ABCss: C is for cholesterol

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The case studies in this series focus on the ABCss of diabetes care (A_{1c}, blood pressure, cholesterol, smoking, salicylates), how to get them closer to target and how to keep them there.

Case scenario

Christine is 58 years old and has had type 2 diabetes for 11 years. The practice nurse has suggested a GP management plan because the Service Incentive Payment (SIP) cycle of the Commonwealth Government's National Integrated Diabetes Program has highlighted that Christine's ABCss are off target (see Table 1).

Christine has always had problems with her weight and has gained a further 5 kg since starting insulin a year ago. Her current weight is 83 kg, her height is 164 cm (BMI, 30.9 kg/m^2) and her waist circumference is 104 cm, which means she is obese (BMI >30 kg/m^2; waist circumference >88 cm). Christine is very concerned about her weight gain but has not been able to prevent a steady increase. Her physical activity is limited by pain in her knees and ankles, despite NSAID therapy. She continues to smoke, partly because last time she stopped she gained 4 kg in the next three months.

As far as complications are concerned, she had a course of laser therapy for maculopathy 18 months ago but has not required further intervention. Her albumin to creatinine ratio is currently 5.2 mg/mmol. She has been identified as being at a high risk of developing foot problems (as she has a loss of sensation in the distal half of her foot and weak pedal pulses).

Her medications include:

- metformin (850 mg twice daily)
- intermediate acting insulin (isophane insulin; 34 units at bedtime)
- lisinopril/hydrochlorothiazide (40/12.5 mg/day)
- celecoxib (50 mg/day)
- esomeprazole (40 mg/day)
- amitriptyline (25 mg at bedtime, for her night-time foot discomfort).

Questions

- What are Christine's risk factors for a cardiovascular event and what is her five-year risk of a myocardial infarction or stroke?
- To target her cholesterol, what SNAP recommendations (quit Smoking, better Nutrition, moderate Alcohol and more Physical activity) could be made and how successful might these be in lowering her cholesterol?
- If statin therapy were prescribed for Christine, would she be eligible for PBS subsidy of this treatment?
- Three months after Christine begins statin therapy (40 mg simvastatin daily) her cholesterol has decreased to 5.7 mmol/L. Is this what was expected? Should her cholesterol be more actively targeted?
- Two weeks after Christine's statin dose is doubled she complains of aching muscles, particularly in the shoulders and neck after she has been gardening. Statin myotoxicity is suspected. What other factors should be assessed?
- Assuming there are no contributing factors to her myalgia that could be changed, what other ways are there for managing her cholesterol?

Risk factors for a cardiovascular event

Christine has most of the risk factors for a cardiovascular event: she is nearly 60 years old, she has had type 2 diabetes for more than 10 years and all her ABCss are off target. She also has microalbuminuria and evidence of existing macro - vascular disease (weak pulses).

There are several cardiovascular risk calculators for men and women with no history of cardiovascular disease. These include the National Prescribing Service's version of the New Zealand Cardiovascular Risk Calculator (www.nps.org.au/site.php?page=1&content=/resources/

Table 1. Christine's ABCss values

Factor	Christine's value	Target value
A_{1c}	7.6	<7.0%
Blood pressure	142/75 mmHg	<130/80 mmHg
Cholesterol*	7.4 mmol/L	<4 mmol/L
Smoking	15 cigarettes/day	0
Salicylates	0	75 to 150 mg/day

* Christine's value (target value): LDL cholesterol, 5.5 mmol/L (<2.5 mmol/L); HDL cholesterol, 1.1 mmol/L (>1 mmol/L); triglycerides, 1.6 mmol/L (<1.5 mmol/L).

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Cholesterol lowering therapy: PBS eligibility criteria relevant to patients with diabetes, 1 October 2006[1*]

Statins and fibrates

Very high risk categories

Patients qualify for PBS subsidy of therapy with statins or fibrates regardless of their cholesterol level if they are identified as having in one of the following:

- symptomatic vascular disease (coronary heart disease, cerebral vascular disease, peripheral vascular disease)
- diabetes mellitus with microalbuminuria (defined as urinary albumin excretion rate above 20 μg/min or urinary albumin to creatinine ratio greater than 2.5 for males and 3.5 for females)
- diabetes mellitus in Aboriginal or Torres Strait Islander patients
- diabetes mellitus in patients aged 60 years or more
- familial hypercholesterolaemia (symptomatic before age of 55 years in two or more first degree relatives or before age of 45 years in one or more first degree relatives).

Other categories

Patients with diabetes mellitus who are not included in the above very high risk categories are required to have a total cholesterol level above 5.5 mmol/L to qualify for PBS subsidy of therapy with statins or fibrates.

Ezetimibe

Patients qualify for PBS subsidy of therapy with ezetimibe or ezetimibe plus simvastatin if, after three months of statin therapy and lifestyle change, their total cholesterol level:

- exceeds 4 mmol/L and they are in one of the above very high risk categories
- exceeds the initial level qualifying for statin or fibrate therapy.

The full PBS eligibility criteria additionally list lipid levels for other patients not identified as being in very high risk categories.

content/hpro_cv_risk_calcu.html), the UKPDS Risk Engine (www.dtu. ox.ac.uk/index.php?maindoc=/riskengine/index.php) and those included in medical desktop software. None is entirely satisfactory. For example, neither the New Zealand nor the UKPDS calculators consider microalbuminuria or antiplatelet therapy, although the latter does consider duration of diabetes, presence of atrial fibrillation, ethnicity and A_{1c} in addition to the age, gender, levels of blood pressure, cholesterol, smoking habit and presence of diabetes considered by the NPS version of the New Zealand calculator.

According to these risk engines, Christine's five-year risk of a cardiovascular event (a myocardial infarction or stroke) is greater than 15%. She is at even higher risk given the risk factors not considered by these tools.

Lifestyle changes to reduce cholesterol

Of the four SNAP recommendations to reduce behavioural risk factors that affect the health of the general population, three are applicable to Christine to help her reduce her cholesterol levels: quitting smoking, better nutrition and more physical activity. As is often the case, the three are linked. Christine is unlikely to seriously consider quitting smoking if she expects her weight to increase. Unless she can 'Eat less and walk more' – the key message for achieving a healthy lifestyle, the cornerstone of diabetes management – she is unlikely to lose much weight and also likely to gain weight if she stops smoking.

It may be appropriate to consider a Team Care Arrangement to involve a dietitian in her nutrition program and a physiotherapist or an exercise physiologist in her activity schedule. A diabetes educator could advise on the changes required in her hypoglycaemic medication as she increases her activity and decreases her weight.

The focus on lifestyle issues would be:

- eat less – less food, less total fat, less saturated and trans fats.
- walk more – every day, each week, every week.

Behaviours associated with successful weight loss and successful maintenance of that loss should be encouraged. The people who succeed keep track of their food intake and their activity (such as with a food diary and a pedometer), are guided as to the steps they should take, and are monitored and supported through those steps. Nursing and allied health colleagues can help: the practice nurse can review progress on each practice visit, the diabetes educator can provide specialised advice and the physiotherapist or exercise physiologist can advise on and supervise the activity program.

Successful lifestyle change will result in some weight loss, improvement in glycaemic control and perhaps reduction in hypoglycaemic medication. Weight loss and decreased total, saturated and trans fat intakes can be expected to reduce cholesterol by about 10% (in Christine's case, this would be from 7.4 to 6.7 mmol/L).

Christine's eligibility for subsidised statin therapy

Christine meets the most recent eligibility criteria for PBS subsidy of cholesterol-lowering therapy (introduced 1 October 2006), as having diabetes mellitus with an albumin to creatinine ratio of more than 3.5 mg/mmol (hers is 5.2 mg/mmol) puts her into a very high risk category (see the box on this page).[1] These new eligibility criteria allow patients in very high risk categories to have access to subsidised cholesterol lowering drugs regardless of their cholesterol levels.

As Christine is at very high risk of a cardiovascular event and is unlikely to reach targets with lifestyle changes alone, it may be worth starting both lifestyle changes and statin therapy at once, rather than waiting to see the effect of lifestyle changes alone. After all, Christine has been working hard to achieve a healthy lifestyle for years.

Both simvastatin and atorvastatin

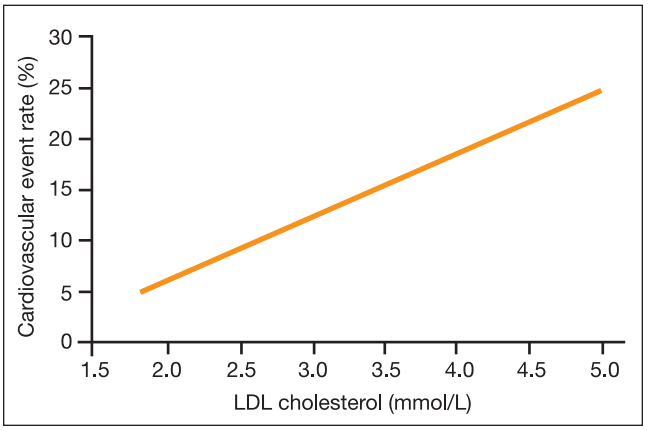

Figure 1 (above). Secondary prevention studies have shown that the lower the cholesterol level, the lower the risk of cardiovascular events.[4]

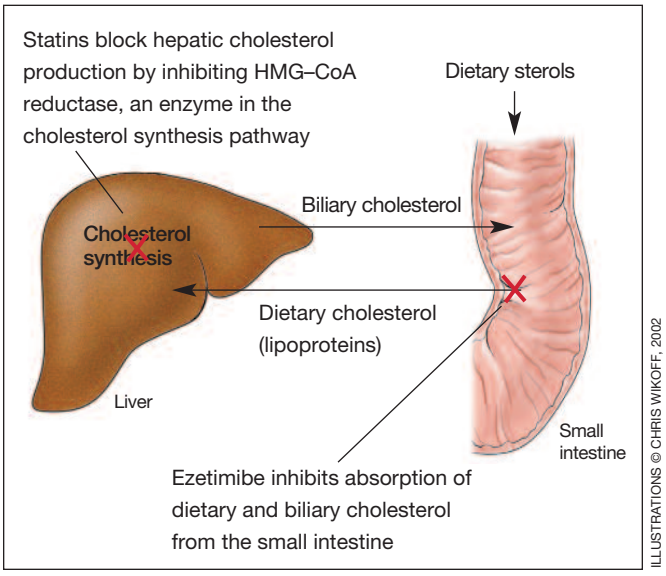

Figure 2 (right). Sites of action of statins and ezetimibe on cholesterol metabolism.

(Lipitor) have recently been shown to decrease coronary and cardiovascular events in people like Christine.[2,3] Although many patients are started on a statin at a dose of 5 or 10 mg daily, it should be remembered that the doses used in studies demonstrating the efficacy of simvastatin and atorvastatin were 40 mg and 10 mg daily, respectively.

Statin therapy

A decrease in Christine's cholesterol level to 5.7 mmol/L after three months' therapy with simvastatin 40 mg/day would be expected. A starting dose of 40 mg of simvastatin or 10 mg of atorvastatin daily is likely to decrease the total cholesterol by some 15 to 20%. Taking into account the 10% or so reduction in cholesterol level as a result of lifestyle changes (in Christine's case, from 7.4 to 6.7 mmol/L), this translates into a decrease in cholesterol of about 1 mmol/L due to the statin. As cardiovascular risk decreases with decreasing cholesterol levels (Figure 1),[4] Christine's risk could be further reduced since her new cholesterol level (5.7 mmol/l) is still above the target level (<4 mmol/L).

The next step is to check that Christine is actually taking the statin and will continue to take it. Her lifestyle should then be reviewed to see if she is able and/or willing to make further lifestyle change.

The final consideration would be to double Christine's statin dose. However, doubling the statin dose unfortunately does not double the cholesterol lowering effect but more than doubles the risk of side effects (myalgia, creatine kinase rises and abnormal liver function tests, for example).[5] For cholesterol lowering, the 'rule of 6s' applies – each dose doubling results in a further 6% decrease in cholesterol, rather than the initial 15 to 20% decrease being repeated.[6]

Statin myopathy

Christine's simvastatin dose is doubled to 80 mg daily and two weeks later she complains of aching muscles, particularly in the shoulders and neck after she had been gardening. Statin myotoxicity was suspected.

Checking her creatine kinase (CK) levels could be considered, but a normal CK does not mean that the statin is not affecting muscles. Also, an abnormal CK can be caused by factors other than statins.

It would, however, be useful to check whether there are other factors in Christine's case that might potentiate the muscle side effects of statins (Table 2).[7] If there are and if they could be changed, it might be possible to continue with the statin at the current dose rather than stopping it or reducing the dose to a level not associated with problems. Most of the factors potentially contributing to statin myopathy affect muscle themselves and are easy to remember and assess. Some of the medications are also easily remembered – for example, the fibrates because they may be coprescribed, and the mycins (macrolide-type antibiotics) and azoles (antifungal agents) because they commonly cause drug interactions. A desktop tool such as 'MIMS Interactive' or a pharmacist Home Medication Review can be useful sources of advice on potentially contributing medications.

Assuming none of these factors are relevant in Christine's case, it would be prudent to stop the statin, allow the muscle problem to abate and then resume the statin at the previous dose that did not cause problems. Of course, reducing the statin dose would mean that Christine's total and LDL cholesterol levels and her cardiovascular risk would increase.

Other medications

If there are no contributing factors to Christine's myalgia that could be changed,

Table 2. Factors increasing statin myotoxicity

Major illness
- Severe infection
- Surgery
- Trauma
- Hypoxia
- Hypothermia
- Uncontrolled seizures

Chronic illness
- Debilitation or advanced age
- Chronic renal or liver failure

Endocrine and metabolic disorders
- Hypothyroidism
- Hyponatraemia
- Metabolic acidosis

Medications
Concurrent administration of other drugs utilising the cytochrome P450 enzyme system (CYP3A4 is the isoenzyme most often involved in drug metabolism)
- Fibrates (gemfibrozil more than fenofibrate)
- Macrolide antibiotics
- Azole antifungals
- Calcium channel blockers (such as verapamil and diltiazem)
- Antidepressants (such as fluoxetine and fluvoxamine)
- Warfarin
- Cyclosporin

Others
- Concomitant use of recreational drugs – e.g. ecstasy (a CYP2D6 substrate)
- Grapefruit juice (a CYP3A4 inhibitor)

another way to reduce her cholesterol would be to add a medication to reduce gastrointestinal cholesterol absorption to reinforce the statin effect on cholesterol synthesis. In the past, this has not been practical because the medications available (bile acid sequestrant resins) were unpalatable and long term adherence was unusual.

In August 2004, ezetemibe (Ezetrol) was added to the range of hypolipidaemic medications available on the PBS. Ezetemibe is an oral, once daily medication that selectively binds to the cell surface receptor for cholesterol in the small intestine, reducing the absorption of both exogenous (dietary) and endogenous (biliary) cholesterol. Its mode of action is complementary to that of statins (Figure 2), and it is used concomitantly.

As Christine's total cholesterol level is still above the target level of 4 mmol/L after three months of statin therapy and lifestyle changes, she would be eligible for a PBS subsidised prescription of ezetimibe or the combination preparation simvastatin and ezetemibe (Vytorin).

Other medications that could be used to reduce Christine's total and LDL cholesterol are:
- bile acid sequestrants (colestipol [Colestid], cholestyramine [Questran Lite]) – however, as previously noted, these are unlikely to be acceptable to her
- nicotinic acid – but this is likely to increase Christine's blood glucose and has a range of other unpleasant side effects.

The fibrates and omega-3 fatty acids (fish oils) are not appropriate agents in Christine's case as they target triglycerides and HDL rather than LDL cholesterol.

Key points
- Calculation of five-year risk of cardio - vascular events identifies patients in whom cholesterol lowering is a priority.
- Lifestyle change can be expected to reduce total cholesterol by about 10%.
- Recently introduced revised guidelines make most high risk Australians with diabetes eligible for PBS subsidised cholesterol lowering therapy.
- Statin therapy (such as simvastatin 40 mg daily or atorvastatin 10 mg daily) can be expected to reduce total cholesterol by 15 to 20% but, according to the 'rule of 6s', doubling the statin dose only reduces cholesterol by a further 6%.
- If statin therapy does not lower a patient's total cholesterol to the target level, consider the use of ezetimibe (10 mg daily) to block cholesterol absorption. MT

Acknowledgement

The author would like to thank the reviewers of this article for their helpful suggestions.

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DECLARATION OF INTEREST: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article.