How do the Australian guidelines for lipid-lowering drugs perform in practice? Cardiovascular disease risk in the AusDiab Study, 1999–2000

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ABSTRACT

Objective: To determine how well the current Pharmaceutical Benefits Scheme (PBS) eligibility criteria for subsidy of lipid-lowering drugs compare with current national guidelines for determining the population at high risk of developing cardiovascular disease (CVD).

Design and participants: Analyses of the population-based, cross-sectional Australian Diabetes, Obesity and Lifestyle (AusDiab) study, conducted in 1999–2000. The 1991 Framingham risk prediction equation was used to compute 5-year risk of developing first-time CVD in 8286 participants aged 30–74 years with neither CVD nor diabetes. Based on the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand guidelines, people with either 5-year CVD risk ⩾ 15% or with 5-year CVD risk of 10%–< 15% and the metabolic syndrome were defined as having estimated high absolute CVD risk.

Main outcome measures: 5-year CVD risk; estimated population with high CVD risk.

Results: Among participants without prevalent CVD or diabetes, 7.9% of men and 1.5% of women had a 5-year CVD risk ⩾ 15%. Of the estimated residential Australian population in 2000 aged 30–74 years without CVD or diabetes, 717 000 people were considered to be at high absolute CVD risk. Among the high-risk AusDiab participants without CVD or diabetes, only 16.9% of men and 15.4% of women were being treated with lipid-lowering drugs. Of the 9.6% of participants free of CVD and diabetes who were untreated but eligible for subsidy under PBS criteria, only 27.4% had an estimated high absolute CVD risk.

Conclusion: Strategies for CVD prevention using lipid-lowering medications can be improved by adoption of the absolute-risk approach.

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The 2004–2005 National Health Survey showed that 3.8% of the Australian population had at least one of the four major manifestations of cardiovascular disease (CVD): coronary heart disease (CHD), stroke, peripheral vascular disease, and heart failure.[1] These four common manifestations of CVD accounted for 30.4% of Australian deaths in 2005.[2]

Diabetes substantially increases cardiovascular risk, and people with diabetes are generally regarded as having CHD risk equivalence.[3] As the population-attributable risk of CVD related to other risk factors such as dyslipidaemia and elevated blood pressure is very high, accurate identification of asymptomatic people without diabetes who are nevertheless at high risk of developing CVD events should inform the most effective use of preventive therapies.

Traditionally, treatment decisions for modifiable risk factors have been based on single risk factor thresholds for cholesterol or blood pressure. However, the relationship between risk factors and CVD outcomes is continuous, and estimating an individual's "absolute risk" of future CVD events based on the intensity and integrated effects of multiple independent risk factors is a more efficient and cost-effective strategy.[4] This approach has been recommended in several clinical practice guidelines.[3,5-7]

The updated National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand (NHFA/CSANZ) *Position statement on lipid management — 2005* suggests that, in addition to those with CVD, diabetes, chronic kidney disease, familial hypercholesterolaemia, or an Aboriginal or Torres Strait Islander background, people with either a 5-year CVD risk ⩾ 15% (using the 1991 Framingham risk prediction equation) or with a 5-year CVD risk of 10%–<15% and the metabolic syndrome or a family history of premature CHD should also be considered at high risk.[5] These criteria are yet to be adopted in guidelines governing eligibility for subsidy of lipid-lowering drugs under the Pharmaceutical Benefits Scheme (PBS),[8] which is still determined primarily by cholesterol levels.

We applied the high-risk definition as adapted from the NHFA/CSANZ position statement on lipid management[5] to determine population estimates of people with high CVD risk based on participants in the Australian Diabetes, Obesity and Lifestyle (AusDiab) study, the most recent population-based, biomedical risk factor survey in Australia.[9] We also examined the proportion of people with high CVD risk who were untreated but eligible for subsidy of lipid-lowering drugs under the PBS.

METHODS

AusDiab study

The baseline AusDiab study recruited 11 247 adults (5048 men, 6199 women; 55.3% of those who completed an initial household interview) aged 25 years or over from 42 randomly selected census collector districts across Australia in 1999–2000.[9] The study was approved by the Ethics Committee of the International Diabetes Institute and the Monash University Standing Committee on Ethics in Research involving Humans. Written informed consent was obtained from all participants.

Estimation of absolute CVD risk

The 1991 Framingham risk prediction equation for CVD was used to compute participants' 5-year risk of developing a first CVD event.[10] This multivariable equation uses age, sex, smoking status, blood pressure, total and high-density lipoprotein (HDL) cholesterol levels, presence of diabetes, and electrocardiogram (ECG) evidence of left ventricular hypertrophy (LVH) to predict risk of a CVD event within 4–12 years. CVD

1 Characteristics of participants aged 30–74 years in the AusDiab study*

	Men ($n = 4312$)	Women ($n = 5214$)
Age (years)	48.3 (0.6)	48.9 (0.8)
Systolic BP (mmHg)	130.3 (0.7)	124.8 (0.9)†
Diastolic BP (mmHg)	75.0 (0.5)	67.7 (0.4)†
Total cholesterol (mmol/L)	5.6 (0.03)	5.6 (0.04)
HDL cholesterol (mmol/L)	1.3 (0.01)	1.5 (0.01)†
Lipid-lowering therapy	8.2%	7.1%†
Current smoking	20.1%	15.7%†
Self-reported CVD	7.1%	5.0%†
Diabetes	8.0%	5.7%†
ECG-LVH‡	4.9%	1.6%†
Impaired GFR	5.7%	8.3%†

BP = blood pressure. CVD = cardiovascular disease. ECG-LVH = left ventricular hypertrophy on electrocardiogram. GFR = glomerular filtration rate. HDL = high-density lipoprotein.
* Values are mean (SE) or percentage.
† $P < 0.05$ for comparison between sexes.
‡ Calculated for people aged over 40 years. ◆

is defined as including myocardial infarction, angina pectoris, coronary insufficiency, CHD death, stroke, congestive heart failure, and peripheral vascular disease.

Subjects

Of the 11 247 AusDiab participants, 9832 were aged 30–74 years, reflecting the age range in the Framingham cohort from which the risk prediction equation was developed.[10] We excluded participants who were pregnant (46), had unclassified diabetes status (132), or who were missing data for blood pressure, total and HDL cholesterol (42) or smoking status (178), which are required for calculation of risk using the Framingham equation. Some participants fell into more than one exclusion category. Of the remaining 9526 participants (4312 men, 5214 women), 1240 had previous CVD (angina, CHD or stroke) or diabetes (self-reported or diagnosed at survey).

Measurements

A standard 12-lead ECG was performed in participants aged over 40 years and in younger participants who requested it. LVH was diagnosed according to the Minnesota code 3-1.[11] Participants lacking data for LVH were assumed not to have it. Glomerular filtration rate (GFR) was calculated with the Cockcroft–Gault formula, including a correction factor of 0.85 for women and adjustment for body surface area. Impaired GFR was defined as estimated GFR < 60 mL/min/1.73 m^2. There were 64 participants lacking GFR data.

Estimated high absolute CVD risk

Based on the NHFA/CSANZ position statement, people with a 5-year CVD risk ⩾ 15%, or 5-year CVD risk of 10%–< 15% with concomitant metabolic syndrome, were defined as having high absolute CVD risk.[5] The metabolic syndrome was defined according to the International Diabetes Federation definition.[12]

PBS eligibility criteria for lipid-lowering drugs

The 2006 updated PBS eligibility criteria for lipid-lowering drugs[8] were used to determine how many people were theoretically eligible for subsidy. They are:

- people with CVD;
- people with diabetes and one of microalbuminuria, age over 60 years, or total cholesterol > 5.5 mmol/L;
- Indigenous people with diabetes or total cholesterol > 6.5 mmol/L or total cholesterol > 5.5 mmol/L and HDL cholesterol < 1 mmol/L;
- people with hypertension and total cholesterol > 6.5 mmol/L or total cholesterol > 5.5 mmol/L and HDL cholesterol < 1 mmol/L;
- people with HDL cholesterol < 1 mmol/L and total cholesterol > 6.5 mmol/L;
- men aged 35–75 years or postmenopausal women aged up to 75 years with total cholesterol > 7.5 mmol/L or triglycerides > 4 mmol/L; and
- people not otherwise included with total cholesterol > 9 mmol/L or triglycerides > 8 mmol/L.

Statistical analyses

AusDiab data were weighted to match the age and sex distribution of the 1998 estimated residential population of Australia aged 30–74 years.[9] The estimated residential population at 30 June 2000 was used to project the number of Australians estimated to be at high CVD risk.[13]

All analyses were performed using Stata, version 10.0 (StataCorp, College Station, Tex, USA) with the survey prefix commands. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the AusDiab study participants aged 30–74 years are shown in Box 1. Compared with women, men had higher levels of systolic and diastolic blood pressure, lower levels of HDL cholesterol and higher prevalence of self-reported CVD and diabetes (all $P < 0.05$). Men were also more likely to smoke and use lipid-lowering therapy than women (both $P < 0.05$). In the AusDiab participants aged over 40 years who did not have prevalent CVD, LVH was present in 4.9% of men and 1.6% of women. There were 2143 participants without data for LVH who were all assumed not to have it; 83.2% of them were aged less than 40 years.

Absolute CVD risk estimates in participants without CVD or diabetes

Among the 8286 participants who had neither CVD nor diabetes, 7.9% of men were estimated to have a 5-year CVD risk ⩾ 15%, and 9.1% to have a 5-year CVD risk of 10%–< 15%. Among women, these proportions were 1.5% and 3.9%, respectively.

Population estimates of high CVD risk

Of the AusDiab participants aged 30–74 years, 695 men (13.5%) and 545 women (9.7%) had prevalent CVD or diabetes. Based on their 5-year CVD risk, an additional 11.0% of men and 3.6% of women with neither CVD nor diabetes were estimated to have a high absolute CVD risk. If people with Aboriginal or Torres Strait Islander background or impaired GFR were also assigned to the high-risk category, then a further 1.4% of men and 5.8% of women were considered to be at high CVD risk. In all, 22.5% were in the high-risk category (25.9% of men, 19.2% of women).

By applying the age- and sex-specific proportions of participants with high CVD risk to the estimated residential Australian population aged 30–74 years in 2000, about 2.19 million Australians (1.30 million men, 0.89 million women) were in the high-risk category (Box 2). They included around 717 000 people (551 000 men, 166 000 women) without prevalent CVD or diabetes but with an estimated high absolute CVD risk.

2 Projected population estimates of high cardiovascular disease (CVD) risk in Australians aged 30–74 years at 30 June 2000

	Number of people with high CVD risk*	Number of people with CVD or diabetes	Number of people without CVD or diabetes but with estimated high absolute risk†
Total	2 193 890	1 144 346	717 046
Men	1 300 558	678 402	551 263
30–34 years	1 967	1 330	0
35–44 years	80 914	59 299	12 567
45–54 years	241 040	142 663	93 913
55–64 years	430 647	234 152	181 581
65–74 years	545 990	240 957	263 203
Women	893 332	465 944	165 783
30–34 years	18 098	8 908	0
35–44 years	58 032	45 951	0
45–54 years	140 475	107 640	10 465
55–64 years	206 686	105 724	50 682
65–74 years	470 040	197 721	104 636

* Based on the Australian *Position statement on lipid management — 2005*,[5] comprising people with prevalent CVD, diabetes, chronic kidney disease, estimated high absolute risk† or an Aboriginal or Torres Strait Islander background. † Defined as either 5-year CVD risk ⩾ 15% or 5-year CVD risk 10%–< 15% with the metabolic syndrome. ◆

Use of lipid-lowering therapy in people at high CVD risk

Among the AusDiab participants aged 30–74 years, 39.0% of people with prevalent CVD (41.9% of men, 34.9% of women) and 24.4% of people with either known or newly diagnosed diabetes (24.6% of men, 24.1% of women) reported being treated with lipid-lowering drugs — much lower than the proportions eligible for such medications (ie, 100% of those with CVD and 83.6% of those with diabetes, under the PBS guidelines[8]). Of the people with known diabetes, only 34.8% (38.4% of men, 29.6% of women) were being treated with lipid-lowering drugs.

Among the participants with neither CVD nor diabetes but with an estimated high CVD risk, 16.9% of men and 15.4% of women were being treated with lipid-lowering drugs, including 16.5% of men and 27.9% of women with a 5-year CVD risk ⩾ 15%, and 17.7% of men and 8.2% of women with a 5-year CVD risk of 10%–< 15% and the metabolic syndrome.

Among all participants free of CVD and diabetes, 4.8% (4.9% of men, 4.7% of women) reported being treated with lipid-lowering drugs. Despite being treated, 44.2% of these men and 13.1% of the women were still assessed to be at high absolute CVD risk based on their risk factor levels.

In contrast, 9.6% of people who were untreated and without CVD and diabetes met the PBS criteria for eligibility for subsidy of therapy based on their abnormal lipid levels (Box 3). Among this subgroup, only 13.4% had a 5-year CVD risk ⩾ 15%, and 27.4% had an estimated high absolute CVD risk.

DISCUSSION

We have shown that policy measures encouraging use of lipid-lowering therapies based largely on cholesterol levels directs treatment away from those who are at higher risk and have most to gain from such treatment. This accords with other analyses, which have shown that the 10% of individuals with highest risk-factor levels for physiological variables such as cholesterol account for only 20%–30% of the total number of cases of ischaemic heart disease, stroke and diabetes.[14]

To our knowledge, this study is the first to describe population estimates of people with high CVD risk in a contemporary Australian population. The NHFA/CSANZ position statement on lipid management suggests a "threshold" of 15% 5-year CVD risk for drug treatment in those without known CVD or diabetes.[5] We estimated that 717 000 Australians aged 30–74 years reached this threshold. However, more than 80% of people in this high-risk population were not being treated with lipid-lowering medication, indicating that current primary prevention of CVD is suboptimal. Our finding that 13% of women and 44% of men with neither CVD nor diabetes who were already being treated with lipid-lowering medications were still assessed to be at high CVD risk strongly suggests that their treatment may have been inadequate.

According to the PBS criteria, nearly 10% of people who were untreated and without prevalent CVD or diabetes were eligible for subsidy of lipid-lowering drugs. However, more than 70% of these people were not estimated to be at high absolute CVD risk as defined by the NHFA/CSANZ position statement. Similar results were also found in an earlier Australian study, which showed that of patients deemed suitable for

3 Weighted percentages (95% CIs) of participants by eligibility for PBS subsidy of lipid-lowering drugs,[8] treatment status and CVD risk

	Eligible by PBS criteria but not being treated with lipid-lowering drugs			
PBS subsidy eligibility criteria	Total	5-year CVD risk ⩾ 15%*	Estimated high absolute risk*†	Being treated
People free of CVD and diabetes	9.6 (8.1, 11.2)	13.4 (9.6, 17.1)	27.4 (23.3, 31.5)	4.8 (3.5, 6.1)
Hypertension	28.4 (25.6, 31.3)	17.7 (12.9, 22.5)	34.4 (28.8, 39.9)	12.9 (8.3, 17.5)
Low HDL cholesterol‡	14.4 (11.2, 17.6)	14.1 (4.8, 23.4)	33.8 (21.0, 46.5)	8.5 (3.1, 13.9)
People not eligible under the above§	6.0 (4.7, 7.3)	4.0 (–0.3, 8.2)	9.6 (4.6, 14.7)	3.5 (2.4, 4.7)
Other	0.2 (0.02, 0.4)	19.8 (–6.6, 46.2)	30.5 (2.2, 58.8)	0.4 (0.1, 0.7)

CVD = cardiovascular disease. HDL = high-density lipoprotein. PBS = Pharmaceutical Benefits Scheme. * Percentage of high-risk group among people who were untreated but eligible by PBS criteria. † Defined as either 5-year CVD risk ⩾ 15% or 5-year CVD risk 10%–< 15% with the metabolic syndrome. ‡ Defined as serum HDL cholesterol < 1 mmol/L. § Men aged 35–75 years and postmenopausal women aged up to 75 years. ◆

lipid-lowering drugs by PBS guidelines, 63% had a 10-year risk of CHD of less than 20%.[15] These findings favour using absolute or "global" risk assessment to determine who should receive drug therapies for primary prevention.

There are some limitations to our analyses. People who did not have ECG results were assumed not to have LVH, thereby possibly underestimating the high-risk distributions. However, LVH on ECG is very uncommon, found in less than 5% of people in this study who were aged over 40 years and free of CVD and diabetes. Lack of information on family history of premature CHD and familial hypercholesterolaemia might also have led to underestimation of risk. Finally, because the AusDiab study was conducted in 1999–2000, data on reported use of lipid-lowering medication might not reflect current clinical practice.

Several other aspects need to be considered. Prediction equations or risk scores derived from the Framingham Heart Study are the most widely used to assess CVD risk, and their validity in Australians has been confirmed in the Busselton and Dubbo studies.[16,17] Both the Busselton and Dubbo groups have developed multivariate risk equations, but these have some limitations for general use. The prediction algorithm derived from the Busselton Health Study only allows estimation of risk of hospitalisation or death due to CHD within the next 10 years.[18] The CVD risk prediction equation from the Dubbo Study is only applicable to older Australians aged 60–79 years.[17] Contemporary population-specific risk prediction equations for future CVD or CHD events need to be further developed and validated.

Despite these limitations and considerations, our findings can inform health policy and clinical practice. As the greatest absolute risk reduction results from treatment of those at highest risk, we propose that criteria to support use of lipid-lowering medications in those without manifest CVD or diabetes should be revised.

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COMPETING INTERESTS

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