CASE STUDY

Challenging cases in lipid management and CVD prevention

A retrospective and an update

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Case studies representing challenges in lipid management and cardiovascular disease prevention that have already been published in Cardiology Today are revisited to see whether the key messages remain current and to give updates as necessary.

Over the past three years, I have presented 13 informative case discussions in *Cardiology Today* representing challenges in lipid management and cardiovascular disease (CVD) prevention. Some of the histories have generated personal correspondence with readers and this has been gratifying. In retrospect, these case histories could be grouped into several themes. It is now timely to revisit the various thematic groups to see whether the key messages remain current and to update as necessary.

Patients with adverse events while taking statins

Case 1 (vol 1, issue 1): *A 64-year-old man with angina taking the maximum dose of atorvastatin at 80 mg/day was noted to have a minor degree of liver dysfunction (alanine transaminase level 80 IU/L, reference range <45 IU/L).*

Although statin therapy may occasionally be associated with significant liver dysfunction requiring drug cessation, the minor elevation in this case had fully resolved within six weeks without cessation of therapy. The precise cause of a transient and minor increase in serum transaminase levels is often uncertain. Some authorities have even counselled against regular measurement of liver enzymes in this context. I am more conservative and prefer to monitor liver enzymes at say half-yearly intervals alongside the lipid profile. This is not an expensive exercise and it does have motivational value for the patient.

An elevated gamma-glutamyl transferase level with a normal transaminase level is not a feature of statin hepatotoxicity and usually has a number of different causations, most commonly fatty change, high alcohol intake, diabetes and obesity.

This man suffered a myocardial infarction after some years while taking statin therapy, serving as a reminder that statin therapy cannot abolish CVD risk.

Case 2 (vol 1, issue 2): *A 46-year-old healthy woman was anxious about her coronary risk and convinced her GP to prescribe atorvastatin 10 mg/day. Within three weeks she returned complaining of mood changes and myalgia in her arms and legs. The muscle enzyme creatine kinase was not materially raised (creatine kinase level 210 IU/L, reference range <230 IU/L). She suspended treatment and her symptoms rapidly resolved. She expressed regret about her desire to use statin therapy and requested specialist review of prognosis and management.*

Her symptoms were most likely related to

Key points

- **Statin drugs form part of the standard cardiovascular disease therapy, especially in high-risk patients.**
- **A small proportion of patients receiving statin therapy will manifest adverse events, notably myalgia, liver dysfunction or central nervous system symptoms. In some instances therapy cannot be continued.**
- **Patients with familial hypercholesterolaemia are often unable to achieve goal lipid levels and novel therapy with an inhibitor of the key protein PCSK9 holds hope for the future. This therapy may also be helpful in patients unable to tolerate statins.**
- **In patients with severe hypertriglyceridaemia, fenofibrate may be a relevant therapy if underlying problems such as high alcohol intake, diabetes or obesity have been excluded or resolved.**
- **Overly sensational and unbalanced media reporting continues to alarm patients who are taking statins, often leading to cessation of therapy.**
- **Novel risk factors such as lipoprotein(a) and homocysteine should be assessed if patients have unexplained coronary artery disease.**
- **Use of statins in the elderly requires empirical clinical judgements, often in the absence of strong clinical evidence.**

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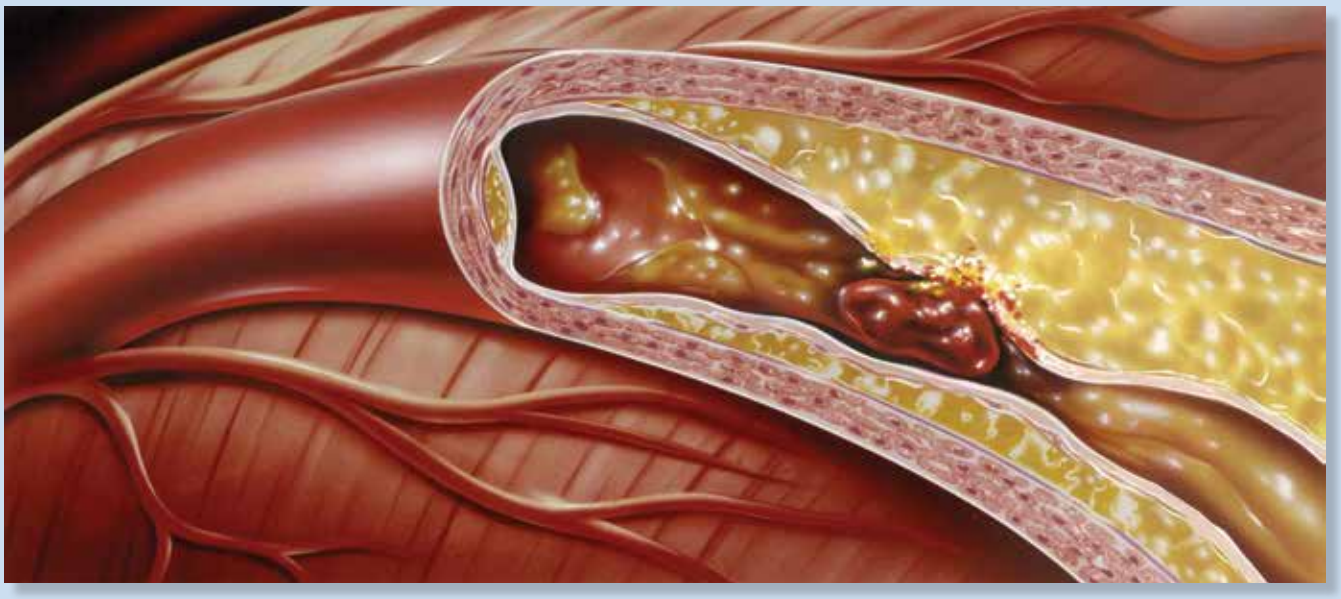

statin therapy, although other diagnoses (e.g. viral illness, fibromyalgia, connective tissue disorder) were possible. Based on her age, gender, lipid levels, favourable blood pressure and absence of diabetes or cigarette smoking, her five-year absolute risk of CVD was very low at about 1.5%, 15% being a threshold for high CVD risk in her situation. The easiest way to avoid future adverse events was to avoid statin therapy because this was not strongly indicated in her case. She was managed with diet and lifestyle advice with occasional review of risk factors.

Case 3 (vol 1, issue 3): *A 59-year-old woman had suffered a myocardial infarction two years previously and was using standard postinfarction therapy, including atorvastatin 80 mg/day. She developed generalised myalgia in association with a small increase in creatine kinase level from 210 to 265 IU/L (reference range <230 IU/L). Her symptoms resolved within two weeks of statin cessation and it was deemed too risky for a return to high-dose statin, even though it was clinically indicated. She was cautiously started on a very small dose of rosuvastatin, 5 mg on two mornings each week. She remained free of myalgia and much later the dose was increased to 5 mg daily with good control of her lipid profile (LDL-cholesterol [LDL-C] 2.1 mmol/L versus pretreatment value of 3.8 mmol/L).*

Unless highly elevated, creatine kinase readings are not a good indicator of statin-induced muscle problems. The use of rosuvastatin in secondary prevention is not evidence based. On the other hand, there is a widely held view that all statins have a similarly beneficial effect in this setting. Low-dose rosuvastatin was a useful compromise here as there remained the possibility of return of myalgia at higher dosage.

Case 4 (vol 3, issue 3): *A 36-year-old man with a highly adverse family history of premature CVD had elevated LDL-C levels (5.3 mmol/L), lowish HDL-cholesterol levels (0.9 mmol/L), elevated triglyceride levels (3.7 mmol/L) and abdominal obesity, an example of the metabolic syndrome. He was judged to be at high coronary risk and was given dietary advice. Subsequent weight reduction was small and changes in lipid levels were marginal.*

He was prescribed atorvastatin 10 mg/day, later increased to 20 mg/day, but he returned later with generalised myalgia and leg cramps. Statin therapy was suspended and his lipid profile reverted to prestatin levels. Further investigation by this consultant revealed a diagnosis of hypothyroidism on the basis of autoimmune thyroiditis.

His elevated LDL-C level was attributed to hypothyroidism and he was started on thyroxine 50 µg/day, gradually uptitrated to 100 µg/day with return of thyroid-stimulating hormone levels to within the physiological range. In this situation he still had a residual elevation in LDL-C at 3.6 mmol/L (desirable <2.5 mmol/L). The patient requested a return to atorvastatin 10 mg/day, he remained free of side effects, and his subsequent LDL-C level was 2.1 mmol/L.

This man had two separate diagnoses present, hypothyroidism and primary hypercholesterolaemia, each capable of raising LDL-C levels. Muscle problems with statins are more frequent in the presence of concurrent hypothyroidism. All patients with a significantly elevated cholesterol level (say >7.0 mmol/L) require a single thyroid screen with measurement of thyroid-stimulating hormone levels. Side effects with use of statins may not return when hypothyroidism is corrected.

Patients unable to achieve goal lipid levels

Case 5 (vol 2, issue 4): *A 45-year-old man had suffered an acute coronary syndrome three years previously. He was diagnosed with heterozygous familial hypercholesterolaemia based on a total cholesterol level of 10.6 mmol/L, a LDL-C level of 8.8 mmol/L, a similar lipid profile in his 10-year-old daughter and a family history of premature coronary disease in his father. He was given standard medications, including*

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atorvastatin 80 mg/day, ultimately achieving an LDL-C level of 3.8 mmol/L. The patient and GP were frustrated he could not do better.

This consultant reviewed his case, offered supplementary ezetimibe 10 mg/day and the patient's subsequent LDL-C level was in the range of 2.4 to 2.6 mmol/L, representing a 70% reduction from baseline. This was probably the best he would achieve using currently available and palatable therapy. LDL apheresis was discussed but was not available for geographic reasons. He will be a good candidate for new therapy, namely an inhibitor of the key protein proprotein convertase subtilisin/kexin type 9 (PCSK9), which is still under evaluation. This therapy is discussed later in relation to case 13.

Case 6 (vol 3, issue 2): *The 16-year-old daughter of another patient with heterozygous familial hypercholesterolaemia was referred for consultant opinion. Following standard dietary advice, her total cholesterol level was 7.0 mmol/L and LDL-C level was 5.0 mmol/L.*

This was a similar diagnosis to her father and her long-term CVD risk was certainly increased. She needed statin therapy but the timing of its introduction was the key issue. Although some experts now recommend statin therapy for teenagers with this diagnosis, my personal approach was and still is more conservative. Statin therapy in young women with this diagnosis can be delayed until they have completed child-bearing or until they have reached 25 to 30 years of age, unless there are extenuating circumstances (e.g. highly premature CVD in a close relative, very high cholesterol readings in the young person [⩾10 mmol/L], the presence of other major risk factors, or if there is serious anxiety in patient or family). I am much less conservative in young men.

She was treated conservatively and returned for review at the age of 26 years with a similar lipid profile, but with no other coronary risk factors. Pregnancy was not contemplated in the near future and it was mutually agreed that she would start statin therapy. She was offered rosuvastatin 10 mg/day with subsequent GP follow up, with a request for dose titration according to her responses. She was also advised to suspend statin therapy if a pregnancy was contemplated.

Case 7 (vol 3, issue 1): *A previously well 28-year-old woman presented to hospital with acute pancreatitis. Although there are many causes of acute pancreatitis, in her case the cause was suspected to be severe hypertriglyceridaemia (triglyceride level of 78 mmol/L; reference range <2.0 mmol/L), with total cholesterol levels of 16.6 mmol/L. With appropriate management she made a good clinical recovery. She was discharged on a low-fat diet (approximately 10% energy from fat, also some use of medium-chain triglyceride oils) and atorvastatin 40 mg/day, ultimately increased to 80 mg/day; however, her triglyceride levels were still high at 15 mmol/L and cholesterol level at 9.6 mmol/L.*

Triglyceride levels persistently above 10 mmol/L, usually on a genetic basis, but with possible exacerbation by alcohol intake, diabetes, obesity or exogenous oestrogen, are a well recognised cause of acute pancreatitis. But these patients are not ideally managed with statins alone and this patient was subsequently prescribed a fibrate drug (fenofibrate 145 mg/day). At the same time her dose of atorvastatin was reduced to 10 mg/day, later increased to 40 mg/day. Her lipid profile was never ideal, even when she added high-dose omega-3 from fish oil (triglyceride level 4.8 mmol/L, cholesterol level 4.8 mmol/L). A compromise was declared and she has remained well subsequently.

Fenofibrate has an important role in the long-term management of patients with acute pancreatitis caused by severe hypertriglyceridaemia, when other causes have been addressed. It is contraindicated if a patient develops pancreatitis while already using fenofibrate. Fenofibrate can be used with relative safety in combination with submaximal doses of a statin, but that is not true in the case of gemfibrozil.

A second case was also presented, that of a 58-year-old homeless, alcoholic man with a similar clinical presentation of acute pancreatitis to the patient just discussed (triglyceride level 38 mmol/L, cholesterol level 10.1 mmol/L). At the point of hospital discharge, his triglyceride level was 3.9 mmol/L and cholesterol level was 4.6 mmol/L. Hepatic cirrhosis was diagnosed and he was referred to a clinic for alcohol and drug addiction. He failed to attend and his prognosis will be poor. Lipid-modifying drugs would be generally ineffective in his case while alcohol intake continued.

Influence of the media on patient behaviour

Case 8 (vol 2, issue 2): *A 68-year-old man who had suffered an acute coronary syndrome was successfully stented and discharged home on standard medications: aspirin, clopidogrel, ramipril, metoprolol, atorvastatin and allopurinol (he had gout). At follow up he expressed annoyance that a now symptom-free person was taking six different drugs costing about $200 per month.*

In February 2012, he woke up to an alarming front-page newspaper story with the headline 'miracle drugs put thousands at risk'. His take on the story was that statin therapy might lead to dementia and/or diabetes. He stopped taking his statin therapy, as did many other patients on reading this story.

This newspaper story was based on an FDA advisory report of a low risk of new-onset diabetes or cognitive impairment in patients taking statin drugs. This was a cautionary warning to be included in official product information. Regrettably (and predictably) the media report lacked any true perspective. The practical message should have been: although statins have a definite but low risk of important side effects and patients deserve careful monitoring, we possess ample evidence of significant cardiovascular benefit when patients at higher risk are treated with statins.

Case 9 (vol 2, issue 3): *A 63-year-old man without prior history of coronary disease and cholesterol elevation of 8 mmol/L developed myalgia while taking atorvastatin 20 mg/day. He was switched to rosuvastatin reaching 20 mg/day without return of myalgia. Although this patient's cholesterol*

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control was improved, 18 months later his GP diagnosed him with type 2 diabetes. Fasting plasma glucose levels prior to taking rosuvastatin was 5.7 mmol/L (desirable <5.5 mmol/L) and was now at 8.3 mmol/L, yet HbA_{1c} was satisfactory at 6.6% (desirable <7.0%). In fact, his intake of rosuvastatin was erratic, possibly omitting two to three tablets each week.

Subsequently the patient read the same newspaper article mentioned in Case 8 and became quite concerned about his new-onset diabetes and he was referred to this consultant.

The patient's body mass index was 28.4 kg/m^2, waist circumference 105 cm (desirable <95 cm), fasting plasma glucose level 7.3 mmol/L and HbA_{1c} 6.7%. He had gradually developed type 2 diabetes, although his current glycaemic control was acceptable. He had probably developed diabetes for the usual reasons, including age, being overweight and a possible genetic predisposition. His years of potent statin therapy may also have contributed. The mechanism of statin-induced diabetes is uncertain and we do not know if this effect is reversible on statin cessation. There was justification for ongoing statin therapy but he declined to accept this advice.

We have witnessed an unfortunate repeat of this media scenario in a prominent ABC TV science program in late 2013. The program was unbalanced, over-emphasised adverse events with statins, implied that statin therapy was a conspiracy generated by the pharmaceutical industry, promoted naturopathy and failed to give proper credence to the value of statin therapy. Six months later, ABC TV finally acknowledged that the program was unbalanced and it was withdrawn. In the interim period many patients were highly alarmed by such sensational reporting and stopped their medication. It is uncertain how many have now resumed therapy.

Unusual and special situations

Case 10 (vol 4, issue 1): *A well 53-year-old woman with an LDL-C level of 5.5 mmol/L (reference range <2.0 mmol/L) and no other risk factors was treated conservatively with diet and lifestyle advice. She had read that women with coronary disease were often under-diagnosed or under-treated and so pressured her GP into prescribing atorvastatin. The dose ultimately reached 40 mg/day with her LDL-C level falling to 2.8 mmol/L.*

Some years later she presented with chest palpitations and various cardiac investigations were performed. She had a positive stress ECG, leading to CT coronary angiography. Her coronary calcium score was elevated at 184 and the CT coronary angiogram showed significant two-vessel coronary disease. She was successfully stented and discharged on standard medications, including atorvastatin 80 mg/day.

The patient continually pressed her doctors as to why she had developed advanced coronary artery disease at a youngish age despite statin therapy and in the absence of other major risk factors. Referral followed to this consultant.

Although risk factors may not be identifiable in a small proportion of patients with coronary disease, curiosity was aroused and measurement of serum homocysteine and lipoprotein(a) (Lp(a)) was arranged. Homocysteine was in the physiological range at 7.0 µmol/L, whereas Lp(a) was highly elevated at 1000 mg/L (reference range <350 mg/L). In a large meta-analysis, Lp(a) was found to be an independent but modest risk factor for coronary disease or ischaemic stroke, with extreme risk at very high levels – the very situation in this patient.

Lp(a) measurement is not covered by current Medicare reimbursement and should not be part of a routine check up. But in the setting of unexplained coronary disease, measurement of Lp(a) is strongly indicated. Family screening may also be helpful in relevant cases. Regrettably, we currently possess limited means to reduce elevated Lp(a) levels, and there is no evidence to suggest that such a step would be beneficial.

Case 11 (vol 3, issue 4): *An 82-year-old man had suffered an acute coronary syndrome and was stented and discharged well on standard therapy. He had few conventional risk factors beyond age and an LDL-C level slightly elevated at 3.2 mmol/L. Therapy included atorvastatin 40 mg/day. He remained reasonably well and at the age of 92 years his family began to question whether all of his many drugs were essential.*

Should an 82-year-old person be started on a statin? We possess some clinical trial evidence that statin therapy would be beneficial in his age group. Hence, on a purely empirical basis, high-dose statin would usually be prescribed in his situation. Should he continue to take a statin at the age of 92 years? Limited clinical trial evidence supports ongoing benefit in the elderly and it was decided to continue his statin therapy as he seemed to maintain good quality of life and was free of any apparent side effects from statins (or his other drugs).

In a second case, a 92-year-old woman had a cerebral thrombosis with hemiparesis, from which she only made a partial recovery. Her risk factors were age, untreated systolic hypertension and a moderate elevation of LDL-C level at 3.8 mmol/L. Her blood pressure was stabilised with therapy but the attending geriatrician decided against the use of statins.

Although I have now raised the issue of statin therapy in two patients aged 92 years, in the first instance this was a matter of drug continuation and one was reluctant to stop statin therapy. To initiate statin therapy in a 92-year-old person with a major stroke is more problematical because the likelihood of adverse events and drug interactions is increased.

Case 12 (vol 1, issue 4): *A 56-year-old well man was offered a free CT coronary angiogram in the absence of any clinical indication by his radiologist who was his golfing partner. Regrettably, this showed a very high calcium score of 350, a 30% blockage in the left anterior descending artery and early changes in the right coronary artery. He was directed to his GP for investigation and management.*

Body mass index was 29 kg/m^2, blood pressure was 140/90 mmHg and LDL-C level was 3.2 mmol/L. The GP recognised the presence of significant coronary artery

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disease, yet the patient felt perfectly well and could not believe he needed drug therapy. He was reviewed by a cardiologist and a stress ECG was negative, but the cardiologist supported the advice from the GP. Dietary therapy was pursued with little improvement and after further counselling the patient was started on conventional drug therapy.

The presence of coronary artery disease in this man was revealed through a non-conventional pathway. Nonetheless, he had significant coronary disease demonstrated and by default he had become an example of secondary CVD prevention.

CT coronary angiography is not regarded as an appropriate investigation in well patients without cardiac symptoms, nor in those with obvious coronary disease. It is more clearly indicated in patients who seem to be at intermediate coronary risk (e.g. atypical chest pain, those carrying major risk factors) as an aid to further management decisions. A comprehensive discussion of CT coronary angiography and coronary calcium score is available in an article by Christian Hamilton-Craig and Ian Hamilton-Craig titled 'Coronary calcium scan and coronary CT angiography: chalk and cheese' published in the September 2011 issue of *Cardiology Today*.

Case 13 (vol 4, issue 2): *A 58-year-old man with multiple risk factors, including hypertension, recent cigarette smoking and an elevated cholesterol level, was referred for consultant opinion. He was receiving standard antihypertensive therapy but had experienced generalised myalgia and arthralgia when atorvastatin or rosuvastatin had been given.*

He experienced similar side effects with pravastatin. With an LDL-C level of 5.7 mmol/L and complete statin intolerance, he was invited to participate in a clinical trial involving monthly subcutaneous injection of evolocumab, a human monoclonal antibody to a key regulatory protein known as PCSK9. A number of these products were under investigation at this time. He responded safely and effectively to this treatment over the next two years, with an LDL-C level reduced by 55% while taking evolocumab in combination with ezetimibe.

The mechanism of action of the inhibitor of PCSK9 was fully described in the case study in the June 2014 issue of *Cardiology Today*. There are major regulatory hurdles to be overcome before we will see commercial availability of this type of product, perhaps another one to two years from now. Inhibitors to PCSK9 will not replace statin therapy, yet this approach may represent the next major breakthrough in lipid therapy and CVD prevention. Major CVD outcome trials are continuing with these products around the world. **CT**

COMPETING INTERESTS: None. The views expressed in this paper are purely those of the author.

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