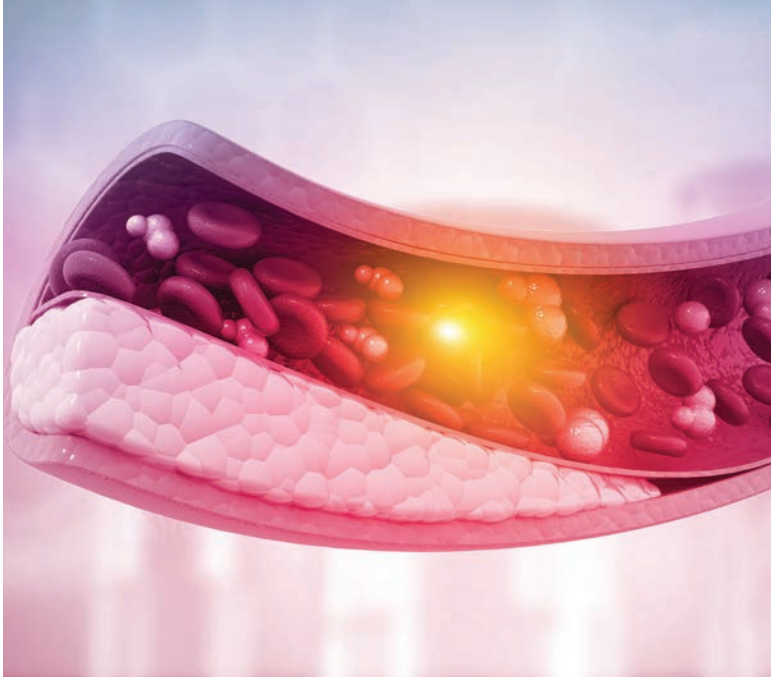
Ongoing challenges in lipid management

A retrospective in nine cases



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Statins are widely accepted therapy for lipid management in patients at increased risk of atherosclerotic cardiovascular disease (CVD). However, mitigation of CVD risk in the event of an adverse effect and the inability to reach lipid targets remain key challenges of lipid management. These patients often require an individualised approach to management, such as with a lower-dose statin or an alternative therapy.

Risk factors for atherosclerotic cardiovascular disease (CVD) are well known. Lipid management plays an important role in managing this risk, in the context of both primary and secondary prevention. Although therapeutic options continue to evolve, the challenges of lipid management (and possibly therapies for CVD risk reduction) remain essentially unchanged. For that reason, this article revisits some key challenges in lipid management and presents case histories, which are grouped into key thematic areas. A summary of the key practice points is presented in the Box.

MedicineToday 2023; 24(11): 47-50

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Patients with adverse events associated with statin therapy

Case 1

A 64-year-old man with angina taking atorvastatin 40 mg daily, in addition to other standard therapy, was noted to have a minor degree of liver dysfunction (alanine transaminase level 60 IU/L, aspartate transaminase level 55 IU/L, reference range <41 IU/L).

Statins, generally atorvastatin or rosuvastatin in everyday practice, remain a cornerstone of lipid-lowering therapy; however, they may occasionally be associated with significant liver dysfunction. An elevation in transaminase level beyond three times the upper reference level requires statin cessation. The relatively minor elevations in this patient resolved completely within six weeks without any cessation of therapy. The precise cause of a transient and minor increase in serum transaminase levels is often uncertain but may be due to a minor intercurrent illness. This clinical situation is best managed by a watch-and-wait approach and rechecking liver enzymes six to eight weeks later, by which time the problem has usually resolved.

Significantly elevated gamma-glutamyltransferase levels, with little or no elevation in transaminase levels, is not a feature of statin-induced hepatotoxicity and usually has other causes, such as fatty liver disease, excessive alcohol consumption, diabetes, obesity and the use of other drugs.

This patient experienced a myocardial infarction some years later while on statin therapy, despite achieving ideal lipid levels, serving as a reminder that statin therapy cannot abolish all future CVD risk.

Case 2

A 59-year-old woman experienced a myocardial infarction two months previously and was subsequently prescribed standard post-infarction therapy, including atorvastatin 80 mg daily. She developed generalised myalgia in association with a small increase in creatine kinase (CK) from 190 to 275 U/L (reference range <200 U/L). Her symptoms resolved within one week of statin cessation and, although a return to high-dose atorvastatin was clinically indicated, it was deemed too risky.

PRACTICE POINTS

- Statin drugs continue to form part of standard therapy in cardiovascular disease prevention or management, 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, this therapy cannot be continued.
- Patients with familial hypercholesterolaemia are often unable to achieve target lipid levels. Additional therapy with evolocumab, an inhibitor of the protein PCSK9, will prove helpful. This approach will also be helpful in other patients who have not reached target levels or in those unable to tolerate statins.
- Lipoprotein(a) should be assessed if patients have unexplained coronary artery disease or in the presence of familial hypercholesterolaemia.
- In patients with severe hypertriglyceridaemia, fenofibrate may be helpful when underlying problems, such as excessive alcohol intake, diabetes or obesity, have been excluded or addressed.
- Sensational and unbalanced media reporting continues to alarm patients using statins, often leading to cessation of therapy.
- Use of statins in older people may require empirical clinical judgements, often in the absence of strong clinical evidence.
- A number of new therapies are under clinical investigation, including the PCSK9 inhibitor inclisiran, bempedoic acid and icosapent ethyl.

She was cautiously started on a very low dose of rosuvastatin 5 mg on two mornings each week. She remained free of myalgia and, one month later, the dose was increased to 5 mg daily. She achieved an ideal LDL-cholesterol (LDL-C) level of 1.4 mmol/L (compared with a pretreatment level of 3.0 mmol/L).

Minor elevations in CK levels are not always indicative of statin-induced muscle problems. The presence of muscle symptoms is much more informative. Although the use of low-dose rosuvastatin in secondary prevention is not strictly evidence-based, it is a widely held view that all statins have a similar beneficial effect in this setting. Low-dose rosuvastatin was a useful compromise in this case, but the possibility of a return of myalgia at a higher dosage remained.

Case 3

A 44-year-old man with a highly adverse family history of premature CVD had elevated total and LDL-C levels (8.3 mmol/L and 5.3 mmol/L, respectively), a borderline low HDL-cholesterol (HDL-C) level (0.9 mmol/L), an elevated triglyceride level (3.7 mmol/L) and abdominal obesity, consistent with the metabolic syndrome. He was deemed to be at high coronary risk and was given advice to lose weight. Subsequent weight reduction was small and changes in his lipid levels were marginal.

He was prescribed atorvastatin 10 mg daily, which was later increased to 20 mg daily. He returned six weeks later with generalised myalgia and leg cramps. Statin use was suspended and his lipid profile reverted to pre-statin levels. Further investigation 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 mcg daily, which was gradually up-titrated to 100 mcg daily, with a return of an elevated thyroid stimulating hormone (TSH) level to the physiological range. With this therapy, he lost a small amount of weight, achieved normal triglyceride and HDL-C levels, and an LDL-C level of 2.0 mmol/L (reference range <2.5 mmol/L).

Muscle problems with statin use are more frequent in the presence of concurrent hypothyroidism. All patients with a significantly elevated cholesterol level (>7.0 mmol/L) require a single thyroid screen with TSH measurement.

Patients unable to achieve target lipid levels

Case 4

A 48-year-old man experienced an acute coronary syndrome. He was diagnosed with familial heterozygous hypercholesterolaemia, based on a total cholesterol level of 10.6 mmol/L, LDL-C level of 8.8 mmol/L and a family history of elevated cholesterol levels and premature coronary artery disease in his father. The patient's TSH level was in the physiological range. He was given standard medications, including atorvastatin 80 mg daily, and eventually achieved an LDL-C level of 4.0 mmol/L. The patient and GP were frustrated that lower LDL-C levels were not achieved.

This consultant reviewed his case and offered supplementary ezetimibe 10 mg daily; the subsequent LDL-C levels were in the range of 2.8 to 3.0 mmol/L. The patient was eligible to receive the PCSK9 inhibitor evolocumab under PBS subsidy criteria, which include having an LDL-C level above 1.8 mmol/L and the presence of symptomatic CVD. A full list of criteria can be found on the PBS website (https://www.pbs.gov.au/). He was commenced on evolocumab 140 mg subcutaneous injection every two weeks. On review three months later, his LDL-C level had reduced to 1.3 mmol/L.

The patient continued using evolocumab, a statin and ezetimibe with good asherence, resulting in stable lipid levels and stable health.

Case 5

A previously well 31-year-old man presented to hospital with acute pancreatitis, thought to be due to severe hypertriglyceridaemia. His triglyceride levels were 48 mmol/L (reference range <2.0 mmol/L), together with a total cholesterol level of 16.6 mmol/L. With appropriate in-hospital management, he made a good clinical recovery. He was discharged on atorvastatin

40 mg daily and advised to consume a low-fat diet (about 10% energy from fat). However, four weeks later, his triglyceride levels were still elevated at 15 mmol/L, with a total cholesterol level of 7.6 mmol/L.

Triglyceride levels persistently above 10 mmol/L usually have a genetic causation and are a well-recognised cause of acute pancreatitis. In some instances, a more modest elevation in triglyceride levels (roughly <5 mmol/L) may be exacerbated by excessive alcohol consumption, diabetes, obesity and exogenous oestrogen or other drugs.

Genetic hypertriglyceridaemia cannot be adequately managed with statins alone. The patient was subsequently prescribed a fibrate drug, fenofibrate 145 mg daily, while the dose of atorvastatin was reduced to 10 mg daily. His ultimate lipid profile was never ideal, even with the addition of high-dose omega-3 from fish oil (triglyceride level 4.8 mmol/L, cholesterol level 4.8 mmol/L). Given the severity of his original lipid problem, the outcome was a good compromise and he has remained well since.

Fenofibrate has an important role in the long-term management of severe hypertriglyceridaemia, particularly when other background factors have been addressed. Fenofibrate can be used with relative safety in combination with submaximal doses of a statin.

Influence of social media on patient behaviour

Case 6

A 60-year-old man with no prior coronary history had an elevated total cholesterol level of 6.8 mmol/L and was managed with rosuvastatin 20 mg daily. His cholesterol levels improved and he achieved an LDL-C level of 2.0 mmol/L. About three years into therapy, he was diagnosed with type 2 diabetes. His fasting plasma glucose level before taking rosuvastatin was 5.7 mmol/L (desirable level <5.5 mmol/L), but was now 8.3 mmol/L. His glycated haemoglobin (HbA_{1c}) level was diagnostic at 50 mmol/mol (6.7%), yet below the treatment target level <53 mmol/mol (<7.0%).

Subsequently, the patient read a newspaper report attributing an increased risk of new-onset diabetes to statin therapy. He became quite concerned about his new-onset diabetes and was referred to this consultant.

In addition to the blood test results described, the patient had a body mass index of 28.4 kg/m^2 and a waist circumference of 105 cm (desirable circumference <95 cm). He had indeed developed type 2 diabetes, most likely due to his age, being overweight and having a possible genetic predisposition. His years of potent statin therapy may also have contributed, although the mechanism of statin-induced diabetes is controversial. His GP advised there was justification for ongoing statin therapy; however, the patient declined to accept this advice. He has continued with standard monitoring, and his glycaemic control has been acceptable.

Unusual and special situations

Case 7

A well 53-year-old woman with an LDL-C level of 4.5 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 underdiagnosed or undertreated and requested her GP prescribe atorvastatin. The dose ultimately reached 40 mg daily and her LDL-C level fell to 2.3 mmol/L.

Five years later, she presented with chest palpitations, and cardiac investigations were performed. She had positive findings on a stress ECG, leading to CT-coronary angiography. Her coronary artery 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 daily.

The patient continually pressed her doctors as to why she had developed significant coronary artery disease at a realtively young age despite being on statin therapy and in the absence of other major risk factors. The patient was referred to this consultant.

Classic risk factors may not be identifiable in a small proportion of patients with coronary disease and, in this patient, measurement of serum homocysteine and lipoprotein(a) [Lp(a)] levels was indicated. Homocysteine was in the physiological range at 7.0 mcmol/L, while the Lp(a) level was highly elevated at 1000 mg/L (250 nmol/L; reference range <300 mg/L or 75 nmol/L). Elevated Lp(a) is an independent risk factor for coronary disease, especially in those with familial hypercholesterolaemia.

Lp(a) measurement is not currently covered by Medicare reimbursement; however, measurement in the setting of unexplained coronary disease or familial hypercholesterolaemia is strongly indicated. Although new therapies to reduce elevated Lp(a) levels are currently under evaluation, other modifiable risk factors may be treated if Lp(a) is elevated.

Case 8

An 84-year-old man had an acute coronary syndrome, was stented and discharged well on standard therapy. He had few conventional risk factors beyond age and a slightly elevated LDL-C level of 3.2 mmol/L. The therapy included atorvastatin 40 mg/day. He remained reasonably well. Six years later, at the age of 90 years, his family began to question whether all of his many drugs were essential.

Should an 84-year-old be started on a statin?

We possess modest clinical trial evidence that a statin would be beneficial in this older age group. On an empirical basis, a high-dose statin would usually be prescribed in his situation.

Should the patient continue to take a statin at 90 years of age?

In the absence of scientific data, it was decided to continue his statin therapy, as he seemed to maintain a good quality of life

and was free of any apparent side effects from the statin or his other medications.

Case 9

A well 56-year-old man was offered a free CT-coronary angiogram by his radiologist golfing partner in the absence of any clinical indication. Regrettably, the angiogram showed a high coronary artery 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.

His body mass index was 29.0 kg/m², blood pressure 140/90 mmHg and LDL-C level 3.2 mmol/L. His GP recognised the presence of significant coronary artery disease and major risk factors, yet the patient felt perfectly well and could not believe he needed drug therapy. On review by a cardiologist, his stress echocardiogram was negative, but the cardiologist supported the advice of the GP that the patient be started on statin therapy. Dietary therapy alone was pursued with little improvement and, after further counselling, the patient was started on conventional drug therapy.

Although revealed through a nonconventional pathway, the presence of significant coronary disease was demonstrated and, by default, this patient had entered the pathway of secondary CVD prevention. Coronary artery calcium score and CT-coronary angiography are not regarded as routine investigations in well patients without cardiac symptoms. They are more clearly indicated in patients who may be at intermediate coronary risk (e.g. those with atypical chest pain or with some risk factors) as an aid to further management decisions.

What does the future hold?

New medications will become available in Australia in future years that may overcome some of these challenges and help more patients achieve target lipid levels.

Inclisiran, another drug that reduces PCSK9 activity, will soon become available for the management of LDL-C. An orally active inhibitor of PCSK9, currently known as MK-6016, has shown efficacy in reducing LDL-C levels and is currently undergoing clinical trials.[1]

Bempedoic acid, an orally active inhibitor of cholesterol synthesis, is a pro-drug that is inactive in muscle and is only activated in the liver.[2] In time, this drug may be a solution for patients having muscle problems with statins.

There is increased interest in very high-dose omega-3 relating to a product known as icosapent ethyl.[3] This product shows promising results in the secondary prevention of CVD events. The mechanism of benefit is uncertain and may be unrelated to any effect on triglyceride readings. Finally, new therapies to reduce elevated Lp(a) levels and other novel antibodies targeting the *apoC3* and *ANGPTL3* genes are under investigation to regulate elevated triglyceride levels and CVD risk.[4,5]

Conclusion

Statin drugs continue to form part of standard therapy in cardiovascular disease prevention and management, especially in high-risk patients. A small proportion of patients receiving statin therapy will manifest adverse events. Patients with familial hypercholesterolaemia are often unable to achieve target lipid levels and additional therapy with evolocumab, an inhibitor of the protein PCSK9, will prove helpful. Lp(a) levels should be assessed if patients have unexplained coronary artery disease or in the presence of familial hypercholesterolaemia. In patients with severe hypertriglyceridaemia, fenofibrate may be helpful when underlying contributing problems, such as excessive alcohol intake, diabetes or obesity, have been excluded or addressed. A number of new therapies are under clinical investigation, including inclisiran, bempedoic acid and icosapent ethyl. MT

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

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