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EDITORIAL

Statins; the Good, the Bad and the Ugly!

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The indications for statin use in the last 20 years have expanded from secondary prevention in patients after acute myocardial infarction (MI) to primary prevention among those at high predicted cardiovascular risk (1).

The National Cholesterol Education Program's Adult Treatment Program (ATP), first published in 1988, recommended using the LDL cholesterol level as the marker to start statin treatment as well as for reaching therapeutic target goals (2). In 2002, the NCEP III guidelines, recommended that those patients who have documented coronary disease should have their LDL cholesterol lowered to less than 100mg/dL (3). The current ACC/AHA-guidelines provide a Class I, Level of Evidence: A-recommendation for initiating statin therapy pre-discharge regardless of the baseline LDL level (3, 4). Furthermore, the guidelines also provide a Class I, Level of Evidence: A-recommendation for LDL target of <100mg/dl and Class IIa, Level of Evidence: A for LDL target of <70mg/dl in ACS (4, 5).

Several data indicates that angiographic (6), intracoronary ultrasound (7), carotid intima-media thickness (8) and magnetic resonance imaging (9) studies have generally shown that lowering LDL to very low levels arrests or even reverses the development of atherosclerosis.

Mechanism of ACS

Acute coronary syndrome is initiated by intra-arterial plaque disruption with subsequent thrombosis in place. This was noticed to occur in particular atherosclerotic plaques which may have any size.

The term "vulnerable" plaques, which is triggered by regular stressful factors as vasoconstrictive and prothrombotic forces causing plaque disruption and thrombosis was first described by Muller JE, in 1994 (10). These vulnerable plaques may not be the responsible for critical arterial narrowing but are identified histologically by their large lipid content, a thin cap, and an inflammatory infiltrate (11, 12). In many cases, the disruption produces only a minor mural thrombosis, which then organizes without causing ischemia or producing symptoms. Because atherosclerosis is a systemic disease and systemic markers of inflammation predict coronary events (13), patients generally experience difficulty at only a single spot in an artery. Recent data on the presence of multiple disrupted plaques in some patients with an acute coronary syndrome suggest that in these cases, vulnerability was related to multifocal vulnerable plaques (14).

Other Good Effects of Statins

The non-lipid lowering benefits have been termed pleiotropic effects. These effects include improving endothelial dysfunction, enhancing atherosclerotic plaque stability, increasing NO bioavailability, decreasing oxidative stress, blunting the inflammatory response, and inhibiting thrombogenesis. Further, the results of several meta-analysis suggests that statin therapy leads to a 26% reduction in the risk of mortality in HF patients (15). The reduction in mortality risk for statins is similar to that reported in clinical trials with angiotensin-converting enzyme inhibitors (18% to 44%) and beta-blocker drugs (23% to 35%) (16-18). The magnitude of benefit of statins in this meta-analysis was similar in patients with ischemic and non-ischemic cardiomyopathy.

It was proved indirectly that it decreases the risk of incidence or recurrence of AF in patients in sinus rhythm with a history of previous AF or undergoing cardiac surgery or after acute coronary syndrome (19). It was also reported in the DEFINITE study, that the use of statins was associated with a 78% reduction in mortality. This reduction was caused, in part, by a reduction in arrhythmic sudden death (20). Statins are also the most effective at decreasing the risk of total stroke incidences. Their benefit is proportional to the percent reduction of total cholesterol and low-density lipoprotein cholesterol (21, 22). However, this beneficial effect is partly lost by an increased risk of hemorrhagic stroke (23).

The non-cardiovascular benefits was seen in reports advising statins for preventing Alzheimer disease, slowing progression of chronic kidney disease, treating osteoporosis and rheumatic diseases, preventing type 2 diabetes, preventing prostate and colon cancer, and even reducing mortality in pneumonia and sepsis (24, 25). Moreover, it was proved that the regular use of statins increase bone

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Abbreviations and Acronyms	
ATP	: Adult Treatment Program
NCEP	: National Cholesterol Education Program
NO	: Nitric Oxide
DEFINITE	: DEFIbrillators in Non-Ischemic cardiomyopathy Treatment Evaluation
TNT	: Treating to New Targets
IDEAL	: Incremental Decrease in End Points Through Aggressive Lipid-Lowering
PROVE IT–TIMI	: Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction
A-to-Z	: Aggrastat-to-Zocor
ACS	: Acute Coronary Syndrome
OTC	: Over The Counter
PRIMO	: Paricalcitol in Renal Failure Induced Cardiac Morbidity in Chronic Kidney Disease
ALT	: Alanine aminotransferase
PPP	: Prospective Pravastatin Pooling
NAFLD	: Non-Alcoholic Fatty Degeneration
HCV	: Hepatitis C Viral infection
WOSCOPS	: West of Scotland Coronary Prevention Study
JUPITER	: Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

mineral density and reduce fracture risk by about 60% (26, 27). In some studies, benefits have occurred that appear to be independent of lipid levels.

Statins are good; why not to double or triple the dose?

The theory of "the lower the better". The concept of lowering LDL-C as much as we can by statins, came from the fact that human race has the highest cholesterol levels among different animal species (28) (Figure 1) and the idea that our race should be more vegetarian than predominantly carnivore is much taking consideration in our modern civilization.

A growing literature supports additional clinical benefit with high-dose statin therapy administered early in the post-acute coronary syndrome (ACS) period (29-32).

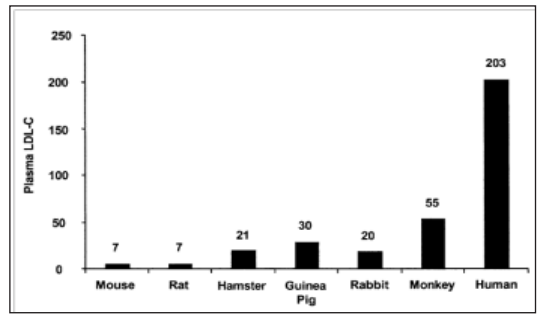

Figure 1: Cholesterol levels by species. Typical values of plasma low density lipoprotein cholesterol (LDL-C) in several species, includinghuman. Adapted from reference "28".

The results of four important trials were published: the TNT and the IDEAL trials involved patients with stable cardiovascular disease, and the PROVE IT–TIMI-22 and A-to-Z trials, involved patients with acute coronary syndromes. A total of 27,548 patients were enrolled in the 4 large trials. The combined analysis yielded a significant 16% odds reduction in coronary death or myocardial infarction ($p < 0.00001$), as well as a significant 16% odds reduction of coronary death or any cardiovascular event ($p < 0.00001$). No difference was observed in total or non-cardiovascular mortality, but a trend toward decreased cardiovascular mortality (odds reduction 12%, $p < 0.054$) was observed (30, 33, 34).

However, another meta-analysis of 12 trials comparing early statin therapy with placebo or usual care demonstrated that initiation of statin therapy within 14 days following onset of ACS did not reduce death, MI, or stroke at 4 months of follow-up (34). Additional meta-analyses of randomized controlled trials demonstrate that early initiation of statins after ACS improves cardiovascular outcomes, although these benefits take 6 months for morbid events (35) and 24 months for fatal events (30, 36) to become evident.

Analyses of major randomized controlled trials of intensive versus moderate LDL lowering failed to reveal a benefit in all-cause or cardiovascular mortality (37-40). Although intensive-dose statin therapy was associated with a reduced risk for important cardiovascular events, it was also associated with an increased risk for statin-induced adverse events. It was also noticed in patients receiving higher doses that treatment intolerance and withdrawal rates is much higher than those reported in the clinical trials (40).

Are Statins Bad or Ugly?

In a large prospective open cohort study on more than 2 million patients in England and Wales using statins, to study their adverse effects in relation to the type, dose,

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and duration. About 71% were prescribed simvastatin, 22% atorvastatin, 4% pravastatin, 2% rosuvastatin, and 1% fluvastatin. Statins were associated with moderately increased risks of moderate or serious liver dysfunction, acute renal failure, moderate or serious myopathy, and cataract. Individual statins were not significantly associated with risk of Parkinson's disease, rheumatoid arthritis, venous thromboembolism, dementia, osteoporotic fracture, gastric cancer, colon cancer, lung cancer, melanoma, renal cancer, breast cancer, or prostate cancer (41).

The low incidence of adverse effects has been suggested that statins should be provided over the counter (OTC) in pharmacies without the need for a prescription to make them accessible to a much wider group of people. This approach has already been adopted in the United Kingdom (42). We should also notice that the allowed statins OTC are of the small doses tablets (simvastatin 10mg/d).

1- Statins and Skeletal Muscles

Fernandez et al. (43), proposed the definition of statin induced myopathy according to the findings described in large meta-analysis as; (1) **Myalgia**-muscle weakness, soreness, tenderness, stiffness, cramping, or aching, either at rest or with exertion, without any elevation in CK. (2) **Myositis**-elevated CK with or without muscle symptoms. The "-itis" suffix is unfortunate since myositis does not correspond to inflammation on biopsy. (3) **Rhabdomyolysis**-muscle symptoms with a CK level 10 times the upper limit of normal or higher. Evidence of renal dysfunction is not required for the diagnosis.

In randomized clinical trials, myalgia was reported in 1% to 5% of patients in the statin groups and placebo groups alike (44), whereas clinical practice would suggest it is more common. Most of the clinical trials excluded patients with renal insufficiency, hepatic insufficiency, a history of muscular complaints, and poorly controlled diabetes, as well as patients taking drugs with possible interactions. Large efficacy trials have excluded up to 30% of the participants in active pre-randomization phases. These trials also focused on rhabdomyolysis rather than on myalgia, fatigue, or other minor muscle complaints (45, 46). In another cross-sectional study, interviewed and examined 3,580 adults taking statins, 22% reported having had musculoskeletal pain (47).

Statin induced myalgia was proved to be dose-dependent and is different for each statin. In the PRIMO study, muscle-related symptoms occurred with the various regimens as follows:

- Fluvastatin XL 40mg-5.1%.
- Pravastatin 40mg-10.9%.
- Atorvastatin 40 to 80mg-14.9%.
- Simvastatin 40 to 80mg-18.2%.

Others have also shown that fluvastatin contributed to the smallest number of reported cases of rhabdomyolysis among statins. More recent studies indicate that rosuvastatin (Crestor), the most hydrophilic statin, may be well tolerated in those who do not tolerate other statins (48-50). The combination of fluvastatin (Lescol) and gemfibrozil (Lopid) has also been found to be safe (51). Risk factors for statin-induced myopathy include female sex, older age, higher doses of statins, a family history of statin-induced myopathy, and hypothyroidism. Drugs that increase the risk include fibric acid derivatives, macrolides, and amiodarone (Cordarone). If a statin and any of the above drugs are both required, certain statins-ie, pravastatin (Pravachol) and rosuvastatin-are recommended, since they are the statins least likely to cause rhabdomyolysis (44, 51).

2- Liver Dysfunction

a. Mildly elevated liver enzymes. It was noticed in many cardiac and non-cardiac patients that the liver transaminases are mildly elevated before or after statin use. In most of the cases there is no other sign or histopathological findings of hepatic injury. This condition was called "*transaminitis*" and is considered a benign lab finding (52, 53).

It was also observed that elevations of alanine aminotransferase (ALT) is more reliable for liver involvement than aspartate aminotransferase (54, 55). Drug-induced liver injury should be considered if ALT level increases by more than 2 to 3 times the upper limit of normal or in conjugated bilirubin level of more than 2 times the upper limit of normal. However, it has been proposed that the level of ALT should increases of more than 10 times the upper limit of normal (56).

In the PPP (Prospective Pravastatin Pooling) project, the percentage of either mild to moderate (>3 but <5 times the upper limit of normal) or severe (>10 times the upper limit of normal) elevations in aminotransferase levels were not significantly different between the statin-treated and the placebo group (0.9% vs 1% and 0.2% vs 0.1%, respectively) (57).

Most cases with mild elevation of ALT improved without the need for drug discontinuation, probably a result of the development of adaptation or tolerance, as seen in (Table 1) (58, 59). Recent studies suggest that statin treatment may improve hepatic steatosis (fatty degeneration). In a small uncontrolled study in patients with increased levels of baseline liver enzymes (<3 times the upper limit of normal) and biopsy-proven NAFLD, a 6-month treatment course with pravastatin improved liver histology and failed to cause further increases in serum aminotransferase levels (60).

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Table 1: Rates of aminotransferase elevation and drug discontinuation for various statins:

Statin	Reference	Patients	Incidence Of Elevation	Discontinuation
Atorvastatin (Lipitor)	2,4	1,072	0–0.7%	N/A
Cerivastatin (Baycol)	1,2	1,263	0–0.5%	N/A
Fluvastatin (Lescol)	3	822	1.2%	0.6%
Lovastatin (Mevacor)	1,5	3,304	0.6%	0.2%
Pravastatin (Pravachol)	6,7	5,170	1.3%	0.1%
Rosuvastatin (Crestor)	11	1,123	0%	0%
Simvastatin (Zocor)	8	10,269	1.8%	0.5%

After; Russo MW and Jacobson IM. How to use statins in patients with chronic liver disease. Cleveland Clinic Journal of Medicine 2004; 71(1):58-62 (58).

b. Hepatitis C virus infection. Egypt is known worldwide to have the highest incidence of hepatitis C viral (HCV) infection. The reported incidence of sero-positive is 14.7% and those with chronic disease are 9.8% of the total population (61). This epidemic disease started in the early 50s with the use of unsterilized needles for antischistosomiasis injection campaigns (62). In these cases the baseline transaminases may be elevated before the use of statins. However, in a controlled small study, there was no significant difference in the incidence of mild-moderate (P= .94) to severe (P= .87) increases in liver enzyme levels between statin-treated groups with or without HCV infection (63). These findings suggest that there is not a higher risk of alterations in liver biochemistry values in patients with HCV infection (53, 64). Recent reports considered statins to be a potential adjuvant therapy for HCV infection, as they regulate LDL receptors which in turn may reduce the entrance of the HCV to hepatocytes (65).

3- Other Possible Adverse Effects of Statins

a. Risk of developing type 2 Diabetes:

Statin therapy reduces cardiovascular risk in norm glycemic as well as in all types of diabetes. However, its relationship with the development of diabetes is controversial. It was reported in the WOSCOPS study published in 2001, that pravastatin at 40mg/day was reported to be associated with a 30% risk reduction for incident diabetes. However, the WOSCOPS was not sensitive for early diabetes discovery, because it required an increase in fasting glucose >36mg/dl above baseline (70). The recent JUPITER, published in 2008, reported that statin treatment was associated with a small but significant increase in physician-reported diabetes compared with those taking placebo (71). The possible explanation is that statins may decrease adipocyte maturation leading to reduction in insulin-mediated cellular glucose uptake caused by decreased insulin sensitivity, which may possibly result in exacerbation of glucose intolerance (72). It is also possible that statin-induce insulin resistance (73) or may directly affect insulin secretion (74). other report assume that it may uncover diabetes in high-risk individuals (75).

b. Caner:

The relation of statins to different types of cancer was controversial. Large meta-analyses studies including 45,857 matched pairs from an electronic medical records database of 11 million adult Americans, showed that statins have a neutral effect on cancer and cancer death risk and that no type of cancer was affected by statin use and no subtype of statin affected the risk of cancer (66). However, few observational studies found an increased risk of breast cancer related to duration of statins use (67). This was denied by a study on 92,788 women for a median follow-up time of 6.4 years, showing no association between statin use and breast cancer risk. Also the association of statins and prostate cancer was observed with an increased risk among obese men (68). However, in a recent article by Farwell et al. they found a correlation between increased levels of serum cholesterol with higher risk for total and high-grade prostate cancer, which can be reversed by the use of statins (69).

c. Cataract

Increased cataract formation has been found in excremental animals treated with statins (76). However, studies in humans have not found an increased risk of cataract associated with statin exposure (77, 78).

In conclusion; if we want to answer the question; are statins good, bad or really ugly? The definite answer will be that they are not only good but excellent for primary and secondary care of cardiovascular and other possible non-vascular diseases due to their proven pleotropic effects. The decision to give large doses of statin should be considered in context of every separate case to avoid possible adverse effects. The mild elevation of liver enzymes should not prevent physicians from describing statins as a primary or secondary treatment for patients with hypercholesterolemia. Also, we should stress on how to discover, assess and follow their prominent effects on the skeletal muscles. Lastly, we cannot give our final judgment on their long standing good or bad effects from the discussed short or intermediate studies and meta-analysis.

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