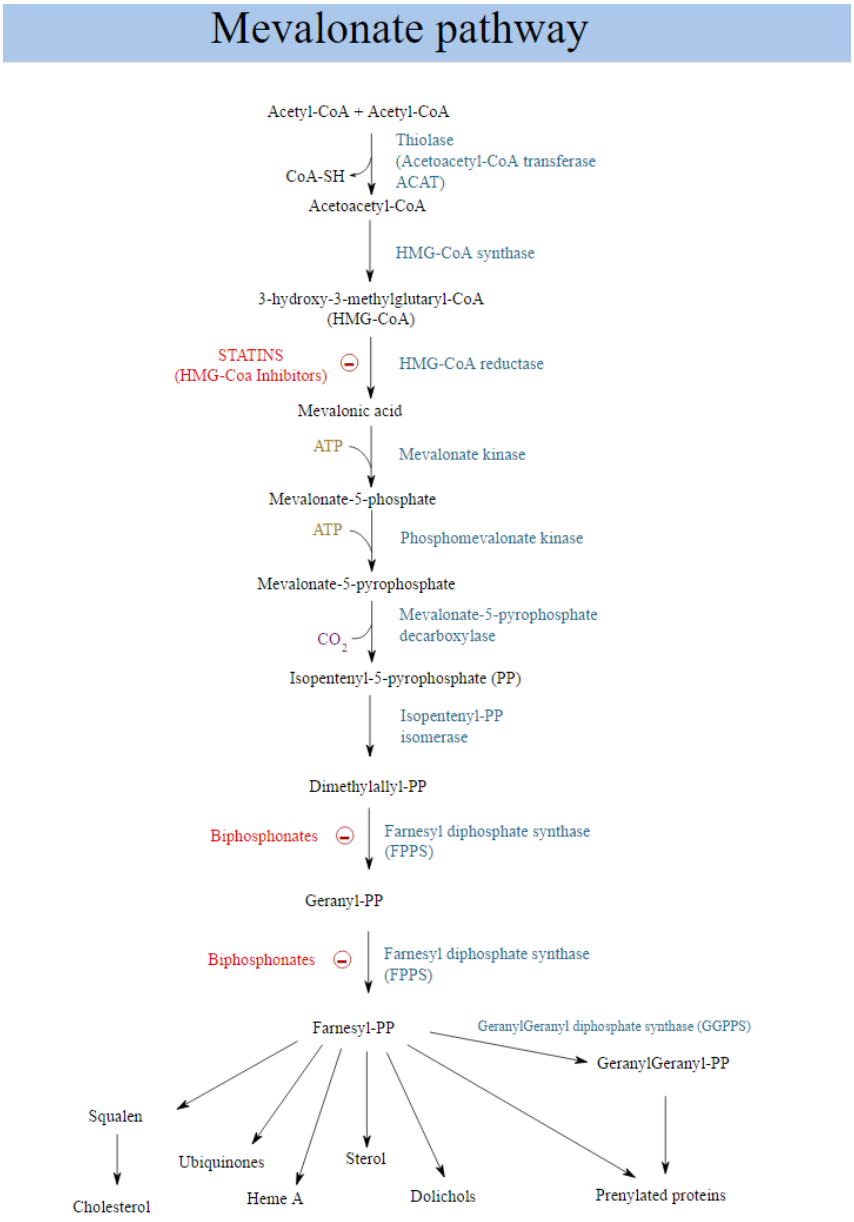
HMG-CoA reductase inhibitors = Statins



Statins inhibit HMG-CoA reductase in a non-tissue specific manner thereby also inhibiting the following:

1) cholesterol synthesis

2) ubiquinone synthesis

3) sterol synthesis

4)dolichol synthesis

1) Cholesterol function:

- essential lipid constituent of cell membranes

- precursor of steroid hormones

- precursor of bile acids

2) Ubiquinone (CoQ10) function:

- essential for cell energy metabolism

3) Sterol function:

- various, including sexual function, blood pressure regulation, immune modulation

4) Dolichol function:

- responsible for co-translational modification of proteins

- essential building block of substantia nigra (not sure whether imbalance in CoQ10/dolichol there might be causative for Parkinson's disease)

- needed for synthesis of α-dystroglycan, a major protein in the skeletal muscle dystrophin–glycoprotein complex, and deficiencies have been linked to muscle dysfunction[i]

Existing Evidence:

1) Familial Hypercholesterolemia is a genetic disorders marked by extremely high LDL levels (normal HDL and TG, total cholesterol levels of 350-1000 mg/dL). LDL lowering therapies, including statins, are important tools needed to treat these patients.

2) Hypolipidemia - there are two reasons for hypolipidemia, particularly low LDL. One is genetic (abetalipoproteinemia, hypobetalipoproteinemia, chylomicron retention disease), the other one is secondary to other diseases, such as anemia, hyperthyroidism, cancer, infection and chronic liver disease. Studies have shown that patients with low total cholesterol and especially LDL below 50 mg/dL are at increased risk of intracerebral hemorrhage, adrenal failure, sepsis and early death.[ii]

3) LDL cholesterol level does not correlate with all cause mortality in patients above 60.[iii]

4) Various studies have shown that in high CRP patients statin therapy seems to have a beneficial effect irrespective of LDL level.[iv] In fact all the patients in the JUPITER trial with rosuvastatin were considered "normal" or "low" LDL (<130mg/dL).

4) Patients on statins are at significantly elevated risk of diabetes. The JUPITER Trial using rosuvastatin showed a 25% relative increase in the risk of developing diabetes. This compares with a relative risk reduction of all cause mortality of 20% (just about statistically significant) and 44% relative risk reduction in all vascular events. This relative risk reduction is representative of(or even better than) other statin outcome trials.

5) Between 1 to 10% of statin users suffer from myopathy (spectrum of muscle pain/disease). This incidence increases to 25% in athletes and is possibly related to the inhibition of dolichol and CoQ10.

Studies, Thoughts and Theories:

1) The potential causative correlation of statins and cognitive impairment is still a very controversial topic even though the FDA has recently included a warning about "memory loss" as a potential side effect of statins.

There are some studies showing that hypertriglyceridemia in patients over 60 has clearly deleterious effects on small blood vessels in the brain. These studies however do not show any negative effects of LDL on the brain. On the contrary, they indicate a slightly positive effect on small vessel integrity within the brain.[v]

2) High LDL and/or total cholesterol seems to extend survival in patients with ALS (amyotrophic lateral sclerosis.[vi]

Current state of affairs:

PCSK9 inhibitors will start to report outcome studies in 2017. The FDA has decided to wait for these data in order to judge if LDL will remain a valid surrogate endpoint for cardiovascular outcomes or not. Since PCSK9 inhibitors also lower inflammatory markers (IL-6, TNFalpha but not hsCRP) they stand a decent chance of success.

Their potential success largely rests on a novel mechanism of action. Oxidised LDL (oxLDL) upregulates PCSK9 expression that in turn unleashes an inflammatory cascade. Therefore blocking PCSK9 downregulates this inflammatory process.[vii] This mechanism elucidates the role of oxLDL in atherosclerosis and plaque formation due to inflammation. Obviously it would be preferable to measure oxLDL levels in patients rather than just LDL and develop medication to eliminate oxLDL specifically.

There is a gradual realisation within the research community that LDL does not explain the whole picture. In type 2 diabetes hsCRP clearly is a more important marker for cardiovascular disease than LDL. In people with triglyceridemia, triglyceride lowering outweighs any LDL based approaches in terms of long term cardiovascular outcomes. Also low HDL (below 45mg/dl for men and below 40mg/dl for women) is a more important marker of cardiovascular risk independent of LDL levels.

Opinion and future developments:

Increased risk of cardiovascular disease and stroke directly correlates with obesity and type 2 diabetes. Both diseases can be successfully prevented by dietary changes and physical activity. As such these approaches are largely preferable to medical intervention.

We also know that atherosclerosis is promoted through an inflammatory process and that lipids only serve as surrogate markers for atherosclerosis and cardiovascular disease.

It seems that interventions that directly affect the inflammatory cascade may be a much better target for preventing cardiovascular disease:

Prevention of dietary intake of known pro-inflammatory compounds; examples are omega-6 fatty acids; AGEs, trans fatty acids and high levels of fructose and glucose (or of foods that get quickly converted into those)

There are a number of medications in development that should offer a more targeted approach to preventing vascular inflammation and the resulting cardiovascular events; examples are:

Apabetalone (RVX-208): a potent epigenetic complement cascade inhibitor - phase 2 trials have shown a 77% reduction ofcCardiovascular events in high risk diabetic patients (on top of statins!)

Bempedoic Acid: A prodrug to an inhibitor of ATP-Citrate lyase; this drugs hits effectively the same pathway as statins, but due to a liver enzyme being necessary for the conversion to the active drug it only becomes active in the liver, preventing many (but probably not all) off target effects of statins.

In fact there are a number of supplements that could potentially help prevent cardiovascular disease:

- fish oil, in particular high EPA and DPA (not DHA) variants seem to be quite effective, the definitive outcome study for a prescription version is currently under way in the US with a readout scheduled for 2018 (REDUCE-IT study)

-Resveratrol and red wine polyphenols. They have potent anti-oxidant and anti-inflammatory properties that are highly likely to preserve cardiovascular health. [viii]

[i] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3023269/

[ii] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3074286/

[iii] *BMJ Open* 2016 6: doi: 10.1136/bmjopen-2015-010401

[iv] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3023269/

[v] **Plasma lipids and cerebral small vessel disease,** Sabrina Schilling, Christophe Tzourio, Carole Dufouil, et al, *Neurology* 2014;83;1844-1852 Published Online before print October 15, 2014, DOI 10.1212/WNL.0000000000000980

[vi] Neurology. 2008 Mar 25;70(13):1004-9. doi: 10.1212/01.wnl.0000285080.70324.27. Epub 2008 Jan 16.

[vii] https://www.spandidos-publications.com/ijmm/30/4/931

[viii] http://www.jnutbio.com/article/S0955-2863(10)00168-3/pdf