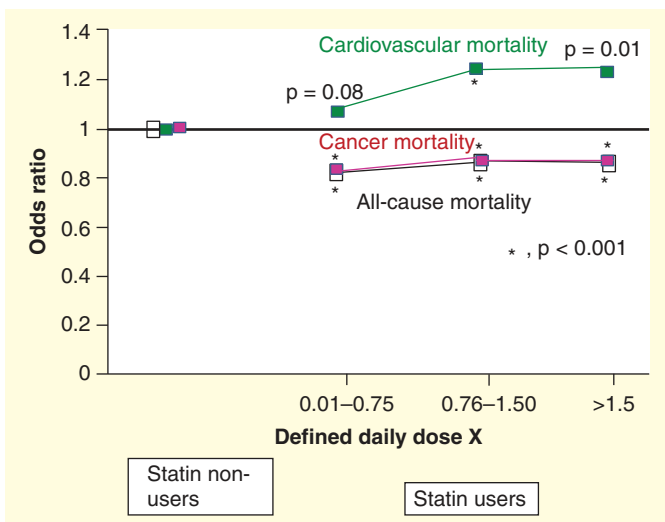
CHD: Coronary heart disease; DM: Diabetes mellitus.

3-month treatment with atorvastatin. Brain natriuretic peptide is a well-known marker for congestive heart failure.

### Statin cardiomyopathy

Statin cardiomyopathy can be defined as an impairment in heart muscle function consequent to statin drug therapy and not explainable by any other underlying pathophysiology. Our current experience with statin cardiomyopathy indicates that it is not at all uncommon, with 130 cases identified during a 4-year period of time presenting to a solo cardiology practice. Although the impairment in heart muscle function, secondary to statin therapy, appears to be common after long-term (average 6 years) statin drug therapy, it is clear that it is not being recognized. In the words of Robertson Davies, 'The eyes see only what the mind is prepared to comprehend'. Physicians in general are not aware that statins can cause heart failure and are clearly not recognizing it. Although vast majority of physicians readily recognize and diagnose heart failure in patients taking statins, the heart failure is almost always attributed to other non-statin-related factors, such as aging, hypertension and coronary artery disease. Furthermore, it is difficult to recognize any adverse drug effect when it is delayed by several years.

The mechanism for the impairment in heart muscle function appears to be related to impaired mitochondrial function, which in turn is related to statin depletion of CoQ<sub>10</sub> [41], selenoproteins [42–44] and 'heme A' [45], all required for normal mitochondrial function. Statin-induced impairment in heart muscle function appears to be permanent, and even though



**Figure 10. Effect of statin dose on mortality from cancer, cardiovascular disease and all cause - A cohort study.** Danes at  $\geq 40$  years of age were followed for 15 years (mean of 2.6 years) after diagnosis with cancer in National Survey [30]. Although the values for statin non-users were included in the statistics of the original report, we did not connect the values from statin-user and nonuser groups in this figure because possible difference in the background cholesterol levels of the two groups had not been adjusted. \* $p < 0.001$  compared with statin nonusers in the original report.

patients may clinically benefit from discontinuation of the statin along with supplemental CoQ<sub>10</sub>, we believe that many years of statin drug therapy result in the gradual accumulation of mitochondrial DNA damage. A prolonged decrease in mitochondrial CoQ<sub>10</sub> would diminish the ability to protect mitochondrial DNA from free radical damage. After a critical percentage of mitochondrial DNA is mutated, offspring mitochondria will progressively lose their efficiency to produce ATP and simultaneously can generate more free radicals and result in a self-perpetuating vicious cycle. The negative consequences of statin-induced increase in coronary artery disease, coupled with a direct statin toxicity upon the myocardium, can be expected to be additive with enormous clinical implications. With more than one million heart failure hospitalizations every year in the USA [46], the rapidly increasing prevalence of congestive heart failure is now described as an epidemic and it is likely that statin drug therapy is a major contributing factor.

### Statins' other pleiotropic effects on heart disease

Persistent inflammation is considered a major risk factor for atherosclerosis and heart failure. Statins are known to suppress the prenylation of Rho protein and its downstream inflammatory cytokine production through NF- $\kappa$ B. Contrarily, statins decrease LDL levels leading to increased entry of lipopolysaccharide into cells and increased inflammatory cytokine production. Thus, the effect of statins on inflammation is likely to vary depending on the pathophysiological conditions.

Dolichol derived from prenyl-intermediates is essential for glycoprotein and glycolipid biosynthesis, and its suppression by

statins would produce modified glycoproteins, for example, unglycosylated insulin receptor. Although the relationship between the statin suppression of dolichol synthesis and heart disease is yet to be clarified in detail, inborn mutation in dolichol kinase has been shown to be associated with dilated cardiomyopathy [47,48]. A vasodilative molecule, nitric oxide (NO), is synthesized in endothelial cells, and statins inhibit the activation (prenylation) of Rho protein to up-regulate endothelial NO synthase and increase NO production [49]. On the other hand, statins inhibit inducible NO synthase gene expression in macrophages [50]. The impact of long-term endothelial NO synthase activation and inducible NO synthase inhibition on heart disease is not clear.

On the basis of these and other statin pleiotropic effects, statins seem to act as immune suppressive agents and may have beneficial effects on those who have excessive and/or life-threatening immune-inflammatory reactions, such as in transplantations [51]. However, immune suppression may be harmful in those who have no immune/inflammatory disease.

Many observational studies of statins on heart failure, retrospective or prospective studies, have been performed, some of which reported beneficial effects of statins on heart failure but others did not, as reviewed by Bonsu *et al.* [52]. Intervention trials generally provide more reliable conclusions compared with observational studies, and two large-scale, randomized controlled studies, GISSI-HF [53] and CORONA [54], reported no significant beneficial effects of statins in heart failure. In clinical fields, complex aspects of the etiology of heart failure (ischemic, idiopathic and inflammatory causes) should be taken into account rather than high cholesterol levels.

### Expert commentary

Few cardiology specialists around the world have accepted that there is no clinical evidence for 'the lower, the better hypothesis'. The majority of clinicians still appear to accept the results of meta-analysis of reports, including those published before 2004 when new penal regulations on the clinical trials came into effect in the EU, that is, statins are effective in lowering LDL-C levels and thereby preventing CHD incidence. Our group and others [2-4] only adopt the conclusions of papers reported after 2004 by scientists essentially free of conflict of interest that statins are ineffective in preventing CHD. Severe and often irreversible adverse effects of statins and their pharmacological mechanisms have been discussed in this study, indicating that the applicability of statins should be severely restricted. Clinicians should not rely on drug information provided by industry-funded trials, or should they trust study abstracts of clinical publications, which frequently do not provide the full picture and present many deceptions. Nondrug company-funded sources of information are likely to be much more useful and less biased.

### Five-year view

Pharmacological evidence and clinical trial results support the interpretation that statins stimulate atherogenesis by suppressing



vitamin K<sub>2</sub> synthesis and thereby enhancing artery calcification. Statins cause heart failure by depleting the myocardium of CoQ<sub>10</sub>, 'heme A' and selenoproteins, thereby impairing mitochondrial ATP production. In summary, statins are not only ineffective in preventing CHD events but instead are capable of increasing CHD and heart failure.

Physicians who are involved in prescribing cholesterol-lowering medications cannot ignore the moral responsibility of 'informed consent'. Patients must be informed of all statin adverse effects, including the ability to cause CHD and heart failure, onset of diabetes mellitus, carcinogenicity, teratogenicity and central and peripheral nervous disorders besides the well-known rhabdomyolysis and hepatic injury. Most of these adverse effects of statins become apparent after 6 or more years

of statin therapy. Chronic administration could ultimately lead to these statin adverse effects as pharmaceutical and biochemical research has now demonstrated.

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### Key issues

- Pharmacological and biochemical studies reveal the mechanisms of statins to stimulate atherogenesis and heart failure, and some clinical studies support this interpretation.
- Statins are contraindicated in diabetics as statin administration did not prevent diabetics from CHD (ASPEN [55] and 4D study [56]), and statins worsen diabetic control [7]. Detailed mechanism of statin effects in diabetes has been published [7,19].
- 'Informed consent' of statins should include increased coronary artery disease, heart failure, carcinogenicity, teratogenicity and central and peripheral nervous disorders besides the known adverse effects.
- There have been several clinical papers published in which the abstracts are not consistent with the data in the text.

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