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Smith, Jane

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Appropriate primary prevention of cardiovascular disease: does this mean more or less statin use?

***Jane Smith**, Associate professor, General Practice, Faculty of Health Science and Medicine, Centre for Research in Evidence-based Practice, Bond University, Gold Coast, Queensland*

Summary

Treatment with HMG-CoA reductase inhibitors, commonly known as statins, is beneficial for people at high risk of a cardiovascular event. However, guidelines recommend against routine statin treatment for those with a lower risk. They also recommend waiting until after 45 years of age to assess cardiovascular risk in healthy individuals. Aboriginal and Torres Strait Islander people should be assessed from age 35 years. These recommendations are based on current evidence of who is more likely to benefit from statin treatment.

Key words: antilipidaemic drugs, cholesterol, HMG-CoA reductase inhibitors.

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Introduction

Cardiovascular disease is a common problem causing 16% of the total disease burden, second to cancer. The mortality from cardiovascular disease has decreased by at least 80% in the last 50 years, mostly before the introduction of statins (HMG-CoA reductase inhibitors). Although Australians are living longer, greater rates of physical inactivity, obesity and diabetes all threaten this trend.[1]

The absolute risk of developing cardiovascular disease is predictable using risk calculation tools.[2] Statins are known to reduce this risk in people with existing ischaemic cardiovascular disease, or those at high risk of developing it – defined as more than 15% risk of an event in five years. However it is less clear whether people with a lower cardiovascular risk, benefit from statins.

Statin use

The number of patients diagnosed with high cholesterol has doubled between 2004 and 2009.[3] The focus on single risk factors like cholesterol translates to 27% of adult general practice patients being managed for cholesterol[4] – three-quarters of them are treated with statins.

Patients and health providers alike tend to focus on cholesterol, perhaps because it is an easy target to test and treat. A possible consequence of this is that statins are the most prescribed of all drugs both in quantity and cost on the Pharmaceutical Benefits Scheme (PBS). There are three individual statins in the top 10 of all prescribed drugs – atorvastatin, simvastatin and rosuvastatin.[5] Suggestions have been made about both under- and over-prescribing of statins in Australia. Women are far more likely to be treated with statins relative to their risk for cardiovascular disease than men, with the exception of men in the highest socioeconomic group. Rural people are less likely to be treated with a statin.[6]

Cardiovascular risk

The term cardiovascular risk refers to the risk of ischaemic disease defined as acute coronary events, angina, stroke, transient ischaemic events, and peripheral vascular disease with or without fatal outcomes. There are multiple modifiable factors that influence the risk of developing cardiovascular disease (Box 1). Modifying these factors can improve morbidity and mortality and includes lifestyle factors such as increasing physical activity and cardiorespiratory fitness, and not smoking.[7,8] If these interventions do not sufficiently reduce the risk of cardiovascular disease, pharmacological interventions may need to be considered.

Generally people under 45 years are likely to have a low risk of cardiovascular disease, as age is one of the biggest determinants of risk, and multiple risk factors are not common in younger people.

A family history of high cholesterol affects 5–20% of the population, depending on how one defines high cholesterol.

Box 1

Modifiable risk factors for cardiovascular disease

Smoking
High blood pressure
Elevated cholesterol (total or low density lipoprotein)
Decreased high density lipoprotein cholesterol
Diabetes
Obesity (large waist measurement, high body mass index)
Lifestyle (minimal exercise, poor nutrition, high stress, excess alcohol)

This is sometimes confused with familial hypercholesterolaemia (LDL >4.9 mmol/L usually with tendon xanthoma) which affects 1 in 500 (0.2%) people.[9] This is a high risk condition and results in coronary heart disease or stroke at a young age (under 60 years).

Risk calculation

Calculating absolute risk using Framingham data adapted for Australia is well validated, based on multiple factors including cholesterol levels, but is underused.[2] These tools tend to overestimate the risk in those of European descent but underestimate the risk in high risk groups such as Aboriginal and Torres Strait Islander, Pacific Islander or Indian people. Easy-to-use online tools for calculating cardiovascular risk are shown in Box 2.

Table 1 shows who should have a cardiovascular risk calculation. Conversely, some patients' risk is high enough to not need any risk calculation. These are patients who have had a previous cardiovascular event. It also includes some patients with hypercholesterolaemia, diabetes, hypertension or moderate to severe chronic kidney disease (Box 3).

Recommendations for cholesterol testing

About 8% of adult patient encounters in general practice involve cholesterol testing but evidence suggests most of these tests do not result in any benefit to patients.[3,10] The Royal Australian College of General Practitioners guidelines for preventive activities in general practice recommend testing adults over 45 years of age for their cholesterol levels every five years (or from 35 years if Aboriginal and Torres Strait Islander).[11,12] Similar recommendations are given by the National Vascular Disease Prevention Alliance (Table 1).[2]

Evidence

Most of the evidence about the effect of statins in primary prevention is based on treatment of high-risk males aged 55–65 years.[13] There is little evidence about benefit in younger age groups. In those at high risk, statins lower ischaemic event rates and all-cause mortality, and are cost-effective. This has not been shown in lower-risk populations.[14]

Table 1

Who needs risk calculation for cardiovascular disease? [2]

Patient characteristics	Recommendation *
All adults 45–75 years of age	B (strong)
Aboriginal and Torres Strait Islander people from 35 years of age	C (medium)
Diabetes <60 years	C (medium)
Overweight or obese	D (weak)

* Based on the National Vascular Disease Prevention Alliance guidelines

National Health and Medical Research Council gradings:

A Body of evidence can be trusted to guide practice
B Body of evidence can be trusted to guide practice in most situations
C Body of evidence provides some support for recommendation but care should be taken in its application
D Body of evidence is weak and recommendation must be applied with caution

Box 2

Online tools for calculating cardiovascular risk

www.heartfoundation.org.au/information-for-professionals/Clinical-Information/Pages/absolute-risk.aspx [cited 2011 Nov 7]

www.racgp.org.au/redbook/app3 [cited 2011 Nov 7]

National Vascular Disease Prevention Alliance: Australian absolute cardiovascular disease risk calculator. 2010. www.cvdcheck.org.au [cited 2011 Nov 7]

www.knowyournumbers.co.nz/heart-age-forecast.aspx [cited 2011 Nov 7]

Other sources of the same risk calculators are in the Royal Australian College of General Practitioners primary care sidebar and some pathology laboratory reports

Box 3

People at high risk of a cardiovascular event (>15% in the next 5 years) who therefore do not require cardiovascular risk calculation [2]

Characteristics

Known cardiovascular disease

Diabetes with microalbuminuria

(>20 microgram/minute or urinary albumin:creatinine ratio >2.5 mg/mmol for males and >3.5 mg/mmol for females)

Diabetes >60 years

Moderate or severe chronic kidney disease

(eGFR <45 mL/minute/1.73 m^2)

Familial hypercholesterolaemia

Serum cholesterol >7.5 mmol/L

Systolic blood pressure >180 mmHg or diastolic >110 mmHg

eGFR estimated glomerular filtration rate

Systematic reviews of trials differ in their conclusions about the benefits of statins in patients who do not have a high risk. When patients with prior cardiovascular disease are excluded, there is no evidence of benefit from statin therapy on all-cause mortality.[13] This suggests that caution should be used when recommending statins for primary prevention of cardiovascular disease in those at low risk (that is with a risk of cardiovascular disease less than 2% in one year) because of limited benefit and a potential for harm (Table 2).[15,16]

In those with moderate to severe chronic kidney disease, statin treatment reduces cardiovascular events but not overall mortality.[17] However, statin treatment of those with less severe chronic kidney disease appears to reduce cardiovascular events and overall mortality.[18]

PBS listing

The PBS general statement for using lipid-lowering drugs defines patients at risk who would be expected to benefit from statin therapy. The wording is intended to mirror the absolute cardiovascular disease risk calculation, but is an imperfect match.

Conclusion

It is likely that we are over-prescribing statins to low-risk patients. A focus on single risk factors such as high cholesterol promotes statin treatment. This will not benefit patients unless they have a high risk of cardiovascular disease, and it could result in harm. It is appropriate to assess absolute cardiovascular risk in people aged over 45 years (or from 35 years if Aboriginal and Torres Strait Islander) using tools that integrate multiple risk factors.

Table 2

Benefits and harms associated with statin treatment over five years in patients at high risk[†] of cardiovascular disease [16]

Event	Men	Women
	Number needed to treat	
Cardiovascular disease	33	37
	Number needed to harm	
Myopathy	91	259
Liver dysfunction	142	136
Acute renal failure	346	434
Cataract	52	33

[†] Patients had a 20% or more risk of cardiovascular event over 10 years

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Associate professor Smith is a member of the Editorial Advisory Committee of the Australian Medicines Handbook, member of the Advisory Editorial Panel of Australian Prescriber, and an author of the guidelines for preventive activities in general practice.

Self-test questions

The following statements are either true or false (answers on page 195)

1. Statins do not reduce overall mortality in people with severe renal impairment.
2. The National Vascular Disease Prevention Alliance recommends assessing the absolute cardiovascular risk in people over the age of 75.

Top 10 drugs

These tables show the top 10 subsidised drugs for the year July 2010 – June 2011.

Table 1

Top 10 drugs by DDD/1000 pop/day *†

Constituent drug	PBS/RPBS ‡
1. atorvastatin	82.87
2. irbesartan	33.02
3. rosuvastatin	32.37
4. perindopril	29.94
5. paracetamol	26.88
6. ramipril	26.16
7. candesartan	25.25
8. simvastatin	23.90
9. esomeprazole	21.32
10. amlodipine	19.92

DDDs in this table include use in combination products

Table 2

Top 10 drugs by prescription counts †

Drug	PBS/RPBS ‡
1. atorvastatin	11 020 969
2. esomeprazole	6 099 877
3. rosuvastatin	5 975 902
4. paracetamol	4 840 331
5. simvastatin	4 245 616
6. perindopril	3 995 257
7. pantoprazole	3 549 374
8. metformin hydrochloride	3 383 078
9. irbesartan	3 098 162
10. atenolol	3 070 515

Table 3

Top 10 drugs by cost to government †

Drug	Cost to government (A$)	DDD/1000 pop/day * PBS/RPBS ‡	Prescriptions PBS/RPBS ‡
1. atorvastatin	637 426 978	82.87	11 020 969
2. rosuvastatin	334 168 383	32.37	5 975 902
3. ranibizumab	310 399 773	– ¶	146 272
4. esomeprazole	184 167 326	21.32	6 099 877
5. clopidogrel	173 946 446	10.94	2 774 567
6. salmeterol and fluticasone	173 934 061	– §	3 065 047
7. adalimumab	173 892 033	0.33	97 834
8. olanzapine	161 933 986	2.99	950 386
9. simvastatin	139 642 087	23.90	4 245 616
10. etanercept	122 729 015	0.24	69 742

* The defined daily dose (DDD)/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people, in every thousand Australians, are taking the standard dose of a drug every day.

† Based on date of supply. Does not include private prescriptions or prescriptions under PBS co-payment.

‡ PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

¶ The World Health Organization has not allocated a DDD for this drug

§ This combination does not have a DDD allocated

Source: Drug Utilisation Sub-Committee (DUSC) Database, as at September 2011.