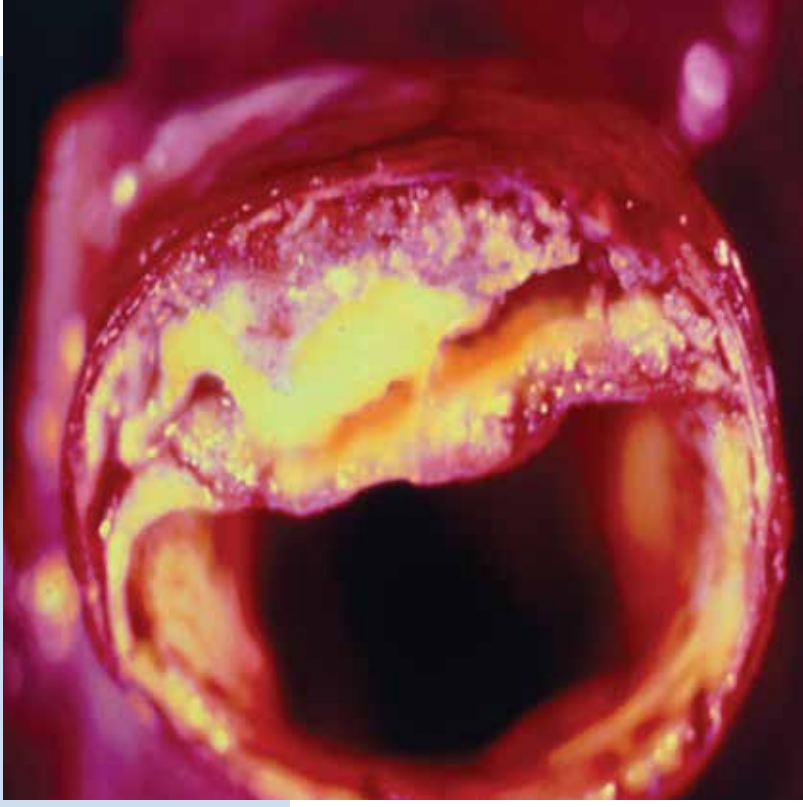
CASE STUDY

A woman with unexpected and unexplained coronary lesions



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All well adults over 45 years of age need assessment of absolute risk of cardiovascular disease before statins are prescribed, unless there are other indications to do so.

Case scenario

Ms FA was a well, 53-year-old woman who attended her GP for a check up in November 2003. She was a nonsmoker, not diabetic and normotensive; however, her mother had developed angina pectoris at 75 years of age and was stented successfully. Ms FA was symptom-free at the time of her check up.

Her body mass index was 26.1 kg/m² and her blood pressure was 130/80 mmHg. There were no abnormal cardiovascular signs and a resting ECG was within normal limits. Dipstick urinalysis showed no abnormality. Her blood tests were as follows:

- *total cholesterol 7.2 mmol/L (reference range <4.0 mmol/L)*
- *triglycerides 1.0 mmol/L (reference range <2.0 mmol/L)*
- *HDL-cholesterol 1.2 mmol/L (reference range >1.0 mmol/L)*
- *LDL-cholesterol 5.5 mmol/L (reference range <2.0 mmol/L).*

Her levels of electrolytes, creatinine, glucose, liver enzymes and thyroid-stimulating hormone and her blood count were all within normal limits.

Ms FA's absolute risk of premature cardiovascular disease (CVD) in the next five years was calculated and found to be 4 to 5%. Her GP informed her that she was at relatively low risk of CVD and recommended a conservative approach, with advice to lose a little weight and to maintain a good level of exercise.

Consultant's comment

Contemporary guidelines suggested that a risk of CVD exceeding 15% represented high risk and would be a threshold for the introduction of statin drugs. Also, Ms FA's mother is not an example of premature CVD. Although applying population data to individuals is always fraught with difficulty, her GP gave the correct advice that statin drugs were not strongly indicated in her case.

Case scenario continued

Ms FA returned to her GP in July 2004 complaining of epigastric discomfort. She had recently returned from an overseas holiday and was still taking antimalarial drugs. A resting ECG and measurement of cardiac enzymes were within normal limits and a stress ECG was negative. The antimalarial drugs were suspended, her symptoms rapidly disappeared and further reassurance was offered.

Ms FA returned for a further check up in August 2007, still anxious about her risk of

Key points

- **All well adults over 45 years of age need assessment of absolute risk of cardiovascular disease (CVD) before statins are prescribed.**
- **People at low risk of CVD will require advice only on lifestyle, diet and physical activity.**
- **A single threshold level of high risk of CVD over five years defined at 15% may not be appropriate in younger patients or in the elderly.**
- **Patients who manifest premature CVD in the absence of classic risk factors need assessment of novel risk factors, such as lipoprotein(a).**

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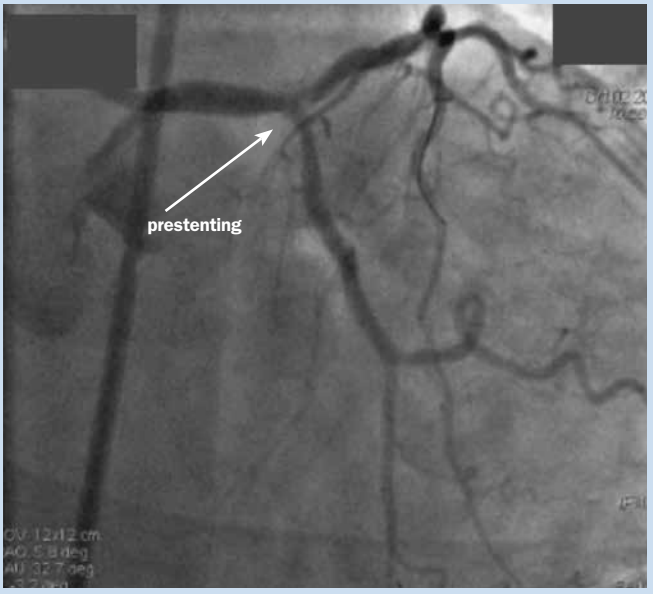

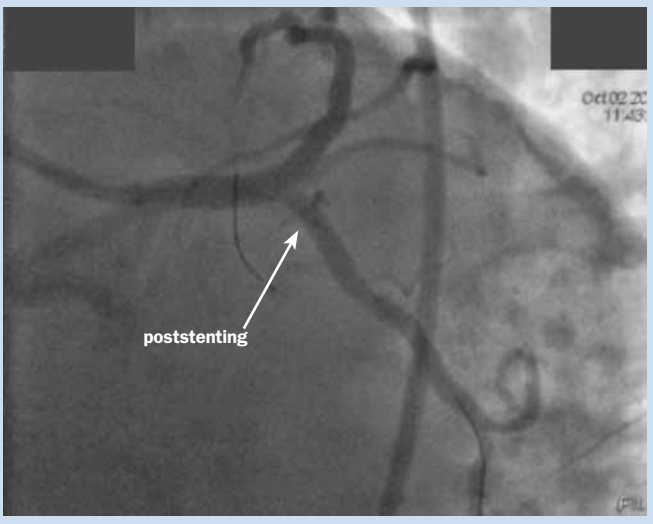

Figures a and b. Circumflex artery (a, top) prestenting and (b, bottom) poststenting.

CVD. Her blood pressure was satisfactory at 132/80 mmHg. Her blood test results were as follows:

- *total cholesterol 7.7 mmol/L*
- *triglycerides 1.0 mmol/L*
- *HDL-cholesterol 1.4 mmol/L*
- *LDL-cholesterol 5.8 mmol/L.*

Other routine blood tests were within normal limits. Her five-year CVD risk was little changed at 5%, but she was not reassured by this statistic. Ms FA had read in magazines that coronary disease is often underdiagnosed in women.

Ms FA pressed her GP to prescribe a statin drug and she was commenced on atorvastatin 10 mg per day, gradually titrated up to 40 mg per day over the next six months. Subsequently, her LDL-cholesterol level averaged 2.8 mmol/L and she was reviewed at half-yearly intervals.

Consultant's comment

The Australian PBS guidelines do not represent a 'textbook of medicine'. Rather they represent a measure of 'affordable care' that the system is willing to subsidise. I believe Ms FA's GP was correct to offer her a statin drug and then titrate the dose. Unfortunately, Ms FA was still manifesting a higher than desirable LDL-cholesterol reading.

Case scenario continued

At a regular review in September 2012, Ms FA complained of palpitations and a Holter ECG examination was performed. This revealed singular ventricular ectopic beats and runs of supraventricular tachycardia lasting eight seconds or longer. She was then referred to a specialist cardiologist for further management.

The cardiologist ordered a stress echocardiogram, which was negative. However, Ms FA had a positive stress ECG even though there was no chest pain during exercise. The cardiologist then followed with a CT coronary angiogram and coronary calcium score.

The CT coronary angiogram showed haemodynamically significant stenosis at the ostium of the circumflex artery (70 to 90%) and in the midsegment of the left anterior descending artery (50 to 70%), plus other minor but diffuse changes. Her coronary calcium score was 184, at the 85th percentile for age and sex, and was consistent with a moderate burden of coronary atherosclerosis. The coronary lesions were successfully stented (Figure), she was discharged on aspirin/clopidogrel, metoprolol 25 mg twice a day and a maximum dose of atorvastatin of 80 mg per day.

Although Ms FA remained clinically well, she continually pressed her doctors as to why she had developed such advanced coronary disease at a youngish age despite taking statin therapy over some years and in the absence of other major risk factors. Eventually she was referred to this consultant for review of the issues.

Consultant's comment

This was a clinical setting of two-vessel coronary artery disease in which the only conventional risk factor present was a modest excess of LDL-cholesterol. Accordingly, serum homocysteine and lipoprotein(a) (Lp(a)) measurements were requested; serum homocysteine was in the physiological range at 7.0 µmol/L, whereas serum Lp(a) was highly elevated at 1000 mg/L.

Lp(a) is an LDL-like particle consisting of an apolipoprotein B100 molecule covalently linked to a very large glycoprotein known as apolipoprotein(a). The physiological roles of Lp(a) are uncertain, but some studies suggest that it might promote thrombosis, inflammation and foam cell formation in the arterial wall.[1] A meta-analysis of 36 long-term prospective studies, involving more than 126,000 subjects and including some from Australia, reported an independent but modest association between Lp(a) and risk of coronary disease or ischaemic stroke, but with extreme risk at very high levels.[1]

Although Lp(a) as a risk factor has never been adopted with great enthusiasm in the USA, our European colleagues recommend screening for Lp(a) in people at intermediate or high risk of CVD. They recommend a desirable level for Lp(a) of less than the 80th percentile

(about 500 mg/L).[2] In the Dubbo Study, 80th percentile for Lp(a) levels was at 350 mg/L.[3] Although Lp(a) appears to be a marker of increased CVD risk, there is a lack of proof that therapy to lower Lp(a) levels will reduce future CVD risk. Concentrations are lowered by high-dose nicotinic acid, yet side effects are problematical and recent intervention studies with nicotinic acid have failed to show CVD prevention.

Why was Ms FA only assessed as low risk by the CVD risk calculator and why did she not benefit from statin therapy? In Australia we are using a risk calculator essentially based on the Framingham equation.[4] This equation is valid and does give a reasonable estimate of absolute CVD risk, although it does not encompass novel risk factors such as Lp(a). However, by declaring that an absolute risk of more than 15% should be regarded as high risk and becoming a threshold for statin treatment, we are assuming that 'one risk level fits all patients'.[4] In younger patients, such as Ms FA at 53 years, a 5% absolute risk might need to be considered high risk, thus avoiding undertreatment.

On the other hand, many older patients will have an absolute risk of more than 15% merely by virtue of their age, thus leading to overtreatment. This is a complex situation and no simple solution is currently at hand.

New cholesterol treatment guidelines were released in the USA in November 2013 which acknowledged the importance of statins in patients with established CVD or those at high risk, but reaffirmed the importance of calculation of absolute CVD risk in low-risk groups.[5] But it still comes back to the unlikely assumption that 'one risk threshold level fits all patients'.

Finally, it is not correct to state that Ms FA did not benefit from statin therapy. Although the use of statins will not abolish every future CVD event, it has been clearly shown to reduce the rate of future CVD events over a finite period. Ms FA had no prior CVD events nor has she experienced any during her time on statin therapy. It is presumed that ongoing high-dose statin therapy will help to stabilise her existing lesions and may help to prevent restenosis of the stented segments. **CT**

References

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