THE NORTHERN HOSPITAL

PRAVASTATIN

"My Dress Hangs There", oil and collage on masonite, 1933, Frida Kahlo

"....High society here turns me off and I feel a bit of rage against all these rich guys, since I have seen thousands of people in the most terrible misery without anything to eat and with no place to sleep, that is what most impressed me here, it is terrifying to see the rich having parties day and night while thousands and thousands of people are dying of hunger....

Although I am very interested in all the industrial and mechanical development of the United States, I find that Americans completely lack sensibility and good taste.

They live as if in an enormous chicken coop that is dirty and uncomfortable. The houses look like bread ovens and all the comfort that they talk about is a myth. I don't know if I am mistaken, but I'm only telling you what I feel....

Frida Kahlo, letter to Dr Eloesser, November 1931.

Frida Kahlo commenced the only collage work she ever did whilst in New York City in 1933. She would finish it only on returning to her home in Mexico City. By this time she had spent four years in America with her husband, Diego Rivera, who had received numerous lucrative commissions there. Frida had become thoroughly disillusioned with American society, and her desire to return home had begun to cause serious relationship problems with her volatile husband, who loved America, not only for the work and adulation he received there, (despite his fractured relationship with the powerful Rockefeller family) but also for its innovation and modern industry. He believed that America was on the brink of becoming a Socialist State. Frida thought all of this was idealistic hogwash.

As Frida became increasingly outspoken about her disillusionment with America, and her wish to return home, Diego became ever more emotionally abusive towards her. On one evening Frida's friend, Lucienne Bloch, the Swiss born American Artist and Stephen Dimitrov, one of Diego's assistants, found her in a volcanic argument with Diego over the matter of wanting to return home. Diego became so upset he picked up one of his canvases that depicted Mexican desert cacti and shouted "I don't want to go back to that!". Frida raged back, "Well, I do want to go back to that!", upon which Diego grabbed a kitchen knife and ripped the canvas to shreds. Lucienne tried to stop him, but Frida held her back, shouting, " No don't! He will kill you!"a statement which says much about how volatile her domestic situation had become.

Diego quieted down, stuffed the torn canvas into his pockets and walked out of the apartment, with Lucienne hurling curses after him in her native French. Lucienne stayed to comfort Frida all day, who was trembling with hurt and rage. "It was", Frida said, "a gesture of hate towards their country". Although Diego had committed a horrible act of emotional violence against Frida, her observation was unfair. Diego cared very deeply for his homeland, just as much as Frida, but he had become disillusioned with it, with the demise of political Muralism in Mexico and the government crack down on Communists. In America he had seen a land of new and virtually unlimited opportunity. Frida was attacking his dream, but at the same time he felt he had no choice but to return home because of her home sickness and increasing dislike of America.

Frida's extraordinary work "My Dress Hangs There", oil and collage on masonite, 1933, records her tension with her husband, her disillusionment with "gringo" society and her increasing sense of isolation and loneliness in New York City. It essentially records a scathing catharticism of the cult of capitalist society. While Frida and Diego mixed in the circles of the super-rich, all around her she saw the desperate state of the ordinary people at the height of the Great Depression. Capitalism was all well and good in America if you happened to have money, but if you did not, then in a society that seemed to live by the motto of "every man for himself", then life was not good at all. She saw at first hand the very best and the very worst of capitalism, at its very epicentre, New York City.

In the background we see Ellis Island with the Statue of Liberty, symbol of the American dream, rising above it, beckoning the oppressed, the poor, the persecuted, from the Old World to come to a new life in America. A large passenger ship steams from the island bringing desperate millions into Manhattan the land of freedom and opportunity. However capitalism is not entirely all that it is made out to be. Both Frida and her husband were ardent communists, and they were quick to see the miseries that the capitalist system had inflicted upon the exploited masses. In collage at the very bottom of the paining we see the massed endless lines of the desperate unemployed at soup kitchens. We see the minute figures of the faceless, starving multitudes in breadlines and demonstrations. In the mid-ground are regimented columns of armed troops ready to charge should things get out of hand. To the right we see an immense garbage bin that overflows with the stinking refuse of a vast metropolis, offal, bones, bottles, blood stained cloth, dead animals, a glove, or is it actually, shockingly, a human hand?

A cathedral rises in the background, perhaps a haven for the poor of sprit, but no, a cross seen in the stained glass window is superimposed by a large "S" that converts it into a dollar sign. The deity of capitalism is the mighty dollar. A ribbon, a powerful and recurring symbol for Frida of connection, joins the tower of the cathedral to Federal Hall; the church is in collusion with the government. And from Federal Hall itself runs a ribbon of another sort, an electrical cable connects a giant telephone atop a soaring skyscraper, which in turn sends its cable on through all the other skyscrapers. The government is in collusion with the captains of industry. Across the base of Federal Hall runs a bar graph recording the immense profits of big business, but none of this obscene wealth filters down to the huddled breadlines below. Revered icons of America are depicted in the statue of George Washington on the steps of City Hall and in the enormous billboard of Mae West in front of the Cathedral. But these are icons from another age - it seems the ideals of Washington, liberty, equality and fraternity are simply a distant memory. The image of Mae West, recalls the golden age of the "roaring twenties" just before the great Wall Street crash. But now even Mae West is a fading memory of another time. Below her a great fire rages out of control, destroying her image that now begins to peel and disintegrate at the edges under the searing heat of the flames.

Standing center stage of the whole depressing work are two large pillars that uphold two great American obsessions - efficient city plumbing - which Frida unkindly represents as an immense toilet on the left - and sports - which she represents as an oversized golden golf trophy, on the right. She slings a clothesline between the two pillars, from which she

hangs one of her favourite Tehuana dresses, a bright embroidered maroon and pea-green reminder of her home, and a symbol of resistance. The dress is empty. She is saying that while my dress may hang in New York City, my soul remains elsewhere, in Mexico.

The Statins were one of the greatest money spinners of all time. A brand new land of hope and opportunity for the suffering multitudes with elevated levels of cholesterol.....and for Big Pharma as well.....Although these agents on the whole increased the happiness of humanity, there are always, as Ms Frida Kahlo, tells us, two sides of the story. The statins for some can have significant toxicity, mainly in the form of potentially serious myopathy and rhabdomyolysis.

"My Dress Hangs There", (Detail) oil and collage on masonite, 1933, Frida Kahlo

PRAVASTATIN

Introduction

Pravastatin, (trade name in Australia "**Pravachol**" amoung others) is a semi-synthetic HMG-CoA reductase inhibitor.

Standard nomenclature designates the suffix "**statin"** to all HMG-CoA reductase inhibitors.

Statins are the first line agent for the treatment of hypercholesterolaemia. They are the most effective oral LDL lowering agents and reduce the risk of cardiovascular events (i.e myocardial infarction and stroke) and mortality in high risk patients.

Myopathy and **rhabdomyolysis** are potentially serious *dose related* adverse effects.

History

Over a century ago the German pathologist **Virchow** observed that the artery walls of patients dying of occlusive vascular disease, such as myocardial infarction, were often thickened and irregular, and contained a yellowish fatty substance subsequently identified as **cholesterol.**

In the 1950s the **Framingham study** established the link between elevated cholesterol levels and atherosclerosis.

Later investigations established that the association with coronary heart disease mortality was attributable mainly to **low-density lipoprotein (LDL)** cholesterol, which typically comprises about 70% of total cholesterol, whereas **high-density lipoprotein (HDL)** cholesterol is *inversely* correlated with coronary heart disease mortality.

Before 1987, the lipid-lowering therapy was limited to dietary changes (reductions in saturated fats and cholesterol), the bile-acid sequestrants (cholestyramine and colestipol), nicotinic acid (niacin), the fibrates and probucol. Unfortunately, all of these treatments were limited by efficacy or tolerability, or both.

The first substance discovered that could inhibit the critical rate limiting enzyme in the synthesis of cholesterol, HMG-CoA reductase, was the **naturally occurring** chemical **compactin**. It was isolated from the mold *Penicillium citrinum* by the Japanese biochemist **Akira Endo** in the mid 1970s. He was awarded the **Japan Prize** in 2006 and the **Lasker Award** in 2008 for his work.

Clinical trials with **compactin** had been proceeding, but for reasons that have never been made public (but which were believed to include serious animal toxicity) the trials were stopped by Sankyo in September 1980.

Trials then began with **lovastatin,** another naturally occurring HMG-CoA reductase inhibitor, closely structurally related to compactin. Lovastatin produced significant

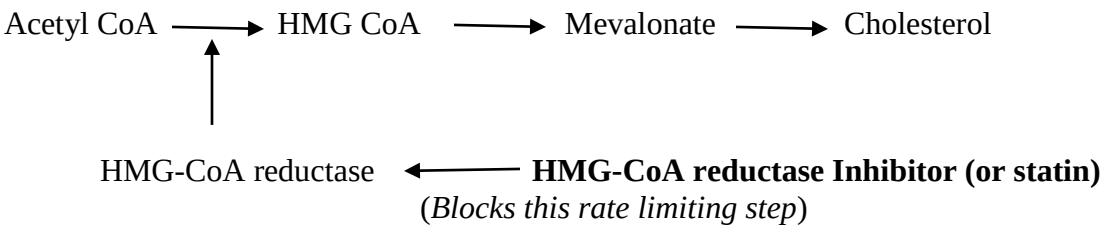
reductions in LDL cholesterol with *minimal* adverse reactions. Lovastatin became the first approved inhibitor of HMG-CoA reductase. It was introduced into clinical practice in 1987 and revolutionized the treatment of hypercholesterolemia. It achieved peak annual sales of more than US $1 billion.

Following the introduction of lovastatin the semisynthetic statins were developed. Simvastatin was introduced in 1988 and **Pravastatin** followed in 1991.

Finally fully synthetic statins were developed and introduced into clinical practice, fluvastatin in 1994, atorvastatin in 1997, cerivastatin in 1998 (later withdrawn due to a high incidence of fatal rhabdomyolysis), and rosuvastatin in 2003.

Chemistry

Atorvastatin is a semi-synthetic HMG-CoA reductase inhibitor.



The **rate limiting** enzyme in the cholesterol biosynthetic pathway, HMG-CoA reductase

See also Appendix 2 below for a more detailed biochemical pathway of cholesterol synthesis in the body

See also Appendix 3 below for a summary of lipid metabolism

Classification

Cholesterol lowering agents include:

1. Statins:
    - Natural agents:
        - ♥ Compactin (not used clinically)
        - ♥ Lovastatin (not available in Australia)
    - Semi-synthetic agents:
        - ♥ Simvastatin (a semisynthetic derivative of lovastatin)
        - ♥ **Pravastatin** (derived from the natural product compactin)

- Fully synthetic agents:
  - ♥ Atorvastatin
  - ♥ Fluvastatin
  - ♥ Rosuvastatin

2. NPC1L-1 inhibitors:
   - Ezetimibe
3. Proprotein convertase subtilisin - kexin type 9 (PCSK9) inhibitors:
   - Evolocumab
   - Alirocumab

Older agents:

4. Bile acid sequestrants (resins):
   - Cholestyramine
5. Fibric acid derivatives (or fibrates)
   - Gemfibrozil

Preparations

Pravastatin sodium as:

Tablets:

- 10 mg
- 20 mg
- 40 mg
- 80 mg

Mechanism of Action

The statins competitively inhibit **HMG-CoA reductase** which is the rate limiting enzyme controlling cholesterol synthesis.

Pharmacodynamics

The statins as a group produce:

1. Reduced concentrations of total cholesterol

2. Profound reductions of apolipoprotein-B-containing lipoproteins, especially LDL cholesterol.

3. Moderate reductions of plasma triglycerides:

    - Statins do decrease triglycerides, although less than fibrates, fish oil or nicotinic acid.

4. Minor increases in HDL cholesterol.

All inhibitors of HMG-CoA reductase produce a *qualitatively* similar effect on the lipid profile.

The mean reduction in LDL cholesterol attainable with the maximal recommended dose of different statins ranges from 35 to 55%. [5]

High levels of LDL contribute to the development of atherosclerotic cardiovascular disease.

Reducing LDL is associated with reductions in cardiovascular events and mortality; the greater the reduction, the greater the benefit.

A 1 mmol/L reduction in LDL, by using a statin, reduces the rate of fatal and non-fatal cardiovascular events by about 20 - 25%.

Raised triglyceride concentrations are a risk factor for coronary heart disease, however, there is no conclusive evidence that reducing them with drugs improves cardiovascular outcomes.

Severe hypertriglyceridaemia (>10 mmol/L) increases the risk of **acute pancreatitis**, and so may be used for this indication, seek specialist advice.

Low levels of HDL appear to be associated with *higher* cardiovascular risk, however there is **no** current evidence that using drugs to raise levels is beneficial.

People at the highest absolute risk of cardiovascular events (e.g. those with pre-existing ischaemic heart disease) will derive the greatest benefit from lipid lowering drugs. Target drug treatment to those at **greatest risk**, rather than considering lipid levels *alone*.

For relative efficacy and potency of commonly used statins, see Appendix 4 below.

Pharmacokinetics

Absorption:

- Pravastatin is administered orally.
- Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio 0.66), which is its primary site of action, and the primary site of cholesterol synthesis and of LDL-C clearance.

Distribution

- Approximately 50% of the circulating drug is bound to plasma proteins.
- It is unknown if pravastatin crosses the human placenta.
- Only very small amounts of pravastatin are distributed in human breast milk .

Metabolism and excretion:

- Approximately 47% of total body clearance is via renal excretion

  Approximately 53% of total body clearance is via by non-renal routes (i.e. biliary excretion and biotransformation).
- Accumulation of drug and/or metabolites may occur in patients with renal or hepatic insufficiency, although, as there are dual routes of elimination, the potential exists for compensatory excretion by the alternate route.
- The major metabolite of pravastatin is the 3-alpha-hydroxy isomer. This metabolite has one-tenth to one-fortieth the HMG-CoA reductase inhibitory activity of the parent compound.
- The plasma elimination half-life of pravastatin (oral) is between 1.5 - 2 hours.

Indications

Current indications for the statins as a group include:

1. Hypercholesterolaemia
2. High risk of coronary heart disease, with or without hypercholesterolaemia

Contra-indications/precautions

These include:

1. Severe intercurrent illness such as infection, trauma, metabolic disorder:

- Increases risk of myopathy, rhabdomyolysis and renal failure; consider withholding statins during significant illness.

  In the case of **surgery** treatment should be *continued* during the perioperative period, especially if there are symptoms of an ACS.

  Avoid stopping statins if there are symptoms of an ACS because stopping is associated with an increased rate of cardiac events (especially in the first week after stopping).

2. Renal impairment:

   - Impairment increases the risk of myopathy and rhabdomyolysis.

3. Hepatic impairment:

   - Statins do not appear to worsen liver disease, however, chronic liver disease itself can increase the concentration of atorvastatin, which may therefore increase the risk of adverse effects; seek specialist advice.

4 Elderly:

   - The elderly (especially > 80 years) are at greater risk of myopathy.

5. Avoid grapefruit juice

   - May effect atorvastatin metabolism, and so increase the risk of toxicity.

6. Pregnancy - breast feeding - contraindicated (see below).

   - Avoid in women planning to conceive or who are using inadequate contraception.

Pregnancy

Pravastatin is a category D drug with respect to pregnancy.

Category D drug are those drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

Cholesterol is essential for embryonic development and fetoplacental growth. The inhibition of HMG-CoA reductase by statins may have a negative impact on the development of the placenta and interfere with fetal development.

Abnormal pregnancy outcomes, including central nervous system (CNS) malformations, limb deficiencies and cleft palates have been reported. However, the absolute risk of teratogenicity of statins appears to be small. A case of prolonged inadvertent use of pravastatin throughout the first 5 months of pregnancy reported no adverse pregnancy and neonatal effects.

Pravastatin has been trialed as a medicine to prevent preeclampsia in high risk pregnant women, and recurrent miscarriages with no adverse effects reported. However, further information is required to determine the safety of the medicine in pregnancy.

Therefore, women who are pregnant or planning pregnancy should discontinue pravastatin for the duration of the pregnancy.

Inadvertent exposure to statins during early pregnancy does not appear to increase the risk of congenital malformations or adverse pregnancy outcomes. However, fetal ultrasound is recommended before decisions are made regarding further pregnancy management.

Consider an alternative, such as dietary modifications, to reduce cholesterol where possible.

Breast feeding

Reports describing the use pravastatin during breastfeeding have not been located.

Very small amounts of pravastatin have been found to be excreted in breast milk.

There are concerns that the use of statins in breastfeeding may disrupt cholesterol biosynthesis and interfere with infant development.

Therefore, treatment is recommended to be with-held where possible and consider an alternative, such as dietary modifications, to reduce cholesterol.

Adverse Effects

Adverse effects from the statins as a group include the following

1. GIT upset:
    - Usually only mild and transient.
2. Myalgia
3. Allergic reactions (rare)
4. Dermatological hypersensitivity reactions (rare)

5 Liver impairment:

- Elevated liver aminotransferases occur in a small percentage pf patients, around 0.5 - 2%.

  This effect it dose dependent, generally responds to a reduction in dosage.

6. Diabetes mellitus:

   - Statins are associated with a *slightly* increased risk for new onset diabetes which appears highest in those who are *already more likely* to develop diabetes.

     A meta-analysis reported that, on average, treating 255 patients with statins for 4 years resulted in 1 additional case of diabetes (while possibly preventing > 5 major coronary events). [2]

7. Myopathy / rhabdomyolysis:

   The risk of myopathy (with or without CK elevation) and rhabdomyolysis is related to:

   - Dose:

     - ♥ The risk of statin induced myopathy increases with increasing plasma concentration.

       Most statins are metabolised by CYP (i.e cytochrome P450) and their metabolism and risk of adverse effects may be affected by treatment with other drugs.

       There are fewer interactions with fluvastatin, pravastatin and rosuvastatin than with atorvastatin or simvastatin.

   - Severe concurrent illness, such as:

     - ♥ Infection, trauma, metabolic disorders, (but *excluding* ACS and surgery)

       Severe intercurrent illness increases the risk of myopathy, rhabdomyolysis and renal failure; consider withholding statin during significant illness.

   - Certain drug interactions:

     - ♥ Sodium fusidate

   - Elderly:

- ♥ The risk of myopathy is higher in the elderly, especially if frail, age > 80 years or with multiple comorbidities; use cautiously and start at low dosage.

Effects on ocular muscles may cause visual disturbances (e.g. diplopia or blurred vision).

There have been rare reports of an **autoimmune necrotising myopathy,** generally with CK concentration >10 times the upper limit of normal and with anti-HMG-CoA reductase autoantibodies, which does not resolve solely on stopping the statin.

Dosing

Before starting drug treatment, obtain a plasma lipid profile:

- Total cholesterol (TC)
- HDL/ LDL
- Triglycerides

Identify secondary causes of dyslipidaemia, e.g. diabetes, hypothyroidism, and treat these as required.

Reduce other modifiable cardiovascular risk factors

Markedly raised cholesterol levels (e.g. TC > **7.5 mmol/L**) and family history of premature coronary heart disease may indicate familial hypercholesterolaemia; seek specialist advice

Usual adult dosing for **Pravastatin** is:

- 20 - 80 mg daily (in 1 or 2 doses).

  Doses are increased after 4 weeks as necessary.

Renal impairment / elderly:

- Oral, initially 10 mg once daily; the adjust as above.

Unstable angina, post MI

- Oral, initially 40 mg once daily; then adjust as above.

Monitoring:

Monitor aminotransferase and CK at baseline, repeat during treatment if indicated clinically.

Monitor closely for myopathy (with or without CK elevation) and rhabdomyolysis

Stop the statin if:

1. Aminotransferase concentrations are persistently elevated to > 3 times ULN

2. CK concentrations become elevated.

3. There is persistent unexplained muscle pain (even if CK is normal)

If raised CK concentrations persist after stopping the statin, consider other causes for myopathy (such as asymptomatic hypothyroidism or neuromuscular diseases), some of which may be **unmasked by statin treatment.**

Treatment may be resumed after at least 4 weeks if myopathy/myositis was mild and CK concentration, if raised, has returned to normal.

Consider:

1. Whether a precipitant (e.g. trauma, surgery) or a drug interaction contributed to this adverse effect

2. Using a lower dose (as these adverse effects are dose-related)

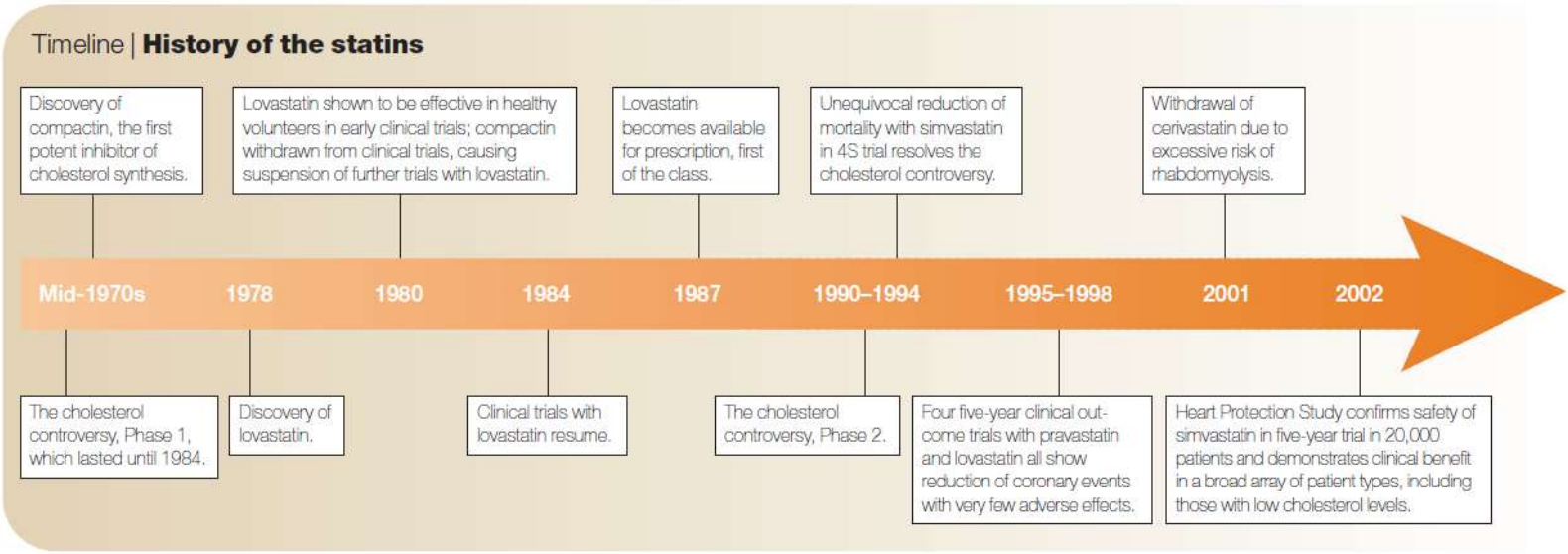
3. Using an alternative statin (although there are few data comparing risk between agents)

If the problem recurs on rechallenge, stop statins permanently

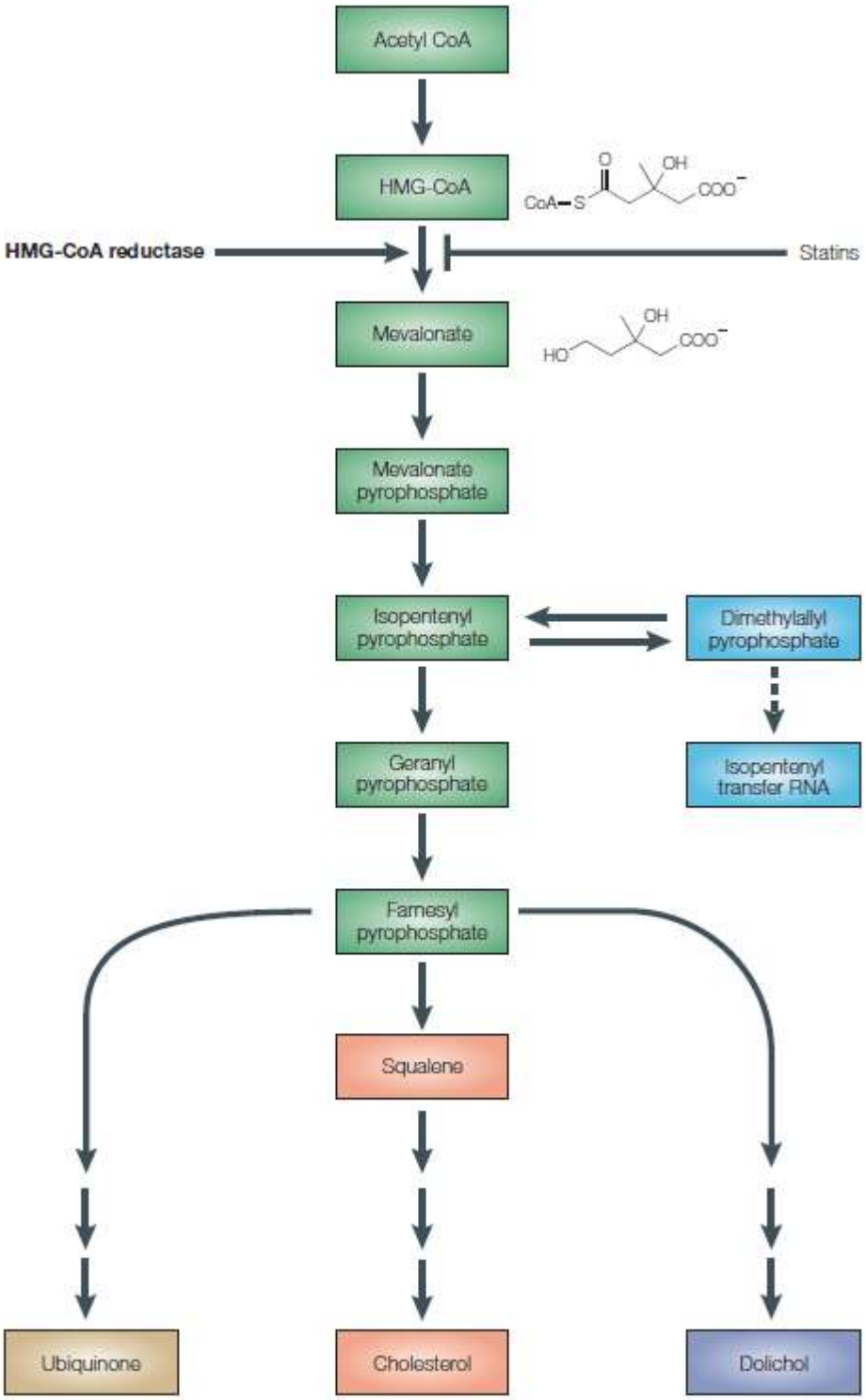
See Appendix 5 for a suggested protocol for managing statin associated muscle symptoms (SAMS)

Appendix 1

History of the Statins:

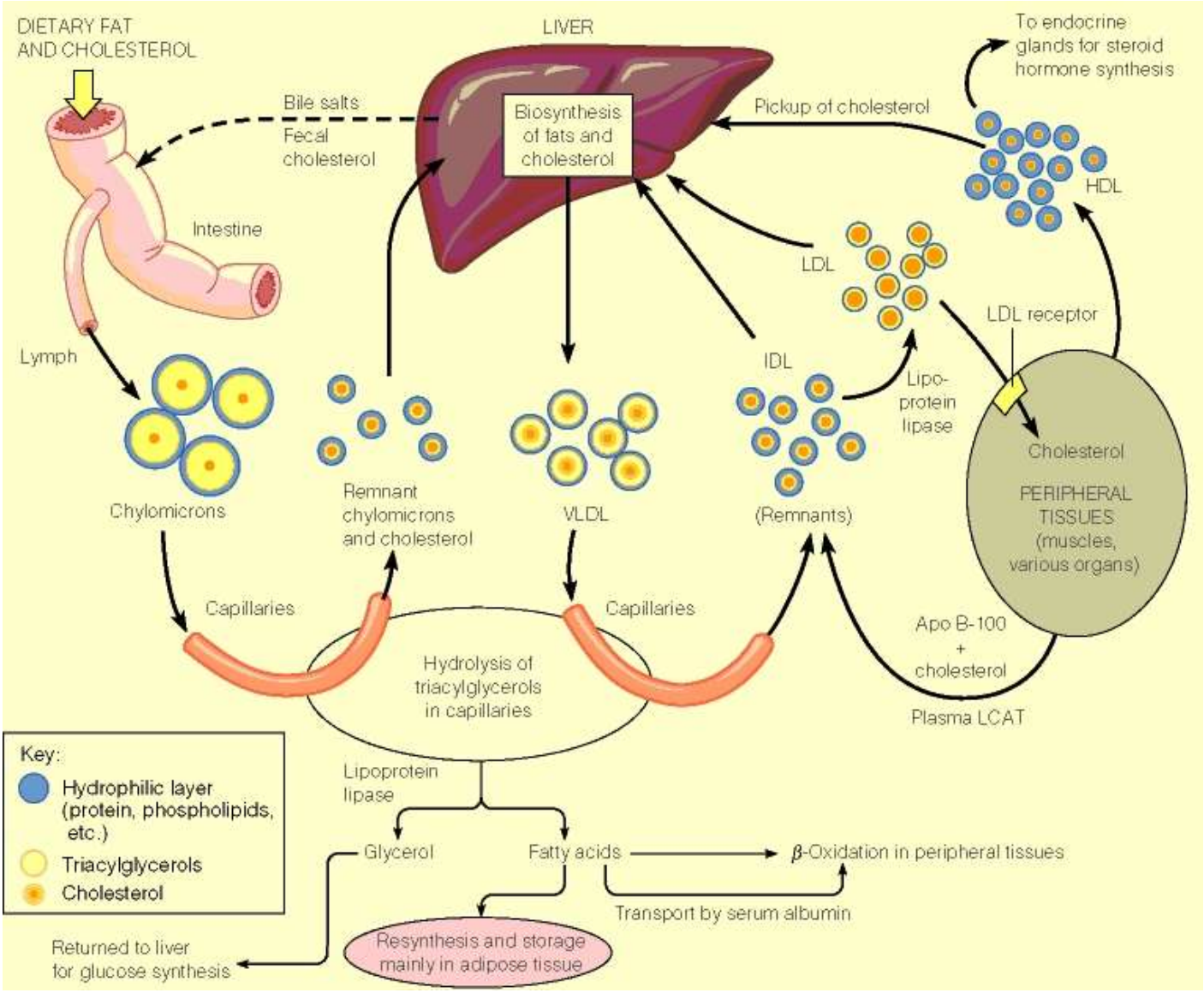


Appendix 2



The cholesterol biosynthesis pathway. Cholesterol biosynthesis is a complex process involving more than 30 enzymes. A simplified version is shown here, which highlights the step inhibited by statins, and shows the chemical structures of the starting material (HMG-CoA) and product (mevalonate) of this step.

Appendix 3 *Summary of lipid metabolism:*



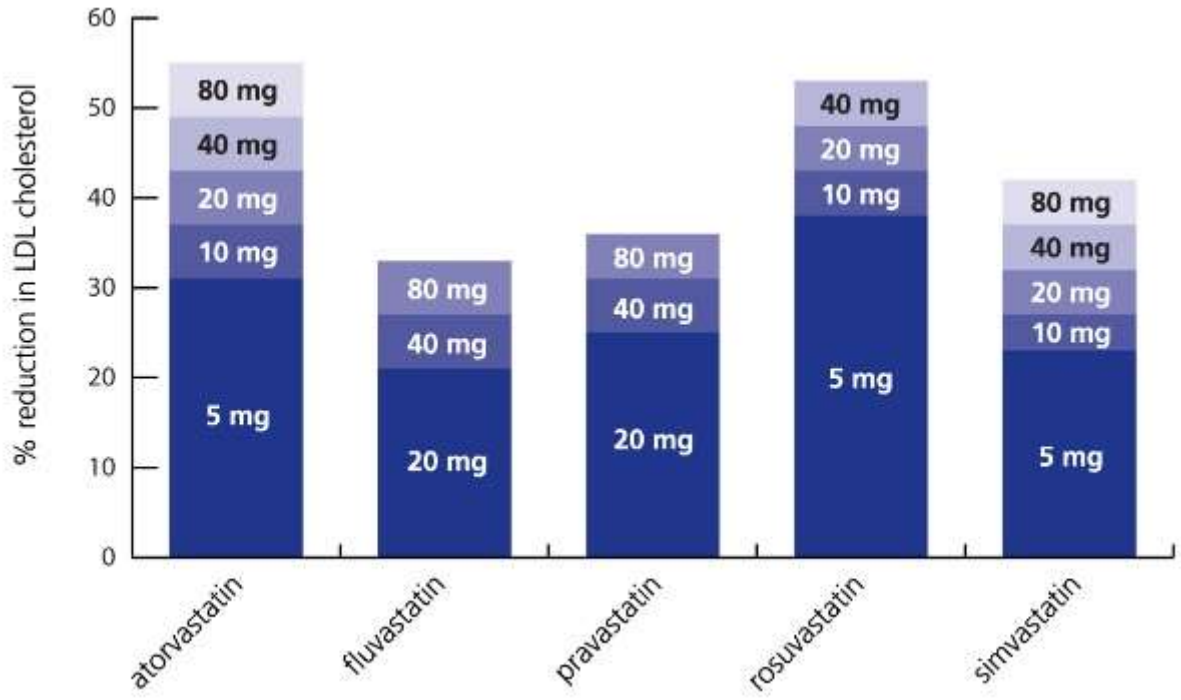
Note that LDL transports cholesterol to the peripheral tissues. HDL takes it from the tissues, back to the liver. (Diagram: Dr. James Thompson; http://www.apsubiology.org/)

LDL transports lipids, particularly cholesterol, and neutral fats (triglycerides), from the liver to most somatic tissue cells for their various metabolic needs.

HDL transports lipids, particularly cholesterol, and neutral fats (triglycerides), back to the liver for ***catabolism and elimination****.*

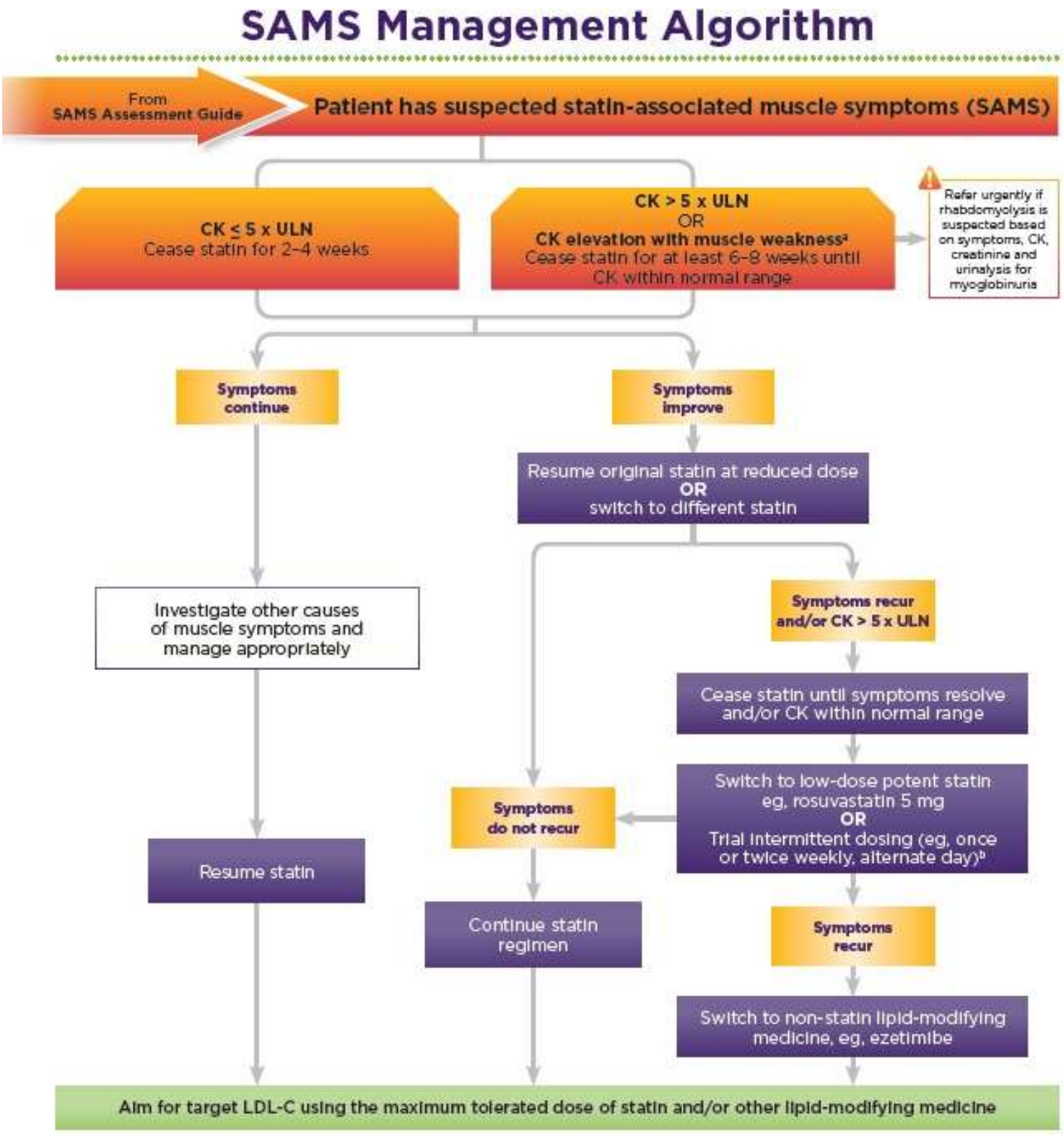
Coronary heart disease mortality is attributable mainly to ***low-density lipoprotein (LDL)*** *cholesterol, which typically comprises about 70% of total cholesterol, whereas* ***high-density lipoprotein (HDL)*** *cholesterol is inversely correlated with coronary heart disease mortality.*

Appendix 4



Relative efficacy and potency of commonly used statins - effects on LDL cholesterol levels, (AMH - Statins - July 2018).

Appendix 5 - *Management of Statin Associated Muscle Symptoms:*



CK = creatine kinase, LDL-C = low density lipoprotein cholesterol, ULN = upper limit of normal
[a] CK > ULN and weakness demonstrated upon physical examination. [b] Higher potency statins with a long half-life are preferred for intermittent dosing eg, rosuvastatin and atorvastatin

2017 NPS MedicineWise

"My Dress Hangs There", (Detail) oil and collage on masonite, 1933, Frida Kahlo

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4. Pravastatin, in RWH Pregnancy & Breastfeeding Guidelines, 15 December 2017

5. Jonathan A. Tobert, "Lovastatin and Beyond: The History of the HMG-CoA Reductase Inhibitors. Nature Reviews: Drug Discovery vol. 2 July 2003. P. 517-526.

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