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Original Article

Lest we Forget: The Darker Side of the Hypocholesterolemic Statin Drugs

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ABSTRACT
Cholesterol-lowering statin drugs have been over-sold to the medical profession and over-prescribed by physicians, without due concern for their long-term disabling side-effects. These include acute renal failure, development of cataracts, diabetes, liver dysfunction and disabling myopathy. Most were predictable and have been well-documented: yet there has been little reduction in statin usage. The situation is made worse by more recent a) claims for off-label efficacy e.g. as anti-inflammatory agents and b) availability in some countries (e.g. UK) as over-the-counter medications. [1] Is it now time to carefully reconsider the need for such over-prescribing, with the promise of yet more to come (OTC availability, the 'polypill')?

Key words: Statins, Adverse effects, Cholesterol, Coenzyme Q, Dolichol, Polyisoprenoids.

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PREAMBLE

"Tell the truth and shame the devil."[1]

"Cholesterol is not the great killer it has been made out to be and the statin drugs that 'treat' cholesterol are not the great saviours they are touted to be."[2]

A *Caveat:* (warning for readers). This article discusses several uncertainties in the prevention and management of ischaemic heart disease. The opinions offered may not be defensible as - and when - more data accrue. Meanwhile, it would be reprehensible to continue to postpone/avoid discussing this urgent question: how dangerous are the statins, used as cholesterol-lowering agents? As the title (Pharmacognosy Communications) of this Journal indicates, we need to know as much as we can establish about the efficacy and safety, i.e. benefits and toxicity of any medication. This is especially needed for any drugs so widely prescribed as the statins, especially for extended use, when their potential for causing harm may be quite considerable.

INTRODUCTION

A detailed report of the merit versus toxicity of a range of statins was published a few years ago in the British Medical Journal.[3] The conclusion of these authors was that statin treatments only benefited 2 per cent of the patients' cohort (n=2x10^5 subjects), whilst causing serious side-effects in 4 per cent. This is an enormous dis-connect from so many promotional reports of statin's efficacy in short term trials, supported by pharmaceutical companies and published in 'mainline' medical journals (often carrying advertising for these same drugs). Adverse effects were rarely discussed.

A recent commentary on these findings[4] reminded readers that "The implied message in the advertisements for statin drugs is that if 10,000 people took the drugs (we're promised) heart attacks will be prevented in all 10,000 people. This is a wild exaggeration. The facts are that statin drugs may only 'work' in about 2.7 per cent of those who take them. Yet they cause serious damage in about 4.4 per cent of those who use them. That is, for about 96 out of 100 people, statins do nothing except make the drug companies rich and pollute the water ways every time you flush the toilet". Strong words indeed!

Something is seriously wrong here. Why do we still have a government-approved attack on our wellbeing and health costs along with uncertain benefits for such enormous financial outlays? To answer this question, we need to re-examine some of the assumptions that underlie this. Currently, the medical profession (ably abetted by drug propagandists) may be promoting ill-health and (i) not only undermining patients' wellbeing, but (ii) adding crippling health costs to over-burdened health systems. Gresham's Law, originally coined to describe the debasement of the metal coinage in England, that 'the bad drives out the good' seems to be re-enacted in this sad situation. As treatment costs rise, the apparent therapeutic ratios (benefits/toxicities) decline with ever-continuing usage. Nevertheless, in the UK the number of prescriptions for statins now exceeds one million per week.[1]

Dubious Background of hypocholesterolemic statin drugs

The Merck Manual of Diagnosis and Therapy defines type II hyperlipo proteinemia as an elevation of low density lipoprotein (LDL). It then lists the main reasons for therapy are to (i) prevent premature development of atherosclerosis, (ii) lessen the likelihood of coronary heart disease and myocardial infarction and (iii) prevent unsightly cholesterol-containing xanthomas growing further. These are all preventive measures.

What is to be treated is a number, the quantity of cholesterol in a venous blood sample as an indicator of LDL content. Values above a flexible threshold (currently about 4.2 mmol/L) are deemed a likely risk for future coronary disease. However it is only one risk factor among many; that includes smoking, lack of exercise, elevated blood pressure, poor diet, undue stress and co-morbidities e.g. diabetes, etc. These other factors can be controlled with or without drugs and usually without exclusive patents.

Novel drugs to reduce (LDL) cholesterol levels in the circulation were then promoted as good, even essential, medicine. Esterified cholesterol, one component of LDL that could be readily measured in a blood sample, was identified as the drug 'target'. This allowed almost immediate assessment of a statin's potency; but the real criteria of its worth would be delayed for perhaps decades, until very convincing statistics were available about possible extensions to life span ie avoiding early mortality.

The basic assumption was that LDL must be controlled; is based on the presumptions that (i) elevated LDL levels were indeed pro-pathogenic and (ii) they are surrogate markers for potential morbidity and mortality.

This message was vigorously promoted to physicians and their patients to avert early development of cardiovascular disease.

For the pharmaceutical industry, a drug to decrease serum cholesterol (and by implication, LDL) was an opportunity to capture a life-long market. It trades on the fear that nobody wants to die prematurely, particularly by ignoring the message "LDL cholesterol is bad for you" (and might kill you faster than the statins). Actually, two assumptions were made to support this strategy: (i) that elevated LDL levels are indeed toxic; so, they must be controlled (Table 1); and (ii) targeting the cholesterol component of LDL is the way to go (Table 2). Numerous clinical studies of these new drugs then focussed on how effective they were for lowering serum cholesterol levels today; and, by implication, for as long as they would be consumed in the future. Little concern was voiced about their safety over the long-term i.e. the periods required to establish the statins' true value.

Instead we find authorative opinions* that 'cholesterol is a common ailment (alongside hypertension, pain and depression)' and 'the discovery of the linkage between cholesterol and atherosclerosis is widely viewed as one of the 10 greatest discoveries in medicine'. So, there you have it; sloppy nomenclature and sloppy thinking to accept these statements as facts without question. These words are followed by the statement, 'the statins have done so much for patients, pharmaceutical companies and employees and shareholders and even the American economy'.[5] implying that if it's OK for business, it really must be OK!

Table 2: Dubious Assumptions About Cholesterol As A Drug Target

a)	"Cholesterol is bad" per se_ BUT it may only be pathogenic when i) deposited as gall stones, impeding bile flow, or ii) there is a serious imbalance between low density and high-density serum lipoproteins (containing cholesterol).
b)	"Hypercholesterolemia is a principal cause of heart disease." BUT high blood pressure, poor diet and lack of exercise are just as significant risk factors.
c)	"Lowering serum cholesterol levels is good medicine" AND just happens to generate huge profits for drug companies.
d)	"Statins do this and are therefore desirable" BUT they also impede the biosynthesis of other essential physiological entities e.g. steroid hormones, bile salts, coenzyme Q, dolichol, etc (Table 6).
e)	'The benefits of statins far outweigh their side effects" BUT try telling this to patients suffering prolonged and crippling adverse effects after statin 'therapy', particularly derangements of their neurological and muscular functions or who have now developed diabetes.
f)	"If they're being so widely prescribed, they must be needed and should be good for us." BUT in fact, they aren't really so good. Forceful advertising has trumped basic science.
g)	"They are essential to complement other approaches to treating/preventing heart disease." BUT many elderly people do live healthy lives by concentrating on lowering their blood pressure and reducing other risk factors for cardiovascular disease (e.g. high salt, high fat diets, smoking, lack of exercise) including controlling pro-thrombotic events with low dose aspirin, vitamin K antagonists, etc. That is: all achieved without using statins and being exposed to their likely future adverse effects.

Table 1: Questionable Assumptions About The Statins

- We need these drugs to postpone mortality from cardiovascular disease (CVD); other (and healthier) options being insufficient.
- Damaging the critical roles of cholesterol and endogenous polyisoprenoids in the body economy, is a risk worth taking.
- Measuring serum cholesterol is a good marker of pre-morbidity.
- Using statins and other hypocholesterolemic drugs for a lifetime will be safe: that any adverse effects arising from (very) extended use will be manageable.
- When statins are available, using more logical (and certainly cheaper) therapies e.g. vitamin E supplements and other lipo-soluble antoxidants to protect lipoproteins from oxidative damage - are then not worth considering.
- Drug companies know best; their management of the supply of (mis-) information, even down to what is taught in medical schools, is a 'service' to education.

Table 3: What The Statins Do

1. Inhibit the enzymic reduction of HMG-coenzyme A to form mevalonate, the first unique step in the hepatic/intestinal biosynthesis of cholesterol.
2. Also inhibit the biosynthesis of essential polyisoprenoids (Table 6)
3. Reducing hepatic cholesterol synthesis then lowers the LDL cholesterol by ≤35 per cent; usually accompanied by a compensatory increase in hepatic LDL receptors, to abstract needed cholesterol from the blood.
4. Lower LDL, as monitored by a reduction in serum cholesterol. This supposedly reduces the risk of myocardial infarction and total mortality in older patients, free of coronary heart disease.
5. Statins have little effect on HDL cholesterol but may decrease serum triglycerides (possibly beneficial).
6. Come with high long-term costs, both financial (Table 4) and uncertain safety (Table 5).

Table 4: Statins are Not Cheap

Wholesale costs (US$) for 30 days treatment in 2014 were:

Name	Origin*	Cost (US$)
Atorvastatin	Warner-Lambert, 1991	173
Fluvastatin	Sandoz, 1984	113
Lovastatin**	Merck and Co, 1980	71
Pitavastatin	Nissan Chem, 1989	152
Pravastatin	Sankyo, 1981	98
Rosuvastatin	Shionogi, 1993	194
Simvastatin	Merck and Co, 1981	85

From Baron,[6]

*Company holding original US patent (date)

**Natural product isolated from fungi (see also Mevastatin, Sankyo, 1975)

Notes: Prices may be considerably higher at point of sale (with dispensing fees, local taxes, etc.)

These drugs are prescribed for daily use, for perhaps the rest of the patient's life; thereby greatly increasing likely expression of their adverse effects, however slow their onset.

Table 5: Principal Adverse Effects of Statins

A) Well-established, associated with:

- Myopathies involving sarcomere disruption in skeletal muscle

diagnosed by pain, stiffness and >10-fold increase in serum creatinine kinase; sometimes also by the presence of serum antibodies to HMG-CoA reductase.

- Cataracts
- Type II diabetes

B) Less certain; being less frequent (but still potentially harmful):

- Myopathy involving vascular smooth muscle (Table 7)
- Angio-oedema
- Ulcerative colitis
- Peripheral neuropathy
- Drug interactions involving hepatic detoxication by cytochrome P_{450} enzymes
- Induction of apoptosis, activated cell death in myotubes and myoblasts, sometimes accompanied by acute kidney injury

C) Rare, but may be very debilitating:

- Rhabdomyolysis – an extreme form of myositis that can be life-threatening
- Depression
- Chronic fatigue
- Parkinson's disease

NOTES:

1. Some of these may be considered infrequent. Most reports of longer term adverse reactions are limited to observations over five months but rarely for more than five years. Yet younger patients might be expected to take statins daily for 25 years or more!
2. An important area of preventive medicine is to remove harmful but avoidable factors e.g. bad food, bad water and certainly bad drugs e.g. thalidomide during pregnancy and at least one statin Cerivastatin (Bayer), withdrawn in 2001.

Table 6: What causes these toxicities?

A) Cholesterol depletion affecting:

- Cholesterol incorporation into membrane architecture of nearly all cells in the body.
- Biogenesis of essential physiological regulators, derived by enzymic oxidation of cholesterol (C_{27}) to form:
  - a) sex hormones: progesterone (C_{21}), androgens (C_{19}), estrogens (C_{18})
  - b) adrenal hormones (C_{21}) eg cortisol, aldosterone
  - c) cholanic acids (C_{24}), conjugated with glycine or taurine to form biodetergent 'bile salts', essential for absorption of dietary fats and liposoluble vitamins (A, D, E, K).
  - d) Vitamin D_3 (C_{27}), an essential regulator of calcium metabolism and the immune response

B) Impaired biogenesis of mammalian (and endobacterial) polyisoprenoids derived from mevalonate, with key physiological functions:

- Dolichol(s) = polyisoprenoid alcohols (n* = 14-24), essential for (i) synthesis of N-linked glycosides that requires dolichol pyrophosphate (C_{80-100}) and (ii) to anchor certain proteins to biomembranes.
- Farnesyl (C_{15}) or geranyl geranyl (C_{20}) moieties linked as thioethers to G proteins (e.g. Rho, Rab) that regulate a) a wide range of intracellular signalling pathways and b) the distribution and function of certain proteins.
- Ubiquinone/coenzyme Q_{10} (C_{59}), an essential component of the mitochondrial respiratory chain that synthesises ATP

(Deficiencies have been associated with Parkinson's Disease).

- Vitamin K_2, an essential co-factor for hepatic synthesis of blood-clotting proteins.
- Isopentenyl adenosine, present in some types of transfer RNA.
- Haem-A linked to a farnesyl moiety.

C) More complex mechanisms, as yet poorly understood, e.g. those associated with drug-induced cataract formation.

*n = degree of polymerisation of C_5 – isoprene unit

Notes: Farnesol and Dolichol are hydroxterpenes.

contd.

Ubiquinones are benzoquinones with polyisoprenyl (n = 6-10) side chains.

Vitamin Ks are napthoquinones with polyisoprenyl side chains (n = 6).

Some items in Section B may be derived from intestinal bacteria (e.g. Vitamin K) that are also exposed to statins. (Note, however that some bacteria and most plants use an alternative pathway not involving mevalonate to synthesise isoprenoids).[7]

Suppressing cholesterolgenesis may not be so toxic as disrupting isoprenoid synthesis (items in Class B) when these are not so readily available from dietary sources e.g. Dolichol.

Table 7: Statin-Induced Cardiomyopathy[8]

This concept inverts the purpose of statins as agents to prevent/minimise heart disease. It is based upon the findings that statins:

- Promote coronary artery calcification by inhibiting the synthesis of Vitamin K_2 (including that by intestinal flora) which protects arteries from calcification.
- Behave as mitochondrial toxins, impairing cardiac muscle and vascular smooth muscle function, by depleting coenzyme Q_{10} (and therefore ATP generation).
- Inhibit the synthesis of glutathione peroxidase, a selenium-containing enzyme, that suppresses peroxidative stress. This stress is part of the local inflammatory response leading to intravascular LDL oxidation.

One symptom of selenium deficiency is dilated cardiomyopathy.

Table 8: The Dark Side Of Statin Therapy

- This strategy is expensive and to be successful, requires statin users to take them for the rest of their lives i.e. to be exposed to sustained/maximal intoxication (however slow developing).
- It is totally focussed on curbing elevation of (LDL) cholesterol levels in the blood; a questionable symptom but not a disease. (Nevertheless, that's where the money is).
- It diverts attention from other risk factors (RF) for cardiovascular disease that are treatable but nothing like so profitable. These RF include a) high levels of homocysteine in the blood (≥10μ moles/L), readily controlled with a daily OTC folic acid supplement 0.8/mg day, b) smoking, c) insufficient coenzyme Q in the diet and d) low levels of HDL.
- It also diverts attention away from modifications to lifestyle e.g. a) stress management, b) improved dietary intake of fibre, antoxidants, the 'good' fats etc and c) controlling intake of salt, alcohol, trans-fatty acids and other ingested atherogenic 'pollutants'. These alternative (DIY) remedies for improving cardiovascular health do require effort.
- So, many people at risk prefer to accept the managed 'group-thinking' (retailed by their physicians) that it is quite sufficient to swallow yet another pill!
- While huge profits accrue to the drug companies, who will contest the logic of Gresham's Law (that the bad will drive out the good)? Very large sales can now be made from aggressively peddling the 'bad' to the detriment of providing the 'good' i.e. realistic preventive (dietary) medicine, with the longer-term health and wellbeing of the consumer as first priority.
- Sceptics and critics will argue that statins are preventive medicines. If so, do they really have to be so costly (financially or from their adverse effects)?
- 'Replacing medical education with industry promotion, in the guise of scholarship, causes demonstrable harm to trainees, the public and the medical profession'[2]

Table 9: Do we really need statins?

There are safer, healthier ways to help lower LDL cholesterol, if this remains a major concern. They include adding nutriceuticals and/or removing factors promoting stress, dysregulated blood clotting and high blood pressure. Some examples are:

- Reduce reliance on animal-sourced foodstuffs.
- Increase vegetarian foods that supply phytosterols: these plant sterols reduce the absorption of dietary cholesterol, are poorly absorbed and are still oxidised in the liver but not usually incorporated into circulating lipoproteins.
- Increase dietary antoxidants – they can be attractive e.g. red wine, low-sugar cocoa products, etc. They may help reduce an initiating event in atherogenesis, namely the intravascular oxidation of LDL that triggers endovascular inflammation and eventually leads to plaque formation and local obstruction of blood flow.
- Decrease daily intake of unhealthy foodstuffs e.g. salt, sugar, hard fats, processed (and oxidised) liquid fats, hydrogenated seed oils containing unnatural trans fatty acids, and tobacco use.
- Ingest monounsaturated fats with high oleate (18:1) content: these reduce LDL and increase HDL. The inverse occurs with trans fatty acids (formed by industrial hydrogenation of liquid fats) present in shortenings, commercial cooking oils, etc.
- Reduce the proportion of dietary omega-6 polyunsaturated fatty acids (PUFA) and increase omega-3 PUFA e.g. with flaxseed (edible linseed) or fish oils; to help minimise intravascular inflammation.

contd.

- Increase water consumption. The Adventist Health Study of over 20,000 people that began in 1976[9] suggested fluid intake might be a risk factor for coronary heart disease: the relative risk (RR) with water being 0.46 (men) or 0.59 (women) BUT for caloric fluids, the RR was 2.47 (men) or 1.46 (women).
- Increased exercise. A brisk walk for half an hour may reduce the risk of stroke or heart attack by 30-40 per cent.[10]
- Be aware of the publication bias of many medical journals, providing extensive coverage of statin trials (and concurrently earning advertising dollars). Instead, read some of the many less publicised reports and reviews (not supported by advertising) that find little justification for, and merit in, statin therapy. There is only space here to commend a few.[2,11,12,13,14,15]

As many writers have stated: 'A mind is like an umbrella; it functions best when opened'. Voluminous advertising is no guide to either quality or real need for a product. But this has not deterred the pharmaceutical industry from promoting remedies for hair re-growth in males, low libido in females and other 'contrived' diseases.

Table 10: Paradoxes needing further understanding.

These are listed here because, if ignored, we may lose the opportunity for further rational thinking about the roles of LDL and the pharmaceutical industry in the context of cardiovascular health and wellbeing.

1. Mevastatin (Compactin, Merck), the first statin discovered in the 1970s by Akira Endo (Sankyo Co. Tokyo), increases the targeted enzyme HMG-CoA reductase! This is the cell's natural response to deficiencies in the supply of cholesterol and of essential isoprenoids.
2. The first statin given to a patient by Akiro Yamamoto at Osako University in 1978 caused muscle weakness. Endo himself was subsequently prescribed Medacor (Lovastatin) when he had a serum LDL cholesterol level of 150 mg/dL. He took the drug, then chose not to use it but exercised instead, which reduced his LDL cholesterol to 130 mg/dL.[5]
3. George W Merck in 1926 inherited the leadership of Merck and Co (Rahway NJ) as the first company to successfully market a statin (Lovastatin). He formulated the values of the company in 1950 as 'remembering that medicines are for the patient and that medicine is for the people. It is not for profit. Profits follow and if we've remembered that, they have never failed to appear.'[5]
4. What are we to make of the unconventional proposal that it is not only the cardiac muscle but the vascular smooth muscle within the heart that may be affected by statins? (Table 7) Why is there so little published commentary about, or refutation of, this concept in refereed journals?
5. To be considered successful, any new statin or alternative medication has to reduce LDL levels by 30 per cent. But many modifications in nutrition or exercise programs are reported to lower serum cholesterol to the same degree. No profits here: so these alternative, less toxic strategies receive little notice. If the custodians of public health really did their duty, independently of drug company propaganda, we should be reading much more about statin alternatives.
6. By contrast, some custodians of our health have been promoting a 'polypill'; containing a statin, a hypotensive drug and an anti-coagulant. It is proposed that this 'drug cocktail' become mandatory for all senior citizens (over 55 years old perhaps) in the interests of reducing national health costs! In reality these 'costs' might include not only presently known toxicities of individual components but also a lack of freedom to adjust dosage of any individual constituent according to the patient's needs or drug sensitivity. In modern medicine, the concept and practise of 'one size fits all' must surely be obsolete; especially when it might harm normal people/prospective patients.
7. Much confusion has arisen from failure to clearly distinguish (i) patients with established cardiovascular disease who may require statins as a form of rescue therapy from (ii) a healthier population who may or may not need statins as preventive 'medicine'. The first group may have more limited prospects of survival and are treated much as we treat patients with cancer. The second, healthier group is exposed to unsupervised DIY medicine by accessibility to OTC statins, prompted by extravagant advertising (strongly supporting supposed benefits but light on noting real risks) So we have the paradox: No, we don't need statins as there are useful alternatives – but Yes, we must have them when there may be serious restrictions to blood flow caused by persistent deposits of lipids and endoarterial cell proliferation (creating atheromas).
8. Would it be healthier for all i.e. people as well as drug manufacturers, if there was more investment in seriously pursuing strategies (lifestyle or medications) to increase the retrieval and recycling of cholesterol by HDL?[16] Put simply, to focus more on positive, less riskier strategies than just suppressing the LDL levels (See Appendix).

Leaving aside such hype, what really are the facts (biological, economic, etc.) that can be unambiguously assessed about the properties of statins? Some are presented in Tables 3-8. Table 9 summarises some strategies for DIY 'do without statins' that might be followed, assuming there is little risk of an imminent occlusion of critical arteries (e.g. coronary, carotid). Table 10 presents some paradoxes and other oddities in the history of statins. These are generally overlooked in the barrage of managed information, advertising these drugs as essential aids to future wellbeing. Also overlooked are some frank appraisals by many statin-sceptics (Table 9). We would do well to keep looking back in time to find a secure basis from which to face and manage the future (the Janus option). **

ABBREVIATIONS USED

DYI: Do-it-yourself; **HMG:** 3-hydroxy-methylglutaryl; **HDL:** High density serum lipoprotein; **LDL:** Low density serum lipoproteins, **OTC:** over-the-counter.

CONFLICT OF INTEREST

The authors declare no conflict of financial interest.

*From the author of an otherwise excellent book on the history of statins[5] who was involved in the early stages of the development of Lipitor^{R} by Parke-Davis & Co (See p .170 and p .11 for the origin of these quotes).

**Janus was the mythological deity of the ancient Greek cultures, usually depicted as having two heads-one facing backward, the other facing forwards.(Currently it is also the symbol of the International Lions Movement, a non-government organization that sponsors much medical research and improvements in practice.)

REFERENCES

1. Trusler D. Statin prescriptions in UK now total a million each week. Brit Med J. 2011;343:d4250.
2. Dingle P, Uink N. The great cholesterol deception. The truth about cholesterol and cholesterol-lowering medication. South Freemantle WA. Good 4 us. 2005;129.
3. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in Wales: population based cohort study using the Q Research Data Base. Brit Med J. 2010;10:340c2197.
4. Anon. The truth about statin drugs exposed in the British Medical Journal. The New Zealand J Natural Medicine. 2017;26:12. and http://www.natural news.com/028988_statin_drugs_side_effects. html. 2014;28:1209.
5. Li JJ. Triumph of the heart: the story of statins. Oxford OUP. 2009;201.
6. Baron RM. Lipid disorders in Current Medical Diagnosis and Treatment. Eds. Papadakis MA, McPhee SJ, Rabow MW. New York, Lange McGraw Hill, 2014 Chap 28, p.1209
7. Hunter WN. The non-mevalonate pathway of isoprenoid precursor biosynthesis. J Biol Chem. 2007;282:2173-7.
8. Okuyama H, Langsjoen PH, Hamazaki T, Ogushi Y, Homa R, Kobayashi T, *et al.* Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms. Expert Rev Clin Pharmacol. 2015;8:189-99.
9. Chen J, Knutsen SF, Blix GG, Lee JW, Fraser GE. Water, other fluids, and fatal coronary heart disease: the Adventist Health Study. Am J Epidemiol. 2002;155:827-33.
10. Katz DL. Cut your cholesterol. A break-through approach to lowering heart disease risk. Ultimo Sydney. Readers' Digest Australia Pty Ltd. 2004;256.
11. Roberts BH. The truth about statins: risks and alternatives to cholesterol-lowering drugs. Kindle 2012, 256 p.
12. Kowalski RE. The 8-week cholesterol cure. How to lower your blood cholesterol without drugs or deprivation. Melbourne. Bantam/Schwartz. 1987;320.
13. Graveline D, Kendrick M. 2012. The statin damage crisis, Kindle (Amazon Digital Services LLC). 2012;3.
14. Estren MJ. Statins. Miraculous or Misguided? Oakland Ca Ronin Publishing Inc. 2013
15. Davis M. Lipitor: the dark side of statins. New Science that shows how drugs like Lipitor may do more harm than good. Kindle. 51pp.
16. Duffey D, Rader DJ. 2009. Update on strategies to increase HDL quantity and function. Nature Rev Cardiol 6:455-463.
17. Schmitz G, Torzewki M. Eds. 2002. HMG-CoA Reductase Inhibitors. Basel, Birkhauser Verlag. Pp.151.
18. Bersot TP. Drug therapy for hypercholesterolemia and dyslipidemia in Goodman and Gilman's The Pharmacological basis of therapeutics,New York, McGraw Hill Education. 2011;12(31):877-908.
19. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Atherosclerosis and lipoprotein metabolism in Pharmacology7th edn. Elsevier, 2012 Chap. 23. London pp.285-93.
20. Smith LL. Another cholesterol hypothesis: cholesterol as antoxidant. Free Radical Biol Med. 1991;11(1):47-6.

APPENDIX

Some Pathogenic Events Causing Atherosclerosis (ASS): an outline

Preamble

Ischaemic heart disease (IHD) describes a group of clinical syndromes characterised by an imbalance between myocardial blood supply and demand. These IHD syndromes cause more deaths, morbidity and financial burden in Western Societies than any other diseases. In most cases, the cause of myocardial ischaemia is a reduction in coronary blood flow due to atherosclerotic arterial disease. Predisposing factors include smoking, hypertension, hyperhomocysteinemia, haemodynamic aberrations, toxins, viruses and unregulated immunological reactivity.

Focusing on atherosclerosis (ASS)

ASS is not an inevitable consequence of aging but

a chronic inflammatory condition due to altered (LDL) cholesterol disposition and metabolism that, together with other provocative factors cause the ASS lesion, that

leads to the cardinal features of ASS, particularly plaque formation and rupture, local fibrosis, calcification and thrombosis; that are (i) all triggered by an initiating inflammatory event and its consequences and (ii) might also be regulated by statins (as a by-reaction).

Focusing on statins

So, the statins may be accidental modulators of some of these collective cellular and immunological events that underlie chronic inflammation, especially when they escape normal homeostatic physiological regulation and promote ASS. One beneficial effect of the statins is their stabilisation of plaques, preventing their rupture by metalloproteinases produced by activated macrophages.

For further discussion of these pleiotropic effects of statins, see Schmitz and Torzewski[17] and of biochemical events triggering an endothelial inflammatory response.[18,19]

Focusing on molecular pathogenesis

Low Density Lipoproteins (LDL) are essential mediators of healthy nutrition but liable to suffer oxidative damage. When this occurs, they form lumpy aggregates that are scavenged by activated macrophages forming lipid-rich 'foam' cells. These cells produce further inflammatory mediators that promote the proliferation of fibroblasts, forming a type of scar tissue, rich in abnormal (oxidised) lipid that resist the body's normal disposal mechanisms.

LDL oxidation is one of several collateral consequences of the body's response to a local inflammation that is programed to destroy 'non-self', particularly invading micro-organisms and tumours.

Further reflection

A systems analysis would find that the initiation of LDL oxidation may be only one of several triggers for ASS, rather than the presence of higher levels of unoxidised levels of LDL currently viewed as the risk factor (the ideological basis for statins and experimental means to verify their efficacy *in vivo*). It is not only the esterified cholesterol within a lipoprotein particle that is oxidised but the apoprotein as well. A further reductive analysis might suggest it is the unsaturated fatty acids (that esterify the cholesterol) which are the most fragile constituents of the LDL, not the cholesterol itself. If so, cholesterol's real involvement in ASS might be viewed as 'guilt by association', or 'being in the wrong place at the wrong time' ie within an inflammatory locus. [If cholesterol were not so robust, it wouldn't be found so widely distributed in virtually all cell membranes.] It's all very shaky that cholesterol should be selected and promoted as a hard and fast 'target' for rational drug design. It is also paradoxical that unesterified cholesterol has been proposed to be an endogenous antoxidant.[20]