Statins Stimulate Atherosclerosis and Heart Failure: Pharmacological Mechanisms

Expert Review of Clinical Pharmacology

March 2015; Vol. 8; No. 2; pp. 189–199

Harumi Okuyama, Peter H Langsjoen, Tomohito Hamazaki, Yoichi Ogushi, Rokuro Hama, Tetsuyuki Kobayashi, Hajime Uchino

BACKGROUND FROM DAN MURPHY:

The "*cholesterol hypothesis*" essentially holds that the:

- Higher the levels of total cholesterol the higher the risk of heart disease
- Higher the level of LDL cholesterol the higher the risk of heart disease
- Lower the levels of HDL cholesterol, the higher the risk of heart disease

In 2007, the lead author of this article wrote a book titled:
Prevention of Coronary Heart Disease:
From the Cholesterol Hypothesis to Omega-6/Omega-3 Balance
This book concludes that:

- "High blood cholesterol level is not a major causative factor for atherosclerosis"
- "High cholesterol is a predictor of low mortality rates from cancer and all causes."
- High dietary omega-6/omega-3 ratios "is the major risk factor for coronary heart disease."

Congestive Heart Failure occurs when heart cells cannot make adequate levels of ATP. ATP production is dependent upon levels of CoQ10. Statin Drugs impair the synthesis of CoQ10, and therefore reduce production of ATP and therefore increase the risk of Congestive Heart Failure.

Vitamin K1 is abundant in non-hydrogenated vegetable oil and in vegetables. Vitamin K2 prevents the depositing of calcium into arteries, joints, and kidneys. Without adequate levels of vitamin K2 atherosclerosis increases. Statin Drugs inhibit the conversion of Vitamin K1 into vitamin K2, and thereby increase the incidence of atherosclerosis.

KEY POINTS FROM THIS ARTICLE:

1) "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 Q10 and 'heme A', and thereby ATP generation."

2) Vitamin K2 protects arteries from calcification. Statins inhibit the synthesis of vitamin K2.

3) Mitochondrial DNA is more susceptible than nuclear DNA to oxidative stress injury and free radicle damage. The most important protector of mitochondrial DNA from oxidative stress is glutathione peroxidase. Glutathione peroxidase is a protein that requires the mineral selenium for function. Glutathione peroxidase is known as a "selenoprotein." Statins inhibit the biosynthesis of the selenoprotein glutathione peroxidase. "An impairment of selenoprotein biosynthesis may be a factor in congestive heart failure."

4) "The epidemic of heart failure and atherosclerosis that plagues the modern world may paradoxically be aggravated by the pervasive use of statin drugs."

5) "We propose that current statin treatment guidelines be critically reevaluated." "Current statin therapy should be critically and urgently reevaluated."

6) The "good and bad cholesterol hypothesis" is based on the simplified and flawed interpretations that LDL carries triglycerides and cholesterol to peripheral tissues, whereas HDL reverse-transports cholesterol to the liver to excrete excess cholesterol to feces, mostly as bile acids. The flaw is now understood to exist because HDL also transports cholesterol to LDL.

7) Statins drugs are effective in lowering LDL cholesterol "but were essentially ineffective in preventing coronary heart disease."

8) Statins were introduced to clinical medicine in 1987. Initial studies (1990s) showed that statins were effective in lowering LDL cholesterol and also in preventing coronary heart disease. "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."

9) 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 cholesterol but no significant beneficial effects were observed for the prevention of coronary heart disease. Consequently, scientists and physicians who continue to claim that statins are effective in preventing coronary heart disease are mistaken.

10) These authors "support the pharmacological interpretations that statins stimulate the development of atherosclerosis and heart failure."

11) The mitochondria subcellular organelles produce stored energy ATP with the essential enzyme coenzyme Q10 (CoQ10). "Statins inhibit CoQ10 biosynthesis and thereby ATP generation." "Statins are mitochondrion toxic."

12) ATP is essential for normal heart muscle function and other activities in cell life. "Statins are mitochondrial toxins making all cells ATP depleted." "Statins are general cell toxins."

13) "Cholesterol is a major component of cell membranes, functioning to maintain their integrity, which is likely to be affected by statins."

14) The reduced form of CoQ10 (ubiquinol) is a clinically relevant antioxidant, especially in the mitochondria where it "protects mitochondrial DNA from damage."

15) "It is well known that mitochondrial DNA is much more vulnerable to oxidative damage than nuclear DNA."

16) "In the case of statins, ATP generation is impaired by their inhibition of CoQ10 biosynthesis. "Limited supply of ATP could be a major cause for heart muscle and coronary artery damage."

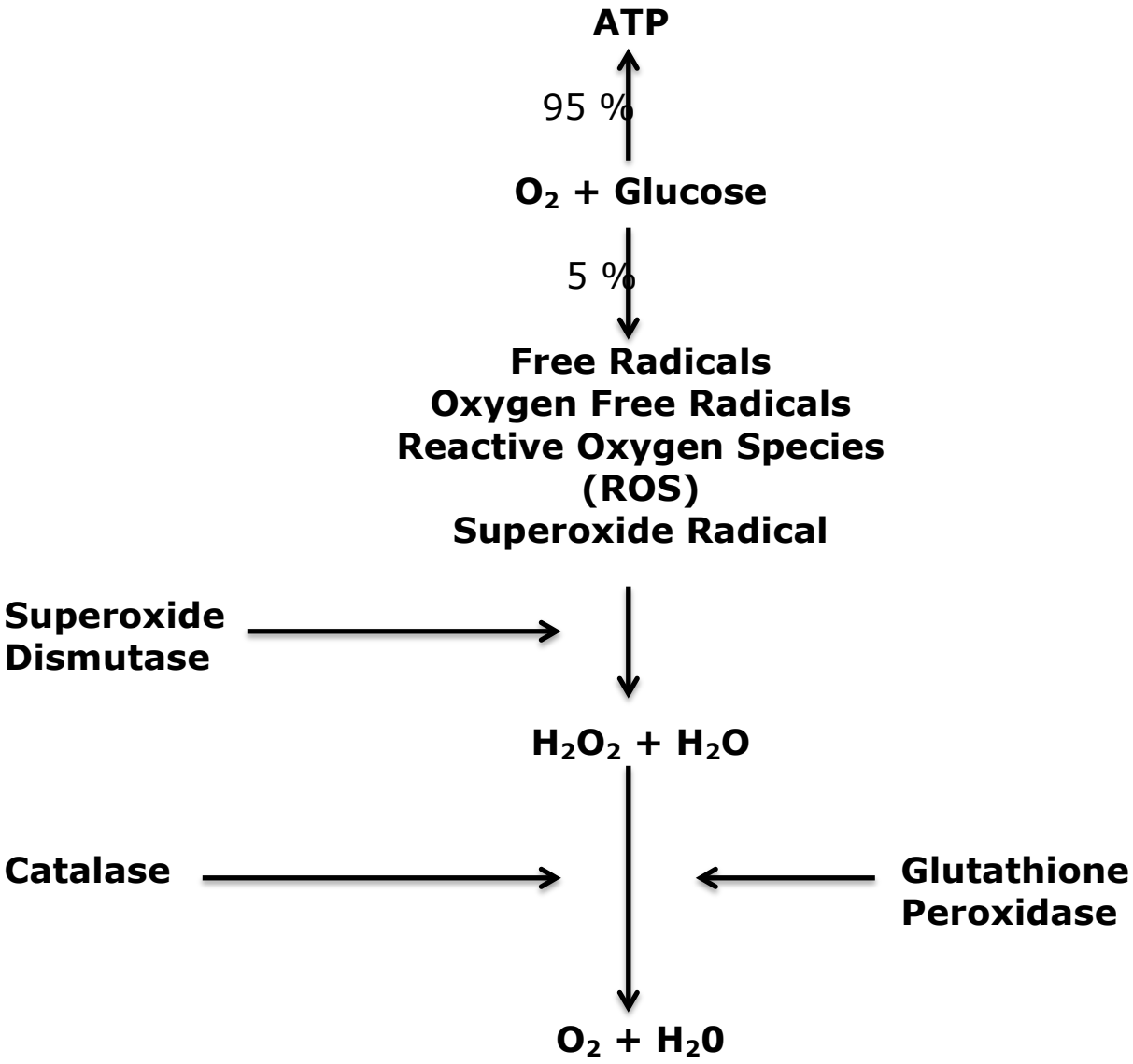
17) As compared to non-users, statin users exhibit:
HIGHER
- Systolic blood pressure
- Elevated glycated hemoglobin (HbA1c) level
- Glucose levels

LOWER
- CoQ10
- Glutathione peroxidase
- Complex IV electron transport protein [key in low-level laser therapy]

18) "Statin administration & selenium deficiency cause heart failure through a common mechanism."

19) Selenium is an essential trace element and is incorporated into selenoproteins. Selenoproteins include glutathione peroxidase. "When glutathione peroxidase synthesis is inhibited by statins, peroxidative stress is elevated, which is generally accepted as causative for atherogenesis, carcinogenesis and aging." **[Very Important]**

20) Statins also lower the levels of antiperoxidative enzymes superoxide dismutase and catalase.



21) Glutathione peroxidase activity is inversely associated with coronary heart disease.

22) Selenoproteins are also "involved in several steps of glucose metabolism and insulin actions, providing a potential etiologic basis for statin-induced diabetes mellitus." "We presented an urgent proposal that statins are contraindicated in patients with diabetes mellitus."

23) "Statins inhibit vitamin K2 synthesis and accelerate artery calcification."

- Vitamin K1 is rich in non-hydrogenated vegetable oils and vegetables.

- The enzymes synthesizing vitamin K2 from vitamin K1 are present in many tissues, including the brain, and statins inhibit the conversion of VK1 to VK2.

- "Statins inhibit vitamin K2 formation, and thereby accelerate coronary artery calcification, an important marker of the progress of atherosclerosis."

24) The authors cite a study indicating "high-frequency statin users were shown to exhibit accelerated coronary artery calcification compared with low-frequency statin users."

25) In a study involving 6,673 subjects, "statin use was associated with a significant increase in the prevalence and extent of coronary plaques containing calcium."

26) Statins can stimulate atherogenesis and heart failure.

27) The authors cite a 2013 study questioning *why the goals of cholesterol levels are set so low?*, noting:

- The risk of death for all causes was lowest at total cholesterol levels at 240 mg/dl.
- When total cholesterol levels went below 180 mg/dl, all causes of death rose significantly and essentially linearly as total cholesterol levels dropped to less than 160 mg/dl. [the lower the total cholesterol, the higher the risk of death from all causes]

- The death rate for cancer was also lowest at 240 mg/dl, and *increased* as total cholesterol levels went lower.

- Strangely, there was very little change in risk of death from *stroke* and/or *cardiovascular disease* when total cholesterol was between 160 mg/dl to 260 mg/dl.

- These authors question the value of lowering total cholesterol to below 240 mg/dl.

28) These authors cite studies that support that the incidence of diabetes mellitus is greater in the statin user group and it appears that statins increase diabetes mellitus.

29) Coronary heart disease mortality in the statin-user group was higher and increases with the length of statin use when compared with the statin nonuser group. These authors interpret the results that statins increased coronary heart disease mortality.

30) These authors note that the statin clinical trials performed in the 1990s that show a relative risk reduction of approximately 30% in coronary heart disease are erroneous.

31) Statin adverse effects on skeletal muscle (damage) are the most commonly reported statin side effects, and include skeletal muscle weakness, muscle pain and skeletal muscle cell death with elevated creatinine kinase levels.
[Statin drug induced muscle damage may be the symptoms that bring such patients to the chiropractic office]

32) Statins decrease the concentration of mitochondria in muscle. "In view of this obvious skeletal muscle toxicity, it would be naive to assume that statins would not likewise negatively impact the much harder working heart muscle cells, which have exceedingly high ATP requirements." In animals, statins increase cardiomyopathic mortality.

33) There is evidence for a causative role for statins in human heart failure:
- The first reported cases of statin-related heart failure was in 1990.
- Statin users can experience dramatic deterioration in myocardial function and clinical status shortly after beginning statins.
- 200 mg/day supplementation with CoQ10 can stabilize these patients.

- Patients with statin induced diastolic dysfunction (an early finding in congestive heart failure), could reverse their pathology to normal after 3 months of supplemental CoQ10 at 300 mg/day.

- "Patients who have been on statin treatment for an average of 6 years presented with overt and often permanent congestive heart failure."

34) Statin adverse effects include:
- Muscle pain and weakness
- Fatigue
- Dyspnea
- Peripheral neuropathy
- Memory loss
- Congestive heart failure

These symptoms can be dramatically improved with statin drug discontinuation and supplementation with 240 mg of CoQ10 per day (but it may take 2 years).

35) "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."

- "Physicians in general are not aware that statins can cause heart failure and are clearly not recognizing it."

- "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 CoQ10 [41], selenoproteins and 'heme A', all required for normal mitochondrial function."

- "Statin-induced impairment in heart muscle function appears to be permanent." Yet, discontinuing statin drugs and supplementation with CoQ10 will clinically benefit these patients.

36) "Prolonged decrease in mitochondrial CoQ10 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."

37) "With more than one million heart failure hospitalizations every year in the USA, 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."

38) "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. However, immune suppression may be harmful in those who have no immune/inflammatory disease."

39) "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."

40) Evidence since 2004 indicates that statins are ineffective in preventing coronary heart disease. The severe and often irreversible adverse effects of statins indicate that their use "should be severely restricted."

41) "Clinicians should not rely on drug information provided by industry-funded trials or should trust study abstracts of clinical publications, which frequently do not provide the full picture and present many deceptions."

42) CONCLUSIONS

- "Statins stimulate atherogenesis by suppressing vitamin K2 synthesis and thereby enhancing artery calcification."

- "Statins cause heart failure by depleting the myocardium of CoQ10, 'heme A' and selenoproteins, thereby impairing mitochondrial ATP production."

- "Statins are not only ineffective in preventing coronary heart disease events but instead are capable of increasing coronary heart disease and heart failure."

- "Physicians who are involved in prescribing cholesterol lowering medications cannot ignore the moral responsibility of 'informed consent'," including their ability to cause:

•• Coronary disease and heart failure
•• Onset of diabetes mellitus
•• Carcinogenicity
•• Teratogenicity
•• Central and peripheral nervous disorders
•• Rhabdomyolysis
•• Hepatic injury

"Most of these adverse effects of statins become apparent after 6 or more years of statin therapy."

COMMENTS FROM DAN MURPHY
I believe that all patients on statin drugs should discuss this article with their physician who put them on the statin drug. Apparently, a critical determinant is whether they relied on studies that were published *before* or *after* 2004.

This is the 9th article we have reviewed pertaining to statin drugs:

Article Review 25-09:
The case for statins: has it really been made?
Journal of the Royal Society of Medicine; 2004

Article Review 26-09:
Do Cholesterol Drugs Do Any Good? Research suggests that, except among high-risk heart patients, the benefits of statins such as Lipitor are overstated
BusinessWeek; 2008

Article Review 07-10:
Carcinogenicity of Lipid-lowering Drugs
Journal of the American Medical Association; 1996

Article Review 22-11:
Statins and All-Cause Mortality in High-Risk Primary Prevention
Archives of Internal Medicine; 2010

Article Review 29-11:
Cholesterol Lowering, Cardiovascular Diseases
Archives of Internal Medicine; 2010

Article Review 39-12:
Should we lower cholesterol as much as possible?
British Medical Journal; 2006

Article Review 31-13:
Statin Use and Risk of Diabetes Mellitus in Postmenopausal Women
Archives of Intern Medicine; 2012

Article Review 06-13:
Statin Use and Musculoskeletal Pain Among Adults With and Without Arthritis
The American Journal of Medicine; 2012

Article Review 30-13:
Effects of Statins on Energy and Fatigue With Exertion
Archives of Internal Medicine; 2012